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Randomized controlled trials on prevention, diagnosis, and treatment of diabetes in African countries - a systematic review

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ABSTRACT

Objectives The epidemiological transition from infectious to chronic diseases leads to novel challenges in African health systems. The prevalence of diabetes mellitus (DM) is increasing dramatically. Undiagnosed and undertreated DM leads to numerous complications including end-organ damage and death. Our objectives were to collect the best locally generated evidence on DM interventions, identify knowledge gaps, and determine underexplored research areas.

Design A systematic review and meta-analysis of randomized controlled trials.

Participants and setting African patients in primary, secondary and tertiary prevention, diagnosis and treatment DM type 1 (DM1), type 2 (DM2) and gestational DM (GDM).

Outcome All-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs.

Data sources Articles published in MEDLINE Ovid, CENTRAL, CINAHL, African Journals Online and African Index Medicus and the International Clinical Trials Registry Platform in English language without time restrictions.

Results Out of 3736 identified publications, we included 60 eligible studies conducted in 15 countries 75 % were conducted in urban health care settings, including 10,112 participants. We included eight studies on DM1, six on GDM, two on pre-DM, 37 on mainly DM2 including seven on DM related complications. The design of the studied intervention was heterogeneous with a focus on educational strategies. The other studies investigated the efficacy of nutritional strategies including food supplementations, pharmacological strategies and strategies to enhance physical activities. Seven studies included interventions on DM-related complications.

Conclusions: Research activities increased in recent years, but available evidence is still not representative for all African countries and rural areas. We detected a lack of evidence in primary health care and locally implemented pharmacological interventions. The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances.

PROSPERO registration number: CRD42019122785.

Keywords: Diabetes mellitus, Africa, systematic review, randomized-controlled trial

Strengths and limitations of this systematic review

- This systematic review includes studies at the highest level of evidence to provide an overview of the best available interventions to prevent, diagnose and treat DM in the African context.
- Inclusion criteria are restricted to randomized controlled trials conducted in African countries published in English language with no restrictions on time of publication.
- We performed a systematic search in four international databases and updated the search in October 2020.
- The main aim of our systematic review is to provide an overview of interventions for DM. Meta-analyses are restricted to regularly reported results on HbA1c as strong clinical outcome indicator of an efficient DM management.
- Limited external validity due to the origin from few countries and urban areas, results concentrate on glycemic control due to short follow-up periods.

INTRODUCTION

Diabetes mellitus (DM) and other non-communicable diseases (NCDs) are responsible for a double burden in African countries due to the epidemiological transition from communicable to non-communicable diseases and resulting disabilities and deaths (1-3). In Africa, around 19.4 million adults are living with DM. Prevalence rates range from 4.7 % in Sub Saharan Africa (SSA) to 12.2 % in the Middle East and North Africa region (4). Due to the increasing prevalence of risk factors such as obesity and westernized lifestyle, the prevalence of DM is expected to increase by 96 % in SSA until 2045 (4). Currently, about 50 to 60 % of adults living with DM in African countries are undiagnosed (4, 5). Low awareness as well as genetic differences and lifestyle habits result in very heterogeneous prevalence rates of DM between different countries in Africa as well as rural and urban regions (6, 7). Undiagnosed and undertreated DM can result in organ damage, and lead to complications like cardiovascular diseases, peripheral neuropathy, retinopathy and diabetic foot (7, 8). Moreover, these factors attribute to substantial financial costs for households and governments (9). Recently, almost one fifth of COVID-19 deaths in African countries occurred among DM patients (10).

The United Nations 2030 Agenda aims to reduce the burden of premature mortality from NCD including DM through improvement in prevention and treatment (11). Measures on DM include early detection in primary health-care settings, lifestyle modifications including diet, physical activity and, if necessary, medication. Since DM patients need regular specialist assessment, a functioning referral system is necessary (12). These general management strategies have to be adjusted to local contexts in African countries including environmental, cultural and social aspects like the relatively young age of patients, co-infections, long distances to health-care facilities, traditional beliefs, decision making in the families and socioeconomic status. Furthermore, there is a huge genetic diversity on the African continent (13, 14) .

The purpose of this review was to collect the best locally generated evidence, regarding preventive, diagnostic and therapeutic intervention on DM, as the lack of evidence is one of the major challenges to prevent and control DM in African countries. Therefore, we aimed to address existing knowledge gaps and identify unexplored research areas in the African context. This may support the formulation of local evidence-based strategies to systematically strengthen clinical and preventive capacities of healthcare systems in African countries.

METHODS

We prospectively registered a protocol of this systematic review in the PROSPERO International Prospective Register of systematic reviews (CRD42019122785). This systematic review follows the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (15) and the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (16).

Inclusion criteria and exclusion criteria

This systematic review includes studies conducted in African countries on the efficacy of interventions for prevention, diagnosis and treatment of patients with DM including prediabetes, type 1 (DM1), type 2 (DM2) and gestational DM (GDM). Primary outcome was defined to be all-cause mortality. Secondary outcomes included glycemic control (HbA1c, fasting serum or plasma glucose, insulin resistance, oral glucose tolerance test), quality of life, treatment adherence, hospital admissions, complications of DM and resulting costs (see Table 1 for detailed inclusion criteria).

We included full-text publications on randomized controlled trials (RCTs) (e.g. individual RCTs, cluster-RCTs and randomized cross-over trials) according to the Consolidated Standards of Reporting Trials (CONSORT) (17) published in English language. We excluded international multicenter studies with less than 50 % of sites in African countries to ensure that the study location was in Africa.

Design and setting	RCTs, mainly conducted in African countries (at least 50 % African countries in international studies)
Population	African patients in primary, secondary or tertiary prevention with a clinical diagnosis of • Prediabetes • Diabetes mellitus type 1 (DM1, due to autoimmune β-cell destruction) • Diabetes mellitus type 2 (DM2, due to a progressive loss of adequate β-cell insulin secretion) • Gestational diabetes (diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation) As described by the authors
Interventions	All interventions to of prevent, diagnose and treat diabetes
Comparison	Placebo or standard care Another intervention or the same intervention with a different dose or timing
Outcome	Primary: all-cause mortality Secondary: • glucose control (HbA1c, oral glucose tolerance test, insulin resistance, fasting serum or blood glucose) • complications • quality of life • hospital admission • treatment adherence Additional: costs at longest follow-up
Publications	Full-text publications according to CONSORT

CONSORT: Consolidated Standards of Reporting Trials; DM: Diabetes mellitus; DM1: Type 1 diabetes; DM2: Type 2 diabetes; GDM: Gestational diabetes; HbA1c: hemoglobin A1c; RCT: randomized controlled trial

Table 1: Inclusion and exclusion criteria

Systematic search

We performed a systematic search in electronic bibliographic databases (MEDLINE Ovid, CENTRAL, International Clinical Trials Registry Platform of the WHO) as planned in the protocol and added a search in CINAHL and regional electronic databases (African Journals Online and African Index Medicus) (see Online Supplemental File 1 material). All searches were performed without time constrictions. The last search was conducted in October 2020. Search strings were based on Medical Subject Headings (MeSH) and terms on DM, Africa, a list of all 54 African countries and terms related to RCTs. All references retrieved from the literature search were exported into a reference manager software (EndNote) (18). Duplicate references were identified in case of congruence of authors, title, year and journal and thusly deleted. The search strategy is avaible in the supplementary file.

Study selection and data extraction.

Two authors independently checked titles and abstracts based on the inclusion criteria (Table 1). The full texts of all potentially eligible papers were assessed for final inclusion. All disagreements were resolved by discussion until consensus was obtained (15). All reported information on the following were extracted and checked by another author:

- publications, registration and design,
- time and place (country, urban/ rural setting and health care setting)
- study population (inclusion and exclusion criteria, sample size and baseline characteristics on age, gender, type and length of DM, body mass index (BMI) and gylcemic control at baseline)
- intervention and control groups with the number of randomized participants per group and duration of the interventions
- outcomes (classified into primary, secondary, non-specified) and
- results on pre-planned outcomes within the longest follow up period with intervention effects with their 95 % confidence intervals (CI) and level of significance.

The study names were defined by the surname of the first author and the year of the first full-text publication of the results. We compared study and patient characteristics across studies to ensure that each included study represents a unique publication of study data. In cross-over RCTs, only data from the first period were used (19).

Quality assessment and risk of bias

Risk of bias was judged based on seven specific categories (sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) of the Cochrane risk of bias tool as 'low', 'high' or 'unclear' (16). Judgments were done by two of the authors and all discrepancies were resolved by discussion.

Judgments on blinding and incomplete outcome data were based on the primary outcome of included studies. Selective outcome reporting was defined as low when the study protocol with pre-defined primary and secondary outcomes was available and high when any result of pre-planned outcomes was missing. Incomplete outcome data was judged as high when more than 10% of randomized participants dropped out from analyses. Other sources of bias were judged as high risk of bias including missing reporting of sample size calculation, no description of a primary endpoint, and relevant differences of main baseline characteristics between intervention and control groups (16).

Data synthesis

The results of all pre-defined outcomes were described. Effect sizes on HbA1c for the longest follow-up period were visualized in forest plots using RevMan (20). Negative mean differences (MDs) describe lower HbA1c in the intervention compared to the control group. Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant. Heterogeneity was interpreted based on the I^2 statistics as not important (I^2 < 30 %), moderate (30-60 %) and substantial (I^2> 60 %) (16).

Patient and Public Involvement

There is no patient involved

RESULTS

A total of 2865 references were identified from electronic databases and 871 additional trials from the Clinical Trials Registry Platform were checked. We evaluated 185 potentially eligible full-text publications and included 60 eligible studies in 68 publications in this review (Figure 1 and Supplementary file).

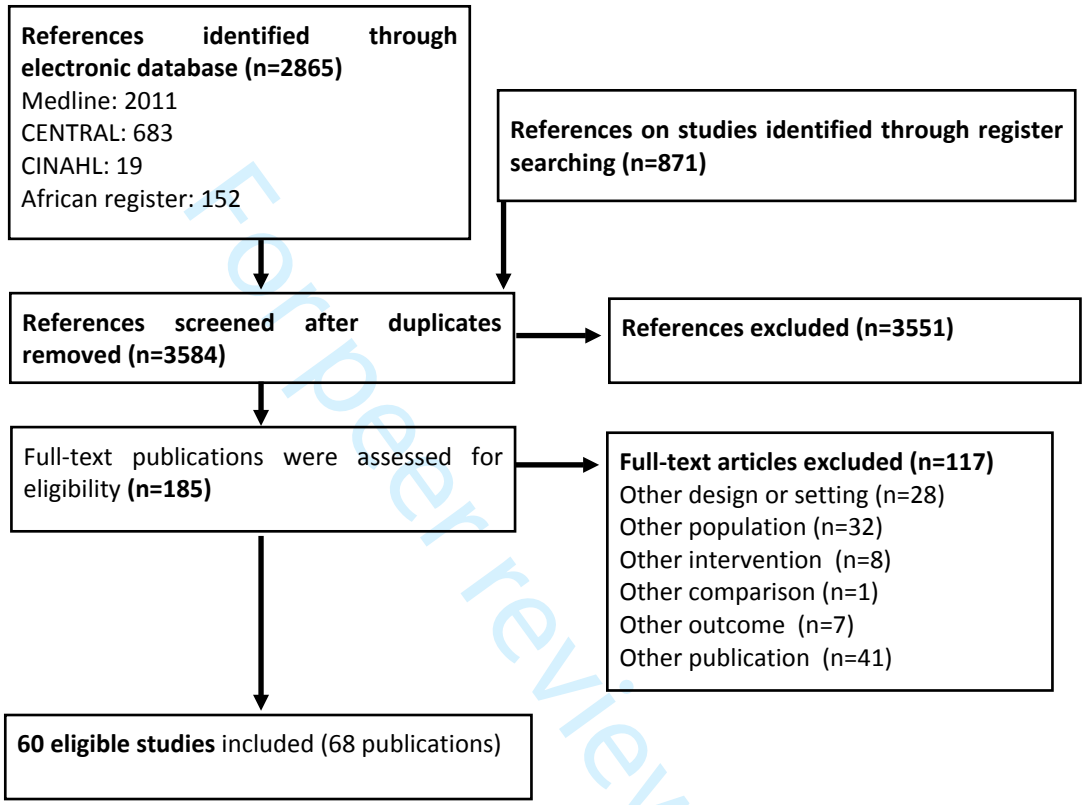

Figure 1: PRISMA flow chart describing the process of study selection

Setting

In total 60 studies, which were conducted in 64 study centers of 15 African countries; North Africa (33 studies from four countries), West Africa (10 studies from three countries), East Africa (seven studies from 7 countries), Central Africa (three studies from two countries) and Southern Africa (11 studies only from South Africa) were included. Two studies (Malek 2015 and Chraibi 2017) were conducted in more than one African country and partially conducted in non-African countries. Chraibi (2017) was conducted in Egypt, Morocco, South Arabia and Vietnam. Malek (2015) included four study centers in Alergia, Tunesia, Egypt and South Africa. Those additional study centers are presented in brackets behind the country names in Figure 2. Egypt, South Africa and Nigeria are the three study centers included most often in this review (Figure 2 and Table 2 available in the supplement).

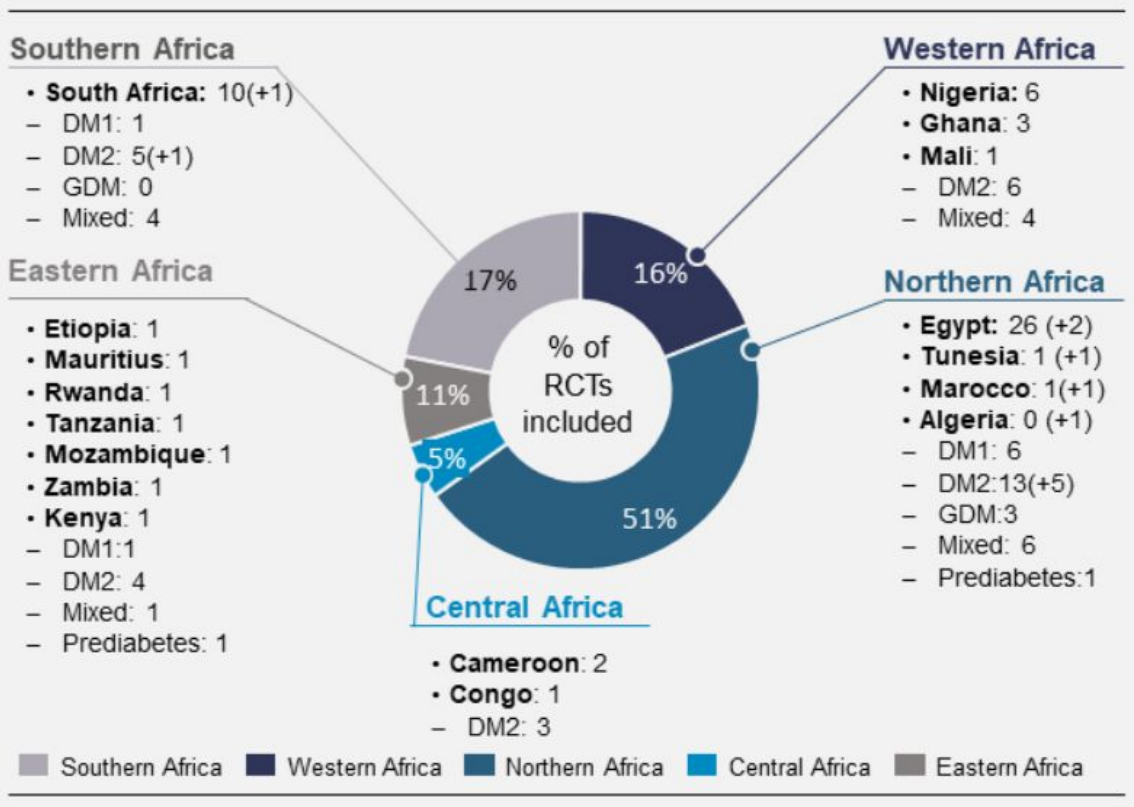

Figure 2: Geographical regions, countries, and type of DM of the included studies

Seventy-five percent of the studies (45/60) were set in urban areas, 5 % (3/60) were in rural areas only. The setting of the remaining 20 % (12/60 studies) was mixed or remained unclear. The majority, 83 % (50/60) of the studies, were conducted in secondary and tertiary health care centers, while 17 % (10/60) took place in primary care settings.

Though the search had no time restrictions, the oldest eligible study (Anderson 2001) was published in 2001. More than 60 % of the studies were published since 2015, and 22 % of them had been published in 2019 or 2020 (see Table 2 available in the supplement).

Design

Fifty parallel-group studies randomized individual participants with DM. Six cluster-randomized studies (Fairall 2016, Labhardt 2011, Mash 2014, Steyn 2013, Utz 2018, Webb 2015) randomly assigned health care facilities to intervention and control groups. In three randomized cross-over studies (Abdulrhman 2013, Krawinkel 2018, van der Hoogt 2017) each participant received different interventions in a random sequence, and in one study (Ghoneim 2013) each patient received two different treatment doses for each eye based on a random allocation of eyes and doses.

Interventions for patients with pre-DM

Two studies randomized a total of 112 overweight or obese patients (BMI 25–35 kg/m^2) with pre-DM (HbA1c 5.7-7.5 %) and a mean age of 32.9 and 47.5 years (see Table 2: Characteristics and results of studies on patients with pre-DM availble in the supplement). These studies stated the efficacy regarding glycemic control of low and high volume, high-intensity interval training strategies (RezkAllah 2019), and the consumption of bitter gourd to improve glucose control (Krawinkel 2018).

Interventions for patients with DM1

A total of 8 studies were conducted including 595 patients diagnosed with DM1 (Abdulrhman 2013, Elbarbary 2016, Elbarbary 2018, Elbarbary 2020, Malipa 2013, Mohamad 2009, Salem 2010, van der Hoogt 2017) (see table 3 Characteristics and results of studies on patients with DM1 available in the supplement). They mainly included children, adolescents, and young adults with a mean age between 10.4-19.9 years. The mean duration of DM ranged from 3.5 to 8.6 years and the mean baseline HbA1c from 7.21 to 9.52 %. The studies investigated heterogeneous strategies. Malipa 2013 showed the efficacy of weekly meetings to improve treatment compliance, reduce impact and worries about DM and improve general life satisfaction in adolescents. Salem 2010 evaluated the efficacy of two exercise programs to reduce cardiovascular risk with no relevant effect on glucose control. Three studies investigated different nutritional strategies and stated the beneficial effects of honey (Abdulrhman 2013) and camel milk (Mohamad 2009) on glucose control. Meals with low fat and protein (van der Hoogt 2017) caused less frequent hypoglycemic events. Elbarbary 2016 showed the efficacy of a low-glucose suspension algorithm during Ramadan to reduce the number of hypo- and hyperglycemic excursions. Two studies on food supplementation stated improved glycemic control with carnosine (Elbarbary 2018), but no benefit from a vitamin B complex (Elbarbary 2020).

Interventions for patients with DM2

A total of 44 studies were conducted including 8881 patients suffering from DM2 or different diabetic illnesses (see Table 4: Characteristics and results of studies on patients with DM2 availble in the supplement). Most studies included patients with a mean age between 50 and 60 years, only four studies included younger patients (Adjei 2015, El Gayar 2019, Matter 2020, Maharaj 2016). Most studies included more females than males. These studies presented a wide variety of patients in different stages of

DM2 and general conditions. They ranged from newly diagnosed DM (El Gayar 2019, Labhardt 2011, Mostafa 2019, Owolabi 2019, Somanah 2012), non-insulin dependency or oral insulin therapy (Adibe 2013, Ali 2019, Fayehun 2018, Maharaj 2016, Malek 2015, Ragheb 2020) to durations of over 10 years with severe DM related complications (Abaza 2017, Nteleki 2015, Tsobigny-Tsague 2018, El-Shakawy 2016, Ghoneim 2013, Saeed 2013, Yakoot 2019). Thus, mean baseline HbA1c ranged from 6.75% to 11.1%. Most studies included high proportions of overweight and obese participants with mean BMIs ranging from 22.4 to 40.8 kg/m².

Educational strategies

A total of 19 studies with 6942 patients and follow-up periods between 2-14 months investigated the impact of educational strategies on diabetes treatment. These included providing information about lifestyle modification measures, dietary recommendations, drug-based therapy, DM-related complications and self-management. Training sessions were provided based on group-based educational sessions or individual treatment plans by nursing staff or pharmacists and complemented by lectures, discussion services, brochures, newsletters, computer programs, electronic communication devices and tele-monitoring systems. Three of these studies were led by nurses (Adibe 2013, Hailu 2018, Labhardt 2011) and two cluster-randomized studies trained nurses to expand their role in the treatment of patients with NCDs (Fairall 2016) or aimed to improve guideline implementation in the treatment of patients with DM (Steyn 2013).

Three studies (Abaza 2017, Adjei 2015, Labhardt 2011) reported results on treatment adherence. All strategies lead to improved adherence, measured by improved perception of patients to treatment recommendations (Abaza 2017) or higher regularity of appointment schedules (Adjei 2015, Labhardt 2011). Two studies (Adibe 2013, Mash 2014) reported results on costs with lower costs for patients receiving educational strategies. Two studies reported fewer admissions to different health-care facilities (hospital or emergency room and clinic visits) (Abaza 2017, Chraibi 2017).

Results on quality of life were reported in two studies with follow-up periods over 12 months and conflicting results. A structured self-care education program by pharmacists and nurses (Adibe 2013) improved quality of life, but no benefit was shown after group education by trained professionals (Mash 2014).

The majority of the educational strategies resulted in lower mean HbA1c levels in the intervention groups with a clinically relevant mean decrease of -0.66 % (95 %-CI -0.94 to -0.39) and substantial heterogeneity between results of different studies (I^2=64 %) (Figure 3).

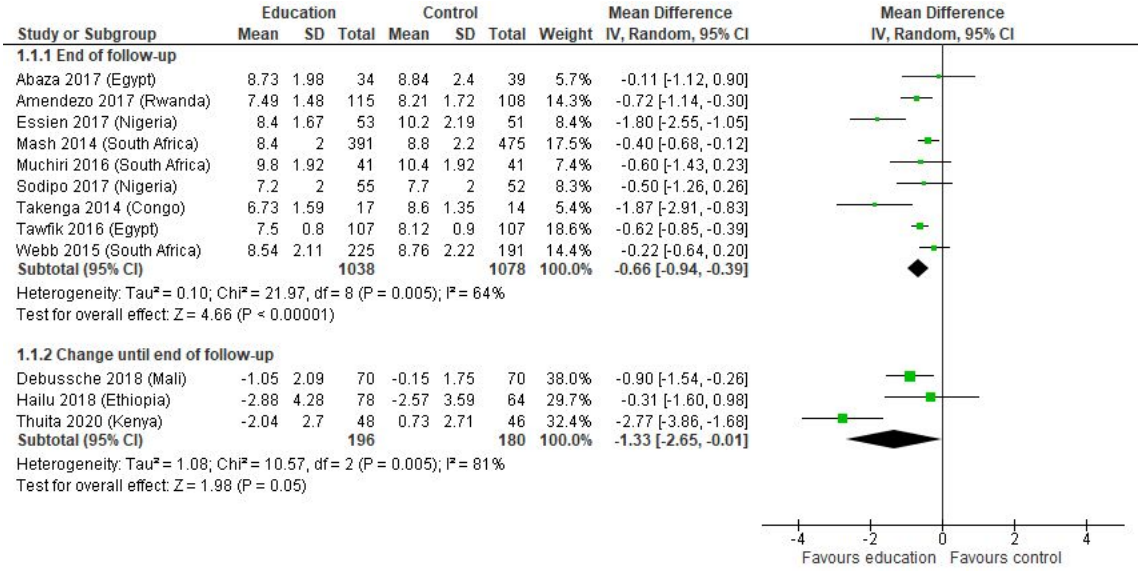

Figure 3: Results of educational strategies on HbA1c levels or changes of HbA1c levels of patients with DM2

Strategies to enhance physical activity

Five studies with 359 participants evaluated the efficacy of different strategies to enhance physical activity on glucose control. Strategies included counselling, setting goals and training sessions with different intensities or both over periods between 8-12 weeks.

Two studies were successful in lowering HbA1c where patients were given goals to accumulate 10,000 steps per day (Fayehun 2018) or patients were allocated to rebound exercise (Maharaj 2016). A third study investigated the effects of aerobic exercise training and was able to decrease fasting plasma glucose (21).

Two other exercise interventions failed to reduce HbA1c by incremental exercises compared to relaxation (Van Rooijen 2004) or higher intensity of exercises (Yan 2014) (Figure 4). Results were not pooled due to considerable heterogeneity with different directions of treatment effects.

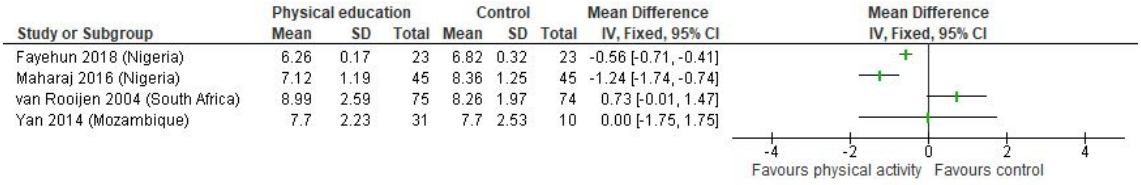

Figure 4: Results of strategies to enhance physical activity on HbA1c levels of patients with DM2

Pharmacological strategies

Three studies with 479 participants tested the efficacy of pharmacological treatment strategies on glucose control of patients with DM2. El-Haggar 2015 found ketotifen and glimepiride an effective dual therapy. Malek 2015 described the non-inferiority of once-daily basal-bolus insulin analogues and thrice daily insulin therapy. Distiller 2014 did not find an additional improvement with exenatide in addition to insulin and metformin therapy on glycemic control.

Strategies on food supplementations

Several different food supplementations were tested in 10 studies including 762 participants. Vitamin D3 supplementation had a positive effect on glycemic control in two studies (Ali 2019, Anyanwu 2016). Four studies tested the effect of plant-based substances. Ginger powder and balantines aegyptiaca (desert date) extract regimes supported glucose control (El Gayar 2019, Rashad 2017). Nigella sativa (black cumin) oil capsules slightly improved glucose control but were inferior to metformin (Moustafa 2019). A regime based on fermented papaya did show beneficial results (Somanah 2012). Anderson 2001 and Matter 2020 showed positive effects of zinc/ chromium in chronic DM and zinc supplementation in diabetic beta-thalassemia major patients. The addition of rutin and vitamin C did not improve the results of oral antidiabetics (Ragheb 2020). The addition of l-carnitine improved diabetic control achieved by glimepiride treatment (El-Sheikh 2019).

Strategies on the treatment of DM related complications

Seven studies with 351 participants and follow-up periods between 3-12 months evaluated different strategies to treat possibly DM-related complications including periodontitis (3 studies), foot ulcerations (2 studies) and macular edema (2 studies).
El-Makaky 2020 and Tsobgny-Tsague 2018 described the benefit of immediate vs. delayed non-surgical periodontal interventions on glucose control and El-Sharkawy 2016 stated the effectiveness of propolis as an additive in periodontitis treatment. Two studies stated a benefit of combined phototherapy and podiatric management (Nteleki 2015) and an additional local ointment application of royal jelly and panthenol (Yakoot 2019) on the healing of lower extremity ulcers. Ghoneim 2013 and Saeed 2013 tested different diabetic macular edema treatment strategies. Both studies described generally positive treatment effects but also considerable adverse events including rise of intra ocular pressure and glaucoma.

Interventions for patients with DM in a pregnant woman

Six studies included a total of 574 pregnant women at increased risk for gestational DM (GDM) (Embaby 2016), with newly diagnosed GDM (Utz 2018, El-Shamy 2018, Ashoush 2016) or with newly diagnosed GDM or pre-existing DM (Beyuo 2015, Ibrahim 2014) between the 20th and 34th week of pregnancy. The mean age ranged from 24.2-33.3 years (see Table 5: Characteristics and results of studies on pregnant women with DM available in the supplements).

Three studies (Ashoush 2016, Beyuo 2015, Ibrahim 2014) with 289 participants examined metformin as an additional medication to insulin in comparison to insulin therapy only. Effects on glycemic control of metformin supported therapy ranged from a relevant decrease (Ashoush 2016) to no effect on fasting plasma glucose, but beneficial effect on two hour plasma glucose in a 75 g OGTT (Beyuo 2015) in women without insulin resistance.Adding metformin to insulin therapy of pregnant women with insulin resistant diabetes was associated with several benefits concerning the time of hospital stay, reduced occurrence of maternal or neonatal hyperglycemia, less neonatal intensive care unit (NICU) admissions and reduced cases of respiratory distress syndrome (Ibrahim 2014).

The other studies (285 participants) investigated non-pharmacological interventions. The tested interventions were aerobic exercise program (treadmill walking) (Embaby 2016), acupressure (El-Shamy 2018) and screening for GDM, followed by nutritional and exercise counseling for positive tested women (Utz 2018). The aerobic exercise program resulted in a relevant reduction of fasting plasma glucose until delivery (Embaby 2016). The acupressure intervention did not manage to show a benefit regarding glycemic control (El-Shamy 2018). Screening, counselling and intensive follow-up were able to improve glycemic control and reduce the number of newborns with macrosomia (Utz 2018).

Potential biases

None of the included studies was categorized as low risk of bias in all seven domains only (see Table 6: Judgement on risk of bias available in the supplements).

The most common restriction on study quality was found in the domain performance bias due to a lack of blinding of participants and personnel in 48 studies. Detection bias due to blinding of the outcome assessors was judged as high or unclear in 38 studies. 14 studies with high risk of bias due to no blinding of participants and personnel, reported adequate methods to ensure blinding of the outcome assessors.

Another frequent problem was an incomplete analyses of outcome data in 26 studies defined as a loss to follow-up over 10 % of randomized participants or per-protocol analyses.

In 23 studies a protocol was available. Risk of bias due to selective outcome reporting was judged as low in 15 studies. High risk of bias, meaning lack of reporting of results of some pre-planned outcomes was judged in eight studies (Abdulrhman 2013, Beyuo 2015, Elbarbary 2020, Matter 2020, Owolabi 2019, Somanah 2012, Utz 2018 Yakoot 2019).

In the domain sequence generation, two studies were assessed as high risk. El- Nteleki 2015 randomized only seven patients into three different treatment groups. Shamy 2018 used a non-probability sampling method on the basis of the hospital admission code and was subsequently judged as high risk in domains sequence generation and allocation concealment.

In 31 studies, we identified further methodological limitations including missing reporting of information on sample-size calculation, definition of primary and secondary target criteria, relevant differences regarding baseline characteristics or reporting of intermediate results only.

DISCUSSION

This systematic review describes interventions from 60 studies to summarize the available evidence on strategies to prevent, diagnose and treat DM with a total of 12,113 participants from 15 African countries. Several promising interventions were identified, which could be useful to improve prevention, diagnosis and treatment, and thus, the prognosis of patients with diabetes.

Proven and effective actions to prevent or delay the onset of DM2 were based on the empowerment of the population, patients and health care providers (22). Recommended interventions include primary prevention programs with simple lifestyle measures to reduce consumption of sugar-sweetened beverages, mandatory detailed labels on food packaging as well as education and awareness campaigns to increase physical activity (23). Health systems must ensure technical and financial resources as well as training of healthcare staff to recognize the symptoms of DM, to perform and interpret diagnostic tests and provide adequate treatment and care (4). Concerning pharmacotherapy, priorisation of metformin, gliclazide and human insulin is recommended (24). Glucometers, needles and test strips should be provided for people with DM (4). Only a fraction of patients have access to the same treatment as recommended in high-income countries (25, 26). Evidence-based guidelines support health care providers and stakeholders in their task to reduce population burden and improve clinical outcomes. Guidelines should be based on the observed spectrum of patients with DM and carefully contextualize interventions concerning specific socio-cultural and economic barriers and facilitators (27). At the moment, most guideline recommendations in LMIC are based on studies conducted in high-income Western countries (28). The need for research in LMIC including Africa has been recognized and may have led to the increasing number of published RCTs from African countries in recent years.

Screening strategies to diagnose DM and its complications

The rate of undiagnosed patients with DM is estimated to be between 3.9 % in SSA (29) and 12 % in North Africa (30). This might be related to genetic disparities in the development level of the health care system and awareness in the general population (13). The high rates of undiagnosed DM highlight a high need for research on and implementation of DM screening strategies in the African context. We identified two studies to improve screening for DM and DM related complications (31-33). Both studies investigated different strategies in primary health care clinics to detect and manage women with GDM (31) and screen diabetic patients for complications (34). Utz 2018 detected a high prevalence of GDM with 23.7% of Moroccan pregnant women.

This underlines the importance of regular screening and management to enable early interventions at a primary care level (31). Screening strategies for diabetic complications in a diabetic population receiving primary care found a high rate of diabetic complications including retinopathy, maculopathy, neuropathy, nephropathy, possible infarction and severe erectile dysfunction (32-34). The high prevalence rates and the low rate of patients receiving recommended treatment by specialists resulted in non-relevant benefits on glucose control underlining the conclusions of two systematic reviews (7, 35) on the need to adapt preventive strategies to reduce DM and its complications.

Intervention for patients with pre-DM for primary prevention of DM

We identified two studies on pre-DM patients (36, 37) with elevated blood glucose levels below diagnosis criteria of DM. RezkAllah et al. (37) were able to improve glucose levels via interval training. Krawinkel et al. (36) demonstrated reduced fasting plasma glucose levels in pre-DM using bitter gourd, a plant with antidiabetic properties that is consumed in many Asian as well as some African countries. Pre-DM is strongly associated with the development of DM and thusly with its long-term consequences (38). Both studies offer effective strategies, but further research is necessary, exemplarily on early educational strategies, as a measure of patient empowerment and early tackling of DM (39).

Educational strategies for patients and health-care providers

Since DM is a disease with complex challenges for patients and health care providers, educational campaigns are necessary to support health care providers and empower patients to manage their disease-associated decisions, lifestyle habits and medication use. Best benefits are proposed to be achieved by continuous individualized education, guided by patients' concerns, preferences and needs (22, 40).

We identified a couple of effective strategies, mainly for patients with DM2 (41-53), one for patients with DM1 (54) and one for pregnant women with GDM (31). Most of these studies investigated long-term interventions to supported patient empowerment based on improved knowledge, motivation, and capacity to take control of their disease (22). Three studies trialed nurse-led) (42, 48, 49, 55) and 2 studies investigated strategies to train healthcare providers in the management of patients with DM (56, 57).

In times of growing digitalization, modern communication technologies might have great potential to improve the accessibility of the African population to high-quality health care services where human resources are limited (58). The number of people having access to mobile services is already high and expected to rise over the next

years (59). Lifestyle focused messages might be an effective low-cost option to keep patients motivated to adhere to healthy lifestyles (58). One small study (Takenga 2014) combined DM self-management with tele-medical approaches and stated a significant decrease of HbA1c levels (51). The application of telemedicine in different areas of DM management showed promising results in previous studies (60). Currently, the COVID-19 pandemic has forced all nations to implement alternative, oftentimes digital strategies including tele-monitoring and teleconsultation to continue care of NCDs (61).
Improvement of patient empowerment resulted in improved adherence and glucose control, fewer admissions to healthcare facilities and lower costs. Only two studies reported on the quality of life with heterogeneous results (42, 55, 62). Adibe et al. (Adibe 2013) (42, 55) showed a benefit with an incremental gain in quality-adjusted life years (QALY) with improved cost-effectiveness of an additional structural self-care education program implemented by pharmacists, physicians and nurses. These findings are supported by results from two systematic reviews showing the usefulness of nurse-led interventions to reduce cardio-metabolic risk factors in adults with chronic conditions in Europe (63, 64).
All included studies were adapted to local contexts and the trialed strategies are potentially adaptable to health care systems in other African and LMIC. Moreover, the tasks of nurses in NCD care could be redefined and expanded in countries with comparably few physicians in order to improve DM diagnostics, treatment and education with regards to local resources.

Strategies to increase physical activity

Seven studies (5 studies on DM2 (21, 65-68), 1 on DM1 (69) and 1 on GDM (70)) on exercise therapy showed generally positive results concerning effectiveness in glycemic control. Of the strategies to enhance physical activity, Fayehun 2018 managed to improve glucose control by setting the goal to accumulate 10,000 steps per day, an intervention that does not require any cost-intensive infrastructure and still managed to show a significant decrease in HbA1c levels after 4 weeks (65). Similarly, Yan 2014 found one-hour walking per day to be equally effective as 3-5 times per day exercise training in HbA1c reduction. Physical activity is generally reviewed as a beneficial intervention in GDM (71), DM1 (72, 73) and DM2 (74, 75). Long-term adherence to this strategy needs to further be assessed.

Pharmacological strategies

We identified only six studies (3 studies on DM2 (76-78), 3 on GDM (79-81)) on pharmacological interventions as a central part of DM care (82) despite known

differences in DM between African and European Americans (13). This can be due to the exclusion criteria as we excluded international studies with few sites in African countries (e.g. (83-88)). Most of the major pharmacological studies only have a few study centers in Africa. Thus, such research is important and more studies like this should be conducted in Africa as it is known that among different ethnic and racial groups the response to drugs can vary. Studies like this could lead to a prioritized used of medications, which are known to show a good response in African population. El-Haggar et al. (77) investigated the addition of ketotifen in obese DM2 patients to glimepiride treatment showing beneficial effects. The beneficial effect of ketotifen as a mast cell stabilizer has been studied in mice receiving a Western diet and diabetic rats resulting in a significant reduction of weight gain and glycemic parameters (89, 90). Further research is necessary to generate more detailed evidence on the use of ketotifen in diabetic patients.

Malek 2015 (78) reported the usability and safety of a basal-bolus insulin regime with stepwise intensification in an African setting as an easy to handle, practical option for DM care. The efficacy of basal-bolus insulin regimes has been previously described in other settings (91, 92). Currently, the available research on pharmacological interventions for DM is sparse in Africa. Further research should consider regional contexts like availability of medication, practicability of the medication (e.g. insulin needs proper storage (93, 94)) lifestyle habits and genetics (95, 96). Consideration of findings from African American cohorts seems advisable (97, 98). Three studies on woman with gestational DM (79-81) tested metformin-based regimes (with or without insulin support) vs. insulin-only regimes. Metformin-based therapy regimes generally showed similar results compared to insulin-only regimes concerning glycemic control. The effectiveness and safety of metformin in GDM has been detailed in other systematic reviews (99, 100).

Strategies on nutrition and food supplementations

Four small studies tested different nutritional interventions (36, 101-103), mainly for children and adolescents with DM1 (101-103) with promising results of long-term consumption of honey (101) and camel milk (102) and a low fat and protein content of meals (103) on metabolic control for DM1 patients. Especially the positive effects of camel milk, based on the traditional treatment of DM in arid areas of Africa and Asia, may offer an interesting management strategy to improve glycemic control, reduce insulin requirement and limit diabetic complications (104). The study on bitter gourd consumption for persons with pre-DM (Krawinkel 2018) (36) was discussed above.

The twelve included studies on food supplementations (2 for DM1, 10 for DM2) showed some promising results for different adjuvant DM therapies including zinc-gluconate (105) and zinc-chromium (106) supplementations, ginger powder (107), Nigella sativa oil capsules (108), L-carnitine (109), L-carnosine (110) as well as vitamin B, C or D supplementation (62, 111-113) on glycemic control. These results are in line with previous results from systematic reviews showing benefits in the prevention of DM and improved glycemic control, lipid profiles and management of DM-related complications (114-126). On the other hand, beneficial effects on glycemic control shown in two studies on vitamin D3 supplementation contrasts findings from recent systematic reviews (127, 128).

New evidence was generated by Rashad 2017 (129) who stated the beneficial effects of balanites aegyptiaca (desert date) extract on glycemic control. This evergreen tree is common in arid regions in Africa and was traditionally used in Egyptian traditional medicine. Helal et al. described similar results in diabetic rats (130).

Strategies on the treatment of DM related complications

Three studies tested the role of periodontitis treatment in diabetic patients (131-133). Tsobgny-Tsague et al. (133) and El-Makaky et al. (131) described the importance of early treatment start, resulting in favorable patient outcomes in periodontal health and glucose control. El-Sharkawy et al. (132) found propolis to be a favorable addition to planing and scaling. In an Ethiopian cohort, only 21% of DM patients received oral health screening (134). The WHO regards oral health as a crucial component of health care with 12-14 % of 35 to 44-year-old Africans suffering from periodontitis (135).

Treatment options for diabetic wounds were tested in two studies (136, 137). Phototherapy in addition to usual care was first trialed in an African cohort of patients suffering from diabetic foot ulcers, showing beneficial wound healing outcomes. Similar results were described in other settings (138). The addition of propolis to usual care regimes showed improved wound healing. These findings are supported by studies from other settings (139, 140).

Strength and limitations

The external validity of this systematic review is limited by the focus on a limited number of countries and urban health care setting. The included studies were set in 15 of the 54 African countries with a focus on the North African region, especially Egypt. Egypt is the country with the highest known prevalence of DM in the African continent (4). This might be related to economic expansion and urbanization, but also due to

specific dietary issues (e.g. white bread, polished rice, trans fats), reduced physical activity due to prohibition of exercise in public places, shortage of exercise facilities, poor physical education in schools. Poor diet and physical inactivity are causing a high rate of overweight and obesity among the Egyptian population (141).

The broad majority of included studies was conducted in urban settings, this is likely due to the better health care infrastructure and thusly the increased practicability of research. Health care workers, including doctors and nurses, seem to prefer providing services in urban areas leading to an even higher deficit of health care access in rural areas. The consequence is limited generalizability of the results on the needs of the rural population. People living in rural areas are rather diagnosed at an advanced stage of the disease and more likely to already suffer from DM related micro-and/or macrovascular complications (6). On the other hand, people living in rural areas probably perform more exercise, consume less processed food and are less obese with resulting lower incidence of DM.

Our pre-planned primary outcome was mortality which was not reported in any of the included studies. Since DM is a chronic disease with a slow progression and long-term development of organ damage, the survival time is higher than the follow-up time of most of the studies. The included studies looked at long-term treatment strategies rather than treatment for acute hypo- or hyperglycemic events that can lead to acutely fatal events. Nevertheless, long-term glucose control, being represented by the HbA1c value is one of the strongest clinical-outcome indicators of efficient DM management and health outcomes (142). It is easy to measure and serves as a representation of the individual's average blood glucose levels in the previous 3 months (142).

This systematic review includes studies as the highest level of evidence to investigate the benefits and harms of interventions (143). We included studies published in the English language without time restrictions. Language bias was shown to be unlikely. Despite the high linguistic diversity on the African continent, the languages mostly spoken are English, Arabic, and French (144). Eventually, we did not exclude any study due to the publication language.

CONCLUSION

This systematic review shows an increasing number of studies due to the rising prevalence and awareness of DM in African countries. However, the number of high-quality studies to improve prevention, early diagnoses and treatment and thus, the prognosis of African patients with DM is still low. Available studies are not representative of all African regions and were mainly conducted in urban areas. Especially primary care settings are underrepresented.

An improvement of the prognosis of DM patients in Africa requires adequate technical and financial resources, training of healthcare staff and the implementation of comprehensive strategies to improve early diagnostics, adherence to medical treatment and subsequent regular checks. The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances.

Ethics approval

No ethical approval is necessary

Authors contribution

Sandholzer-Yilmaz AS developed the concept of the review, performed the initial systematic search in the International Trials Registry, screened the references, extracted study data in 2019, wrote a draft of the manuscript and worked in the coauthors comments on the final version of the manuscript and finally submitted the manuscript.

Kroeber ES updated the systematic search, added a search in 2 regional databases, screened the updated search results and extracted the updated data and wrote the final version of the manuscript.

Unverzagt S has expertise in systematic reviews and is the guarantor of the methodological quality of the systematic review, developed the review concept has registered the protocol, performed the systematic search in 2 databases, screened all references, checked the initial as well as the updated data extraction and wrote the final version of this manuscript.

Ayele W provided expertise on the needs of evidence in the African context, developed the review concept, discussed the protocol and critically read and commented on the manuscript.

Frese T and provided expertise on primary care, developed the review concept, critically read and commented on the manuscript.

Kantelhardt EJ provided expertise on the needs of evidence in the African context, developed the review concept, critically read and commented on the manuscript.

The authors wish it to be known that, in their opinion, the first 2 authors should be regarded as joint first authors.

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Studies on patients with pre-DM

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	 Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Strategies to enhance physical activity						
RezkAllah 2019 ACTRN12617000631303 RCT	Egypt, urban 07/2017-01/2018	Pre-DM, 25-45 yrs, BMI of 25–30 kg/m2, HbA1C 5.7–6.4%, fasting glucose 100–125 mg/dL, sedentary lifestyle No history of diabetes, cancer, prediabetic neuropathy, stroke, pulmonary embolism, or severe musculoskeletal problems restricting physical activity	n=60 45 % females age (yrs): 32.9±5.5 BMI (kg/m²): 28.3±1.4	IG2 (n=20): High-volume high intensity interval training, 40 min/session vs. IG1 (n=20): Low-volume high intensity interval training, 25 min/session Both with 90 % HR maximum, 3 times/week CG (n=20): No exercise intervention Duration: 12 weeks	Primary: HbA1c Other: fasting glucose	After 3 months HbA1c (%): Benefit for IG2 and IG1: Benefit for IG: 4.87±0.34 (-26 %) vs. 5.13±0.57 (-14.5 %) vs. 6.25±0.48 (+3.38 %) (p=0.0001) fasting glucose (mg/dL): Benefit for IG2 and IG1: 90.8±4.13 (-17.8 %) vs. 93.8±4.16 (-13.2 %) vs. 103.8±7.21 (+2.9 %) (p=0.0001)
Strategies on nutrition						
Krawinkel 2018 DRKS 00005131 Cross-over-RCT	Tanzania, urban 10/2013-03/2014	Individuals with pre-DM age (yrs): 30 -65, FPG 5.6-6.9 mmol/l (100–125 mg/dL) on 2 days or on one day + HbA1c 5.7-7.5 %, BMI 27–35 kg/m^2, BP 90/60-160/110 mmHg, waist circumference > 80/90 cm for women / men No chronic disease, taking regular intake of medication, identified glucose-6-phosphatase-dehydrogenase deficiency, heavy alcohol consumption, pregnancy,	n=52 55% female age (yrs): 47.5±8.7 HbA1c (%):5.85±0.43 FPG: (mmol/l): 5.34±0.49 BMI (kg/m²):29.6±2.2	IG/CG (n=30): started with bitter gourd supplementation (2,5 g) over 8 wks, followed by placebo over 8 wks vs. CG/IG (n=31): first placebo over 8 wks, followed by bitter gourd over 8 wks washout period: 4 wks Duration 8 weeks	Primary: FPG Secondary: HbA1c, Insulin, SBP, DBP, lipids	after 8 wks FPG (mmol/l): Benefit for IG/CG: MD 0.31 (0.08-0.54) HbA1c: (%): No differences (MD 0.05)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		lactation				

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DBP: Diastolic blood pressure; DM: diabetes mellitus; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants; MD: mean difference; RCT: randomized controlled trial; SBP: Systolic blood pressure; SD: Standard-deviation; wks: weeks; yrs: years

Table 2: Characteristics and results of studies on patients with pre-DM

Studies on patients with DM1

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Malipa 2013 RCT	Zambia	DM1, 16-19 yrs	n=40 55% females 16-17 yrs: 35 % 18-19 yrs: 65 % Compliance: worse in IG 26.4 vs. 14.6 (p=0.001) Impact of diabetes: 20.5 Worries about diabetes: 20.5 Satisfaction with life: 20.5	IG (n=20): 1 meeting /wk over 8 wks CG (n=20); waiting list Duration: 8 wks	Compliance to treatment (Rating scale for compliance) Quality of life (impact and worries about diabetes, satisfaction with life)	After 2 months: Compliance: better in IG (11.0 vs. 30; p<0.001) Impact of diabetes: better in IG (16.8 vs. 24.2; p=0.045) Worries about diabetes: better in IG (14.32 vs. 26.68; p=0.001) Satisfaction with life: better in IG (28.5 vs. 12.5; p<0.001)
Strategies to enhance physical activity						
Salem 2010 RCT	Egypt, urban 02/2009-11/2009	DM1 for ≥3 years, 12-18 yrs, HbA1c ≥7.5 % for ≥6 months no significant diabetic complications limiting exercise like, uncontrolled hypertension, diabetic keto-acidosis, severe hypoglycemia within the past 3 months, patients on lipid lowering therapy	n=196 61.7 % female age (yrs): 14.78 ± 2.31 HbA1c (%): 8.7±1.7 duration of diabetes (yrs): 4.6 ± 1.9	IG2 (n=73): attended exercise sessions three times/week vs. IG 1 (n=75): attended exercise sessions once times/week vs. CG (n=48): no exercise Duration: 6 months	glycemic control, plasma lipids values, blood pressure, severity and frequency of hypoglycemia, anthropometric measurements and insulin dose	Change over 6 months: HbA1c (%): Benefit for IG2 and IG1: 7.8 ± 1.0 vs. 8.1 ± 1.1 vs. 8.9 ± 1.3% (p=0.2)
Strategies on nutrition						
Abdulrhman 2013 NCT01554566 Cross-over	Egypt, urban, tertiary care 01/2010 -	DM1, age > 2 yrs, HbA1c< 10 % no renal or hepatic impairment, coexisting	n=20 50 % females age (yrs): 11.3 ± 4.3 duration of diabetes (yrs): 4.7±4.5	IG/ CG (n=10): Honey consumption (0.5 ml/kg body weight per day) vs.	Primary: serum lipids, c-peptide Secondary: anthropometric measures (e.g. BMI), fasting and 2h-	After 12 weeks: (IG/CG vs. CG/IG): HbA1c (%): • Benefit with CG/IG: 6.7±0.9 vs. 5.9±0.8 (p<0.01) • no differences in change in period 1: -

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	10 / 2011	diseases or therapies that may affect body weight or serum lipids	HbA1c (%):7.21± 0.76 fasting glucose (mg/dl): 154.5±22.5	CG/IG (n=10): changed after 12 wks and received than honey Duration: 12 wks.	postprandial glucose, HBA1c, serum lipid profile	5.83 ± 13.66 vs. 2.94±8.82 (p=0.105) Fasting glucose (mg/dl): benefit with CG/IG: 142.7 ±26.6 vs. 116.7±19.4 (p<0.01) benefit with IG/CG in period 1:-21.51 ± 10.84 vs. -0.08±5.14 (p=0.001)
Mohamad 2009 RCT	Egypt, urban	DM1, age 17 to 20 yrs no acute metabolic complications like diabetic ketoacidosis, hypoglycaemia, cardiovascular events, renal or acute infections	n=64 30 % female age (yrs): 19.9±6.8 HbA1c (%): 9.52±2.08 fasting glucose (mg/dl): 228.7±13.5 BMI (kg/m²): 18.82±3.01	IG (n=27): camel milk (500 ml) +usual care vs. CG (n=27): usual care for diabetes (i.e. diet, exercise, insulin mixtard) Duration: 16 weeks	Not specified: HbA1c, human C-peptide, lipid profile, serum insulin, anti-insulin antibodies, creatinine clearance, albumin extraction in 24 h urine, BMI, Diabetes QoL score, fasting glucose	After 16 wks HbA1c (%): Benefit for IG: 7.16±1.84 vs. 9.59±2.05 fasting glucose (mg/dl): benefit for IG: 227.2±17.7 vs. 98.9±16.2
van der Hoogt 2017 cross-over RCT	South Africa	DM1, age 4-17 yrs on insulin pump therapy, HbA1c>9,6% for ≥3months, BMI/age z.score -1 to < 3, total daily insulin use of >0,5 u/kg no remission of diabetes, smoking, coeliac disease, cystic fibrosis, diseases or medication that are associated with delayed gastric emptying or altered digestation, glucocorticoids, oral diabetic drugs, no acute illnesses	n=32 41% female age (yrs): 10.4±4.0 HbA1c (%): 8.2±0.8 duration of Diabetes (yrs): 3.5 (1.5-8.0)	IG1 (n=22): 1 home-based low fat and protein meal vs. IG2 (n=22): 1 high fat and protein meal with identical carbohydrate content two meals were consumed at dinner time (18:00) under parental supervision at least 1 day apart within one month Duration: 3months	primary: peak sensor glucose value post-meal, time to peak sensor glucose, time of first and largest correction bolus, total correction insulin, total meal insulin, additional insulin required ,area under the sensor glucose response curve (AUC) (≥ 8 mmol/L), duration of elevated post-prandial glucose	Change over 12 weeks Occurance of hypoglycaemic events: 7 (32 %) vs. 1 patients after IG1 vs. IG2
Medical device						
Elbarbary 2016 RCT	Egypt, urban 06/2014-07/2014	DM1, adolescents and adults who wished to fast the month of Ramadan with insulin pump for ≥6 months and attending the whole	n=73 68.3% female age (yrs): 15.6±2.7 HbA1c (%): 7.65±0.9 BMI (kg/m²):	Insulin pump therapy during Ramadan fasting IG (n=25): sensor with low glucose	Primary: hypoglycaemia Other: glucose value, number of 'full fasted days', emergency hospital visit for diabetes-related	After 1 months: Glucose value (mg/dl): 152.5±17.3 vs. 141±33.8 (p=0.9) Complications: Number of hypoglycaemic excursions:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		education session 2 months before fasting and committed to follow-up the given instructions no diabetic ketoacidosis, episodes of severe hypoglycaemia or symptoms of uncontrolled diabetes in the last 6 months, diabetic microvascular complications or macrovascular disease, pregnant women	24.56±3.5 duration of diabetes (yrs): 5.8±2.9 on pump therapy (yrs): 1.73±0.99	suspension activation vs. CG (n=35): sensor without low glucose suspension activation Duration:1 month	problem	3.68±1.62 vs. 6.7±2.1 (p=0.001) Number of hyperglycaemic excursions: 17.0±4.0 vs. 23.0±7.6 (p=0.001) No severe hypoglycaemic events, no episodes of diabetic ketoacidosis, no hyperglycaemic events associated with ketosis no deaths or device-related SAE
Pharmacological Strategies						
Elbarbary 2018 NCT0292825 RCT	Egypt, urban	DM1, age: 9 - 18 yrs, ≥ 5 yrs disease duration, active diabetic nephropathy in the form of microalbuminuria, HbA1c ≤ 8.5 % no infection, renal impairment due to other causes other than diabetes, other diabetic complications, hypersensitivity to carnosine	n=90 52.3 % female age (yrs): 12.85±3.1 HbA1c (%):7.85±1.95	IG (n=45): 1 g/d carnosine vs. CG (n=45): control/placebo group Patients in both groups received oral ACE-Is captopril 25 mg Duration: 12 wks	Primary: change in tubular damage marker Secondary: urinary albumin excretion (UAE), oxidative stress markers Safety: any AE	After 12 wks: HbA1c (%): • Benefit for IG: 7.4 ±1.3 vs. 8.3±2.4 • change -9.88±7.12 vs. 3.89±2.28 (p=0.005) No adverse reactions were reported
Elbarbary 2020 NCT03594240 RCT	Egypt, urban 03/2017-03/2018	DM1 on insulin therapy with > 5 yrs of disease duration, 12-18 yrs, active nephropathy, HbA1c< 8.5 %, no infections, renal impairment due to other causes than diabetes, other diabetic complications ,	n=80 55% female age (yrs): 15.4 ± 1.6 HbA1c (%):7.95±0.5 fasting glucose (mg/dl): 114.5±21.8 duration of diabetes (years): 8.65 ± 2.65	both groups received oral angiotensis-converting-enzyme inhibitors (captopril) IG (n=40) oral vitamin B complex (B1,B6,B12) once daily vs.	Primary: Cystatin C diet, physical activity, and metformin dosage	after 12 weeks HbA1c (%): Benefit for IG: 7.5±0.6 vs. 8.0±0.6 Fasting glucose (mg/dl): 107.7±14.1 vs. 116.4±17 (p=131)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	 Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		elevated liver enzymes, hyper-or hypothyroidism, hypertension, neoplasm, taking any vitamins or food supplements within 1 months before study start		CG (n=40): placebo Duration: 12 weeks		

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DM1: Type 1 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants ;RCT: randomized controlled trial; SD: Standard-deviation; wks: weeks; yrs: years

Table 3: Characteristics and results of studies on patients with DM1

RCTs mainly including patients with DM2

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Abaza 2017 NCT02868320 RCT	Egypt, urban, tertiary care, 03-07/2015	DM2, mobile phone, capable to read SMS or live with someone who could read	n=73 56 % females age (yrs): 51.5±9.2 majority had had diabetes for > 1 yr hypertension: 41.1 % on insulin: 19.2 % DM complication: 80.8 % HbA1c (%): 9.7±2.7	Diabetes awareness program: paper-based educations material plus IG (n=34): daily messages and weekly reminders addressing various diabetes care categories vs. CG (n=39): paper-based educations material Duration: 12 wks.	Primary: change in Hba1C Secondary: Random blood glucose levels, body weight, adherence of treatment and medication, diabetes self-efficacy and knowledge, rate of hospital/ER visits, frequency of measurements, regular exercise, patients confidence in healthcare provider and satisfaction, healthcare provider's reputation	After 3 months: HbA1c (%): • No differences: 8.73 ±1.98 vs. 8.84±2.40, MD_a: 0.290 (-0.402 to 0.983; p = 0.406) • Benefit with IG: 47 vs. 15 % achieved the targeted 1% drop (p = 0.003) Random blood glucose (mg/dl): • No difference: 181±65 vs. 201±87 (p=0.288) Treatment adherence (scores): • Benefit with IG in SCI 3.42±0.48 vs. 2.52±0.49 (p<0.001) and Morisky: 3.76±0.55 vs. 2.74±1.07 (p<0.001) Hospital /ER admission (%): No differences: 0 vs. 10.3 (p=0.118)
Adibe 2013 RCT	Nigeria, urban, tertiary care	DM2, age≥ 18 yrs with oral hypoglycemic and / or insulin therapy no pregnancy	n=220 58 % females age (yrs): 52.6±7.9 duration of diabetes (yrs): 4.7±2.5, 60.5% with diabetes > 5 yrs on insulin: 13.6 % hypertension: 60.5 %	IG (n=110): structured self-care education and training program by pharmacists and nurses vs. CG (n=110): usual / conventional care Duration: 12 months	Primary: incremental cost-utility ratio, net monetary benefit Other: quality of life	After 12 months: Quality of life: • Benefit with IG: 0.86 ± 0.12 vs. 0.64 ± 0.10 (p=0.0001) improved single attributes except "hearing" functioning of the patients Costs: • benefit of $0.76±0.15 vs. $0.64± 0.15 QALY/patient and year; MD: $ 0.12 (0.07 to 0.16) • incremental cost-utility ratio of $571 per QALY
Adjei 2015	Ghana, urban	DM	n=200 64.5% female	IG: (n=100): electronical reminder for	Primary: Compliance with appointment dates	After 6 months: Adherence to appointment schedules

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT			age (yrs): < 50 yrs: 63 % > 50 yrs: 37 % fasting glucose (mmol/l): 10.4±3.8	clinical appointments of patients + alert system for abnormal laboratory results vs. CG: (n=100): usual diabetes care, paper based method Duration: 6 months	Other: metabolic risk factors, BMI	(%) Benefit for IG: 97.8 vs. 89.4 (p=0.010) Fasting glucose (mmol/l): Benefit for IG: 8.04±2.14 vs. 8.85±2.63; MD 0.4 (-0.59 to -0.36, p=0.022)
Amendezo 2017 NCT02032108 RCT	Rwanda, urban, tertiary care	DM2>3mths, age>21yrs no pregnancy or severe co-morbid illnesses.	n=251 69.3% females age (yrs): 50.9 ±10.9 BMI (kg/m²): 27.9 (27.0-28.5) duration of diabetes : <10 yrs: 73.7%, >10 yrs: 16.3% HbA1c (%): 8.98±8.6-9.3	IG (n=115): standard care plus monthly lifestyle education sessions of 45 min duration vs. CG (n=108): standard care Duration: 12 months	Primary: difference in HbA1c Secondary: fasting glucose, systolic and diastolic blood pressure, BMI	after 12 months: HbA1c (%): Benefit for IG with median reductions of -1.70 (-2.09 to-1.31) vs. -0.52 (-0.95 to -0.10); MD: -0.72 (-1.14 to -0.30; p< 0.001) Fasting glucose (mmol/L): 6.9 (6.45 to 7.36) vs. 9.02 (8.18 to 9.87) (p<0.001)
Chraibi 2017 NCT01589653 RCT	Egypt, Indonesia, Morocco, Saudi Arabia, Vietnam 05/2012-07/2015	DM2 with diagnosis ≥ 12 months, age≥18 , currently being treated with NPH Insulin for ≥ 3 months + metformin (1000-1500 mg) for ≥ 2 months, HbA1c ≥ 7.0% ≤10%, BMI ≤ 40.0 kg/m^2 no treatment with thiazolidinedione, glucagon-like peptide-1 receptor agonists, pramlintide within the last 3 months , >1 IU/kg NPH insulin daily; previous use of premixed or bolus insulin, > 1 severe hypoglycemic episode during	n=155 74.9 % female age (yrs): 54.5 ±10.0 BMI (kg/m²): 29.05±4.9 HbA1c (%): 8.6 ±0.83 fasting glucose (mmol/L): 8.97 duration of diabetes (yrs): 9.5±5.8 African patients: • Egypt: 25.75 % • Morocco: 27.7 % Diabetic nephropathy / neuropathy / retinopathy (%): 3.2 / 16.1 / 3.2	IG (n=76): patient driven titration of Biphasic insulin aspart 30 twice daily, 3 clinic visits vs. CG (n=79): physician driven titration twice daily, 6 clinic visits Titration in both arms according to the titration protocol bases on self-measured plasma glucose values, measured twice daily on 3 preceding days, telephone contact whenever deemed	Primary: change in HbA1c Secondary: proportion of patients achieving the ADA target of HbA1c <7.0 % and the HbA1c target of <6.5 % after 20 weeks, FPG changes, hypoglycemic episodes,	Change over 5 months: HbA1c (%): • Decreased in both arms with non-inferiority between groups: MD -0.23 (-0.54 to 0.08) • More patients reached HbA1c <7.0%: 40.8 vs. 29.1 %, RR: 1.79 (0.87 to 3.65) and <6.5%: 25 vs. 19 %; RR: 1.52 (0.67 to 3.46) • More patients reached target HbA1c levels without severe or minor hypoglycemic episodes: <7.0%: 38 vs. 27.8 %, RR: 1.52 (0.61 to 3.79), <6.5%: 18 vs. 14.8 %; RR 1.13 (0.36 to 3.52) FPG (mmol/l): • Decreased in both arms with no difference between groups: 0.95±0.28

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		the previous 12 month, impaired kidney or hepatic function, proliferative retinopathy or maculopathy requiring treatment	Macroangiopathy (%): 5.2	necessary Duration: 20 weeks		vs. 0.67±0.28; MD: -0.28 (-1.07 to 0.52) Costs • Less frequent clinic visits to healthcare professionals in IG: 4.8±0.65 vs. 7.5±1.42 visits/patient Complications: • hypoglycemic episodes: no difference: 608.4 vs. 789.2 / 100 patient-years of exposure; RR: 0.74 (0.44; 1.23) treatment-emergent AEs: no difference: 324.2 vs. 302.2 events / 100 patient-years of exposure
Debussche 2018 NCT01485913 RCT	Mali, urban, secondary care, 07/2011-02/2013	DM2, age 30-80 yrs, HbA1c ≥ 8 %, no DM1, severe diabetes complications or concomitant illnesses that threatened their functional or vital prognosis	n=151 76.2% female age (yrs): 52.5±9.8 BMI (kg/m²):28.6±5.4	IG (n=76): peer-led structured patient education received culturally tailored structured patient education (3 courses of 4 sessions) delivered in the community by five trained peer educators vs. CG (n=75): conventional care alone Duration:1 yr	Primary: HbA1c Secondary: anthropometric indicators (weight and BMI, waist circumference), SBP, DBP, anti-diabetic and anti-hypertensive treatment, knowledge score, dietary practices	Change to 12 months HbA1c (%): • Benefit in IG: MD 1.05 % (-1.54;-0.56) vs. -0.15 % (-0.56; 0.26) (p = 0.006)
Essien 2017 PACTR201302 00047835 RCT	Nigeria, urban, tertiary care, 09/2013-05/2014	DM1 or DM2, age: ≥ 18 yrs, HbA1c> 8.5 %, able to engage in moderate exercise, no eye disease that would limit the ability to read	n=118 60.2 % female age (yrs): 52.7±10.5 BMI (kg/m²): 28.9±7.5 HbA1c (%):10.7±1.6 type of diabetes • DM1: 14.4 % • DM2: 85.6 %	IG: (n=59): intensive and systematic disease self-management education programme (invitation and encouragement by clinical staff to attend 12 structured teaching sessions) vs.	Primary: HbA1c	After 6 months: HbA1c (%): 8.4 (8 to 8.9) vs. 10.2 (9.8 to 10.7); MD_a: -1.8 (-2.4 to -1.2); (p < 0.0001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				CG (n=59): conventional disease-self-management education Duration: 6 months		
Fairall 2016 ISRCTN20283604 Cluster-RCT	South Africa, urban/rural, primary care, 03/2011 – 11 / 2011	age ≥ 18 yrs , clinics providing service for NCD Patients with DM, hypertension, chronic respiratory disease or depression, with self-reported hypoglycaemic (in case of DM)	n= 38 public sector primary care clinics, 4393 patients, n=1842 with DM 73 % female age (yrs):median, IQR): 52 (42-61) vs. 52 (44-62) BMI (kg/m²): 30±8 HbA1c (%):9 (4-17), in HbA1c in DM≥ 7 %: 77 %	IG (n=2166, 851 with DM): Nurses were trained to use a primary care programme to support and expand nurses`role in NCD care and contains a clinical management tool with enhances prescribing provisions vs. CG (n=2227, 991 with DM): Nurses continued to use the Lung Health and HIV/AIDS approach with usual training Duration: 14 months	Primary (for DM): treatment intensification (addition or increase in dose of metformin and/or sulphonylurea, insulin, ACE-inhibitor, aspirin, statin	over 14 months HbA1c (%): • <7 %: 41 vs. 38 %; RR 1.08 (0.77 to 1.52; p=0.638) • 7-10 %: 69 vs. 55 %; RR 1.30 (1.16 to 1.47; p<0.001) • >10 %: 71 vs. 73 %; RR 0.97 (0.81 to 1.16; p=0.703) Treatment intensification rates* (%): • 57% vs. 50%, RRa: 1.11 (0.99 to 1.26) (p=0.083) for patients with DM
Hailu 2018 NCT03185689 RCT	Ethiopia, urban, 02/2016-10/2017	DM2, age > 18 yrs no DM1 or GDM, pregnant women, severe cognitive or physical impairment, and terminally ill people	n=220 33 % female age (yrs): 54.5±10 BMI (kg/m²):25±4 HbA1c (%):10.5±4	IG (n= 116): Nurse-led disease-management education: 6 sessions, supported with illustrative pictures handbooks and fliers, customized to local conditions by trained nurses vs. CG (n=104): usual follow-up care Duration: 9 months	Primary: patients with target HbA1c (≤ 7 %) Secondary: systolic and diastolic blood pressure, fasting glycose, BMI, waist circumference	Change over 9 months: HbA1c (%): • No difference: 45 % vs. 50 % with target values (p=0.21), MD: 2.88% (-3.85 to -1.92) vs. 2.57% (-3.47 to -1.67) fasting glucose (mg/dl): • Benefit with IG: 36 % vs.25 % with target values, MD: -27 (-45 to -9; p=0.003)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Labhardt 2011 NCT00744458 Cluster-RCT	Cameroon rural, primary care, 08/2008-02/2010	newly detected adult patients with DM2 and /or hypertension in the catchment area of nurse-led health centres, staffed, equipped and trained to care for DM2 and hypertension	n=33 facilities, 221 patients 64% females age (yrs): 59.8±12.7 diabetes: 15.4 % Overweight (BMI 25-29.9 kg/m^2): 28.5 % Obesity (BMI> 30 kg/m^2): 20.4 %	IG 1 (11 centres, n=55): incentive group free treatment for 1 months for patients who regularly attended follow up visits vs. IG 2 (11 centres, n=77): letter group: reminder letters in case of a missed follow-up visit vs. CG (11 centres, n=89): no additional intervention Duration: 12 months	Primary: Patient retention at 1 yr (≥ 12 follow-up visits within 12 months) Secondary: Adherence with timely attendance of follow-up visit schemes and changes in blood pressure and blood glucose levels.	After 12 months: Retention rates (%): • Benefit for IG1 and IG2 vs.CG: 60 vs. 65 vs. 29 %; MD 34 (21 to 46) with no differences between IG1 and IG2; MD -5 (-22 to 12) Loss to follow-up: • Benefit for IG1 and IG2: IG1 vs. CG: HR 0.44 (0.27 to 0.72; p< 0.001) • IG2 vs. CG: HR 0.38 (0.24 to 0.61; p<0.001) Adherence (%): • Benefit for IG1 and IG2: 38 vs. 35 vs. 10; MD 26 (14 to 42), IG1 vs CG: MD 28(13 to 37); IG2 vs. CG: MD 25 (13 to 37) • no difference between IG1 and IG2: MD 3 (-14 to 20) FPG: No differences between groups
Mash 2014 Cluster RCT	South Africa, urban, primary care, 12/2010 -12/2012	DM2 with any therapy attending community health centres in the working class areas of Cape Town Metropole no DM1, dementia, mental illness or acute illness	n=34 public sector community health centres, 1570 patients 73.8% females age (yrs): 56.1±11.6 HbA1c (%): 9.1±2.3	IG (17 health centres, n=710): 4 monthly sessions lasting 60 min with group education about diabetes topics (understanding diabetes and medication, living a healthy lifestyle and preventing complications), delivered by a health promotion officer vs. CG (17 health centres, n=860): usual care: ad hoc advice during consultations and	Primary: improvement of diabetes self-care activities (5 % weight loss, and a 1 % reduction in HbA1c level) Secondary: improved diabetes specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol levels, quality of life	After 12 months: HbA1c (%): No differences: 8.4±2.0 vs. 8.8±2.2; MD_a: 0.01 (-0.27 to 0.28; p=0.967) Adherence (self-care activities): No differences in scores of physical activity, use of diet plan or medication, foot care or frequency of smoking Quality of life: No differences in physical functioning, role or social functioning, mental or general health and pain Costs: Incremental cost effectiveness ratio: 1862 Dollar/ QALY gained

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				occasional educational talks in waiting room Duration: 12 months		
Muchiri 2015 RCT	South Africa, rural, primary care, 04/2010-11/2011	DM2, age 40-70 yrs attending community health centres, HbA1c≥ 8 %, blood sugar levels ≥ 10 mmol/l, duration of diabetes ≥ 1 yr no insulin therapy, pregnant women, full time employed	n=82 86.6 % female age (yrs): 59±7.4 BMI(kg/m²): 30.9±6.9 HbA1c (%): 11.1±2.0 duration of diabetes (yrs): 6	IG (n=41): education materials+ 8 weekly group educational sessions about diabetes and nutrition, follow-up sessions+vegetable gardening CG (n=41): education materials Duration: 12 months	Primary: HbA1c Secondary: Other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c, dietary behaviours	over 12 months HbA1c (%): • no difference: 9.8±1.92 vs. 10.4±1.92; MD −0.63 (-0.26 to 1.50; p=0.16)
Owolabi 2019 PACTR201810599931422 RCT	South Africa urban/rural, primary care 07/2018-04/2019	DM, age ≥18 yrs, DM diagnosed at least in the last 6 months, currently receiving treatment at the selected clinics, on stable medication for ≥ 3 months prior to recruitment, uncontrolled glycaemic control, in possession of a mobile phone, able to retrieve and read SMSs and willing to receive SMSs health or mental conditions that could interfere with the study, pregnant or planning to get pregnant within the next 6 months, debilitated or handicapped in such a way that obtaining anthropometric measurements could be	n=216 84.3 % females age (yrs): 60.6±11.6 DM2 (%): 94 Treated with oral pills (%): 75.5 Duration of DM (yrs): 9.1±7.4 Duration of DM treatment (yrs): 8.8±7.2 Hypertension (%): 83.0 Random blood glucose (mmol/L): 14.34±3.9 BMI(kg/m²): 32.2±6.2	IG (n=108): daily SMS text-messaging SMS at an agreed time of the day, according to their needs, care plan and goal with motivational and support messages, advice on lifestyle behaviours (e.g. diets, physical activity, smoking cessation, medication and appointment reminders) vs. CG (n=108): usual diabetes care Duration: 6 months	Primary: Morning random blood sugar Secondary: co-morbid outcomes (hypertension and obesity), obtained through blood pressure measurement, anthropometric measurements (body weight, BMI) acceptability, feasibility	Over 6 months: Blood glucose levels (mmol/L): -1.58±5.29 vs. -1.95±4.69; MD 0.51(-0.8 to 1.82), MD_a 0.26 (-0.81 to 1.32)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		challenging				
Sodipo 2017 RCT	Nigeria, primary care, 03/2013-11/2013	DM2 ≥ 18 yrs. on antidiabetic medication no patients with emergencies, chronic complications such as nephropathy, neuropathy etc., those already using glucometer	n=120 gender: 50% female age (yrs): 59±10.95 HbA1c (%): 8.7±2.45 fasting glucose (mg/dl): 152±60.9 duration of diabetes (yrs): 50%> 3yrs	IG (n=60): Self-monitoring of blood glucose before and after meals 3 days a week for 12 weeks CG (n=60); non SMBG Duration: 12 wks	HbA1C, fasting glucose	after 3 months: HbA1c (%): No difference: 7.2±2.0 vs.7.7±2.0 (p= 0.174) fasting glucose (mg/dl): No difference: 123.2±35.1 vs. 137.6±50.1 (p=0.087)
Steyn 2013 Cluster-RCT	South Africa, urban, primary care, 1999-2000	public sector primary health care clinics (CHC) with ≥ 25 diabetes and ≥ hypertension patients age ≥15yrs, a documented attendee at the particular CHC with ≥ 4 visits during the previous year for hypertension or diabetes who received treatment for these conditions at each visit no patients being unable to answer a questionnaire	18 community health centres n=1096, of them n= 456 with DM age (yrs): 58.3 ± 11 gender:74 % females BMI (kg/m$^{2)}$: 30.7 ± 6.2 Type of Diabetes: • DM1: 5.8% • DM2: 91.35% uncertain DM type: 2.85%	IG (9 clinics, n=229): introduction of structured clinical record with guidelines prompts after training of doctors in their use and suggestions to incorporate them in regular patient records, contact over 1 year vs. CG (9 clinics, n= 227): usual care with passively disseminated guidelines Duration: 1 year	primary: HbA1C in the diabetes group secondary: uncontrolled glycaemia (HbA1c ≥7%) in the diabetes group.	After 3 months: HbA1c (%): IG: 8.8% vs. 8.8%; MDa -1.0 (-1.1 to -0.9) HbA1c ≥7% (%): no relevant difference: 64.1 vs. 62.6; MD 0.90 (0.53 to 1.53)
Takenga 2014 RCT	Congo, urban	DM2, 35-75 yrs	n=40 20 % females age (yrs): 53.3 ± 10.1 HbA1c (%): 8.63	IG (n=20): self-management of diabetes with Mobil DIAB (telemedical approach) vs. CG (n=20): conventional therapy without telemedical system	primary: HbA1c	after 2 months: HbA1c (%): Benefit for IG: 6.73±1.59 vs. vs. 8.6±1.35 (MD -1.87 (-2.91 to -0.83)

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				Duration: 60 days		
Tawfik 2016 RCT	Egypt, urban, primary care, 05/2015-09/2015	DM2 for ≥ 1 yr, 40-79 yrs attending an outpatient clinic no patients who were already using a similar medication chart, severe or terminal health conditions, or patients with behavioural health issue that could make it difficult to understand the communication	n=255 53.7 % females age (yrs): 55.7±8.35 HbA1c (%): 8.14±1.3 duration of diabetes (yrs): 8.3±1.3	IG (n=127): comprehensive cardiovascular risk communication vs. CG (n=128): standard usual care Duration: 3 months	Primary: HbA1c Secondary: Cardiovascular risk perception, diabetes self-care, cardiovascular risk scores	After 3 months: HbA1c (%): Benefit for IG: 7.5±0.8 vs. 8.12±0.9; MD -0.62 (-0.85 to -0.39) controlled HbA1c (%): 32.7 vs. 29.9
Thuita 2020 PACTR201910518676391 RCT	Kenya Secondary care recruitment 08/2016 - 10/2016	DM2, 20-79 yrs with regular attendance of an outpatient clinic Pregnancy, complications such as renal failure, congestive heart failure, or stroke	n=153 59.5 % females age (yrs). 56±11.6 Family history of DM (%): 46.6 Poor glycaemic control (%) with HbA1c>7%: 77.8 DM for 1-5 yrs (%): 58.2 % Years with DM: 6.7±6.9 Oral medications (%): 82.4 BMP (kg/m2): 27±4.6 HbA1c (%): 8.49±1.9 fasting glucose (mmol/l): 11.0±3.3	IG2 (n=51): nutrition education programme for 2 hrs /week with peer-to-peer support vs. IG1 (n=51): Education programme vs. CG (n=51): Standard care Duration: 8 weeks	Primary: metabolic syndrome prevalence (MetS) Other: anthropometry and clinical data, blood pressure, blood glucose and lipid profile, physical activity levels, food intake	After 6 months: Metabolic syndrome prevalence: lower with IG2: Harmonized criteria:52.1 vs.69.4 vs. 91.3 (p<0.001) WHO: 58.3 vs. 77.6 vs. 89.1 (p=0.003) HbA1c (%): Mean change: no differences -2.04±2.70 vs. 1.48±2.73 vs. -0.73±2.71 High HbA1c: no differences: 47.9 vs. 29.0 vs. 34.8 % fasting glucose (mmol/l): no differences: -2.59±0.66 vs. -2.95±0.64 vs. -1.55±0.68 high fasting glucose: 79.2 vs. 83.7 vs. 91.3 %

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Webb 2015 NCT01275040 Cluster RCT	South Africa, urban, primary care, 06/2010-03/2011	primary health care clinics, patients with clinical diagnosis of DM2 or DM1 for ≥5yrs, age ≥ 18 yrs	n= 12 primary health care clinics n= 599 gender:68.5 % female age (yrs): 57.8±10.5 HbA1c (%): 8.73±2.3 HbA1c ≥ 7 %: 73 % BMI (kg/m$^{2)}$: 30.8±6.7 Typ of diabetes: • DM1: 3.7 %, • DM2: 70.3 % • unknown: 26 % duration of Diabetes: • < 5 yrs: 47.3 % • 5-10 yrs: 22.0 % • > 10 yrs: 20.2 % • unknown: 10.5 %	IG (n=328): mobile screening team visits primary care clinic and provides education and active screening for diabetic complications (foot, kidney, cardiac and renal complications) vs. CG(n=273): no mobile screening team, routine care with similar education for patients. and health care workers Duration: 1 yr	Primary: HbA1c, detected neuropathy, nephropathy and retinopathy, HbA1c categories Secondary: detected complications, referred patients for complication assessment or care, blood pressure and lipid control, costs, LDL cholesterol, creatinine	after 12 months HbA1c (%): no difference: 8.54±2.11 vs. 8,76 ±2.2, MD-0.22 (-0.64, 0.20) screening rate for complications: in IG 60% increase of screening in all complication indicator groups, in both groups testing of HbA1c and renal complications (serum-creatinine) increased , but no significant difference , screening for eye complications, only increased significantly in IG no significant difference in the proportion of actions taken beween IG and CG (p=0.83)
Strategies to enhance physical activity						
Asuako 2017 RCT	Ghana, urban, tertiary care, 08/2015-03/2016	DM, age: 20-68 yrs, ambulant patients, without diabetes complications with < 150 minutes /wk of moderate physical activity no SBP > 140 or DBP> 90 mmHg, bilateral or unilateral lower or upper limbs amputation, use of insulin pump	n=12 83% female age (yrs): 83% were 46-55 yrs. BMI (kg/m²):25.4±4.5 fasting glucose (mmol/l):9.33 ± 5.7 type of diabetes: DM1: 17 % DM2: 83 % duration of diabetes (yrs): • 1-5 yrs: 25 % • 6-10 yrs: 50 % • 10 yrs: 25 %	IG (n=7): walking aerobic exercise sessions without treadmills (3/week) vs. CG (n=5): only activity of daily living Both continued regular medical/clinical routines Duration: 8 weeks	FPG, Lipid profile, body weight, BMI	Change over 2 months: FPG (mmol/l): Benefit for IG: 6.27 ± 0.91 vs. 8.00 ± 0.96; MD 1.73 (-1.88 to -1.59; p<0.001)

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Fayehun 2018	Nigeria, urban 06/2014-11/2014	DM2, age 18-64 yrs, Diagnosed ≥ 12 months, non-insulin dependent, on dietary control ± hypoglycemic agents, able to walk without limitations no pregnant women, smokers, prescription of medications that might impair ability to walk	n= 46 63 % female age (yrs): 54±7.7 (33-64) BMI (kg/m²): 22.4±3.3 HbA1c (%): 6.6 (5.3-9.0) duration of diabetes (yrs):<7 yrs: 70 %, >7 yrs 30 %	IG (n=23): Goal to accumulate 10000 steps per day vs. CG (n=23): normal activity habits Duration: 10 weeks	Primary: HbA1c Secondary: step count	Change over 2.5 months: HbA1c (%): Benefit for IG: 6.26 (6.19 to 6.33) vs. 6.82 (6.69 to 6.95); MD_a: -0.74 (-1.32 to -0.02; p=0.015)
Maharaj 2016 RCT	Nigeria, rural 07/2013-06/2014	DM2, non- insulin dependent, blood glucose levels 6 - 13 mmol/l no cardiac, abdominal or spinal surgery ≤ 6 months, history of fractures of lower limbs, spine, weakness, deformities, loss of sensation in the feet, retinopathy, nephropathy	n=90 52 % females age (yrs): 39.4 ± 8.6 (30-58) BMI (kg/m²): 27.7±5.8 HbA1c (%): 8.79±2.11 duration of diabetes (yrs): 2.5±2.1	IG (n=45): rebound exercise 3 times/week for 20-30 min, moderate intensity of 40-60 % of HR maximum vs. CG (n=45): watched videos and read health magazines Duration: 9 weeks	Primary: HbA1c , FPG, BMI Other: Heart and respiratory rates, blood pressure, oxygen saturation	After 9 weeks HbA1c (%): Benefit for IG: 7.12±1.19 vs. 8.36±1.25; MD_a: 0.904 (0.832 to 0.984; p=0.017) FPG (mmol/l): Benefit for IG: 6.92±1.21 vs. 8.73±1.23; MD_a: 0.787 (0.7345- 0.841; p=0.002)
van Rooijen 2004 RCT	South Africa, urban 03/2002-11/2002	black women with DM2, age 40-65yrs, duration of DM ≥12 months no chest pain on effort, possible previous myocardial infarction and intermittent claudication, cerebro-vascular incidents, arthritis, retinopathy	n=158 gender:100 % females age (yrs): 54-55 HbA1c (%): 9.35	IG (n=80): education+ incremental daily home exercise, use of daily physical activity records+6 fortnightly supervised aerobic exercise classes vs. CG(n=77): education+ relaxation exercise Duration: 12wks	Primary: HbA1c, BMI Secondary: walking distance (6 min walk)	Change over 3 months: HbA1c (%): no difference: 8.99±2.59 vs. 8.26±1.97
Yan 2014	Mozambique,	DM2, male, age 40-70 yrs, diagnosis for ≥ 12 months	n=41 100% male	IG (n=31): low or vigorous intensity	plasma glucose, HbA1c	Change over 3 months: HbA1c (%):

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	urban	no known diseases other than DM2 and hypertension, no diagnosed cardiovascular diseases	age(yrs): 54±2.5 HbA1c: 8.6±0.7 plasma glucose (mmol/l): 9.65±1.2 BMI ($kg/m^{2)}$: 27.1 ± 1.0	exercise 3-5 times/week vs. CG(n=10): walked 1 hour per day as part of their daily lifestyle Duration:12 wks		reduction in both groups with no differences between groups: 7.7±0.4 vs. 7.7±0.8 Plasma glucose (mmol/l): 9.6 ± 0.7 vs. 11.1 ± 1.3
Pharmacological strategies						
Distiller 2014 RCT	South Africa	DM2 for ≥ 1 year with total insulin requirement of >200 U/d for ≥ 3 months, BMI > 30 kg/m^2, HbA1c> 7,5 %, on long-term metformin therapy (1.7–2.5 g/d) no pregnant or with childbearing potential, endocrinopathy, chronic inflammatory or systematic autoimmune disorder, CVD, active carcinoma, chronic illness, renal dysfunction, gastroparesis, no corticosteroids, DPP-4 inhibitors, exenatide, liraglutide, no anticipated change in other concomitant medication or insulin resistence	n=28 50% female age (yrs): 51.7 (36-71) HbA1c (%): 8.95 (7.6-11.3) BMI (kg/m^2): 40.8 (31.2-47)	IG (n=14): regular Insulin (500 U/ml) + metformin + exenatide (5 µg orally twice a day for 1 month and titrated to 10 µg) vs. CG (n=14): regular Insulin (500 U/ml) +metformin Duration: 6 months	Primary: HbA1c Secondary: Body weight, insulin dose, hypoglycemia	Change to 6 months: HbA1c (%): Significant improvement in both groups 8.7→7.7(p=0.002) vs. 9.2→7.5 (p=0.0001) With no difference between groups (MD: 0.28; p=0.80) Complications: Mild hypoglycaemia: 5 vs. 2 persons with 20 vs. 5 events (p ≤ 0.001)
El-Haggar 2015 RCT	Egypt, urban 01/2013-04/2014	DM2, age: 45-55 yrs, obese (BMI≥30 kg/m^2), with duration 5-10 yrs, treated with glimepiride alone no Inflammatory disease,	n=48 79 % female age (yrs): 50.1±4.6 HbA1c (%): 7.83±0.87 fasting glucose (mg/dl): 193±50	IG1 (n=16): glimepiride (3 mg/d) + 2 (1 mg twice/d) vs. IG2 (n=16): glimepiride (3 mg/d) +	not specified: glycemic markers, metabolic markers, adiponectin, interleukin-6, leukotriene B4, mast cell tryptase, lipid panel,	Changes over 12 weeks: HbA1c (%): • Highest benefit for IG1: 7.1±0.86 vs. 8.2±0.82 vs. 8.7±0.93 (p< 0.05) fasting glucose (mg/dl): • Highest benefit for IG1: 199±38 vs.

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		severe hepatic or renal disease, epilepsy pregnant/lactating females	BMI (kg/m²): 37.6±4.6 duration of diabetes (yrs): 7.7 ±2.6	ketotifen (1 mg once/d) vs. CG (n=16): glimepiride (3 mg/d) alone Duration: 12 weeks	BMI	207.7± 47.6 (p< 0.05)
Malek 2015 RCT	Egypt, Algeria, Tunesia, South Africa 03/2010-05/2012	DM2, age ≥ 18 yrs, currently treated with suboptimal dose of oral anti-diabetic drugs; HbA1c 7-11 % (under metformin-monotherapy) and ≤ 10 % (under combination therapy), BMI≤40 kg/m^2 no allergies or contraindications to the product, pregnant or breastfeeding, impaired hepatic or renal function, cardiovascular history, uncontrolled hypertension, proliferative retinopathy, macular oedema	n=403 age (yrs): 52.8±9.6 59.8 % female HbA1c (%): 8.65 BMI (kg/m^2): 29.7±4.5 duration of diabetes (yrs): 7.5±5.1	Stepwise individual insulin intensification of IG (n=200): basal-bolus insulin analogues (insulin detemir +Insulin aspart) vs. CG (n=203): thrice daily biphasic insulin aspart depending on HbA1c-values over 50 wks	Primary: HbA1c Secondary: patients achieving HbA1c < 7.0 %, prandial plasma glucose	Change over 50 weeks: HbA1c (%): Non-inferiority: 7.4 vs. 7.3; MD 0.1 (-0.1 to 0.3 (full-analysis set), MD 0.2 (-0.1 to 0.4 (per protocol) 40.3% and 44.9% achieved HbA1c<7.0% Hypoglycaemia (events/patient year): 9.4 vs. 9.8 Serious adverse events: 6.5 vs. 3.4 % with 1 treatment-related SAE in CG Adverse events: 58.5 vs. 63.1%
Strategies on food supplementation						

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Ali 2019 RCT	Egypt Urban, tertiary care 09/2017 – 04/2018	DM2, oral antidiabetic agents with no change of type and dosage of antidiabetic agents in the past 3 months, ≥ 30 years insulin-dependence, pregnancy, lactation, use of Ca, multivitamins, Vitamin D supplements, use of drugs that affect Vitamin D status, dietary Ca intake > 1500 mg/d, hypo- or hyperthyroidism, smoking, use of antiepileptic drugs, sarcoidosis, tuberculosis, potentially terminal illness, inflammatory bowel disease, liver or kidney disease, malignancy	n=85 age (yrs): 54.6 ±2.8 68 % females BMI (kg/m²): 28.6±3.3 Diabetic duration (yrs): 4.4±2.1 fasting glucose (mg(dL): 168±54.4 fasting serum insulin (µIU/mL): 18.1±8.3 HbA1c(%):8.8±1.8	oral antidiabetic agents as usual + IG 1 (n=22): continuous oral Vitamin D3 (4000 IU/ d) vs. IG 2 (n=22): intermittent regimen of Vitamin D3 (50 000 IU/ week) vs. IG 3 (n=21): single IM injection of 300 000 IU of Vitamin D3 at the start of the study vs. CG (n=20): only oral antidiabetic agents Duration: 3 months	Not specified: serum creatinine, blood urea nitrogen, total and ionized Ca, serum phosphorus, fasting glucose, fasting serum insulin, 25(OH)D3 levels, HbA1c	After 3 months: fasting glucose (mg(dL): higher decrease in IG1 and IG2: -20.9±18.1 vs. -23.0±37.9 vs. -3.5±6.9 vs. 1.0±5.6 (p<0.001) fasting serum insulin (µIU/mL): higher decrease in IG1 and IG2: -4.44±5.2 vs.-5.88±4.6 vs. -1.55±9.4 vs. 0.10±1.0 (p< 0.001) HbA1c (%):higher decrease in IG1 and IG2: -0.81±0.77 vs. -0.82±0.87 vs. -0.34±1.47 vs. 0.05±0.08 (p<0.001)
Anderson 2001 RCT	Tunesia, urban	DM2 ≥ 5y, age< 65 yrs, fasting glucose > 8 mmol/l and HbA1C > 7.5 % no pregnant or lactating women, receiving trace element supplements in past 3 months, with gastric or diuretic treatment, acute renal, acute infection or recent surgery	n=110 age (yrs): 53.2 ±16.8 BMI (kg/m²): 29.1±1.0 HbA1c (%):8.82±3.25 fasting glucose (mmol/l): 11.45±0. 83 duration of diabetes (months): 73.6±66	IG 1 (n=27): Zinc (30 mg/d) vs. IG 2 (n=27): Chromium (400 µg/d) vs. IG 3 (n=27): Zinc (30 mg /d) + Chromium (400 µg /d) vs. CG (n=29): placebo Duration: 6 months	Not specified: HbA1C, fasting glucose plasma concentrations of zinc, copper, selenium, urinary chromium and zinc, Plasma thiobarbituric acid reactive substances, copper-zinc-superoxid dismutase, selenium - glutathione peroxidase	Change over 6 months: HbA1c (%): 7.7±1.6 vs. 7.4±1.4 vs. 8.1±1.6 CG: not reported
Anyanwu 2016	Nigeria, urban	DM2, age 35-65 yrs on oral antidiabetics with vitamin D	n=42 57.6 % female	IG (n=21): Vitamin D3 supplements	Primary: HbA1c Other: fasting glucose,	Changes over 12 wks: HbA1c (%):

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT .		deficiency and poor glycemic control (HbA1c > 6.5 %) no patients on insulin, pregnancy, renal insufficiency, chronic liver disease or alanine transferase > 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state	age (yrs): 51.8±2.05 HbA1c (%): 7.88 fasting glucose (mg/dl): 152.8±56.5	(3000 IU/d) vs. CG(n=21): placebo Duration: 12 weeks	levels of serum Vitamin D, calcium, albumin, phosphate, creatinine, and alanine transaminase	• MD (IG vs. CG): -0.66 (-0.161 to 0.29) vs 0.38 (-0.08 to 0.84); • MD: -1.04 (-2.09 to 0.01) • change from poor glycemic control (HbA1c>6.5 %) to normal HbA1c (%): benefit for IF: 33.3 vs. -9.1 (p<0.05) fasting glucose (mg/dl): 137.2±33.6 vs. 154±67.5 patient adherence (tablet counts, %): 62.2 vs. 59.9
El Gayar 2019 **RCT**	Egypt, urban, outpatients 01/2017-01/2018	DM2 for < 6 months, 30-60 yrs, HbA1c level < 9%, BMI≥30 kg/m^2 no insulin therapy, any injectable or oral antidiabetic medication other than metformin, no smoking, consumption of alcohol or narcotic drugs, no acute illnesses at the baseline or during the study, no pregnancy or lactation, autoimmune disorder, cardiac or renal diseases, thyroid, chronic inflammatory diseases, peptic ulcer, regular consumption of ginger or other herbal drugs, hypersensitivity to ginger, consumption of lipid lowering drugs or oral contraceptive pills or any supplements 2 months before starting the study	n=80 49 % female age (yrs): 46.2 ± 9.1 HbA1c (%): 8.04±0.5 fasting glucose (mg/dl): 176.9±18.3 Fasting serum insulin (mIU/L): 19.3±3.3 BMI (kg/m²): 32.3±1.4	diet, physical activity, and metformin IG (n=40): ginger powder supplementation (600 mg/capsule, 3 capsules/d) vs. CG (n=40): Placebo Duration: 8 weeks	Not specified: glycemic status, lipid profile and beta-cell function	After 8 wks: HbA1c (%): decrease in both groups to 6.94±0.38 vs. 7.26±0.45 Fasting serum insulin (mIU/L): decrease in both groups to 12.86±2.59 vs. 13.21±2.08 fasting glucose (mg/dl): decrease in both groups to 120.88±9.06 vs. 151.70±13.23

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Sheikh 2019 RCT	Egypt, urban	DM2 on glimepiride alone, age ≥30 yrs no insulin sensitizers, steroids, NSAIDs, warfarin or lipid lowering medications, thyroid hormones, valproic acid or suffered from: acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism epilepsy, pregnant and breast-feeding women	n= 72 67 % female age (yrs): 50.6±8.7 HbA1c (%):9.76±1 fasting glucose (mg/dl):194.84±20.8 BMI (kg/m²): 34.4±5.45	IG (n=38): glimepiride 2 mg twice daily + L-carnitine 1 gm twice daily vs. CG (n=34): glimepiride dose 2 mg twice daily Duration: 6 months	HbA1c, fasting glucose, PPBG, fasting insulin, extracellular part of insulin regulated aminopeptidase, tumor necrosis factor-alpha, visfatin and lipid panel, BMI and homeostasis model assessment of insulin resistance	Change over 6 months: HbA1c (%): Benefit for IG: 7.41±0.5 vs. 9.5±0.78 (p<0.001) fasting glucose (mg/dl): Benefit for IG: 179.6±9.3 vs. 192.41±27.4 (p=0.018)
Matter 2020 NCT03851055 RCT	Egypt, urban, outpatients 08/2017 to 08/2018	DM, treated with insulin, 10 to 18 yrs, transfusion dependent beta-thalassemia major no other hemoglobinopathies (e.g. a-thalassemia or sickle thalassemia, disorders that may affect glucose homeostasis other than b-TM, autoimmune diseases, collagen diseases, hypo- or hyperthyroidism, infections, or tumours, or those who were taking any vitamins or food supplements < 1 month before the study and participating in a previous investigational drug study within 3 mo preceding screening	n=80 52.5% females age (yrs): 16.3±1.4 (range 12-18) fasting glucose (mg/dL): 144.5±22.4	diet schedule with optimal macronutrient distribution and pharmacologic treatment IG (n=40): zinc gluconate (2x20 mg/d) vs. CG (n=40): placebo Duration: 3 months	Primary: fasting glucose Secondary: fructosamine, fasting C-peptide, and HOMA-IR safety: any AEs (e.g. nausea, vomiting, abdominal pain, diarrhea, constipation, and reduction of appetite)	After 12 wks: fasting glucose (mg/dL): higher decrease with IG to 116.9±4.6 vs. 144.5±22.9 (p<0.001) HbA1c (%): higher in IG (no results reported) no side effects were reported
Moustafa	Egypt,	DM2, newly diagnosed	n=62	IG (n=29, 21 analysed):	Glycemic control,	After 3 months:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
2019 RCT	urban, outpatients recruitment 02/2016-03/2018	(within a time duration ≤6 months), 18–60 yrs other antidiabetic medications, pregnant and lactating women, major organ dysfunction (hepatic failure, active hepatitis, liver cirrhosis or renal complications), changed their standard medications during the 12 weeks of the study	72% females HbA1c(%): 7.51±1.4 fasting glucose (mg/dl): 154.4±51.6 BMI(kg/m^2): 33.9±6.1 family history of DM (%): 78.5 retinopathy/altered vision (%): 53 GDM (%): 9.2	nigella sativa oil capsules (3x 450 mg/d) vs. CG (n=33, 23 analysed): metformin (2000 mg/d) Duration: 3 months	oxidative stress markers, biochemical parameters, weight/BMI/waist circumference, total antioxidant capacity TAC	HbA1c (%): no difference: 7.01±0.83 vs. 6.55±0.72 fasting glucose (mg/dl): no difference: 119.8±23.7 vs. 120.7±25.4 Complications: no differences in occurrence of chills, sweating, tachycardia, lethargy/ weakness, polydipsia, polyuria, dry skin, polyphagia, blurred vision, foot problems, or tingling/numbness foot problems lower in IG: 4.8% vs. 33.3%, (p = 0.025).
Ragheb 2020 NCT03437902 RCT	Egypt, urban, outpatients care 02/2019-05/2018	DM2, receiving standard oral hypoglycemic agents, ≥ 35 yrs, no history of overt vascular disease, renal or hepatic failure or antioxidant supplementation or insulin therapy, no change of oral hypoglycemic drugs	n=70 age (yrs): 54.9±8.4 70 % females BMI (kg(m^2): 32.5±5.7 HbA1c(%): 8.50±1.86 fasting glucose (mg/dl): 142.8±52.6	IG2 (n=20): Rutin (60) + vitamin C (160 mg) 3x daily vs. IG1 (n=20): Vitamin C (500 mg) 1x daily vs. CG (n=13); only usual oral antidiabetic treatment Duration: 8 weeks	Primary: HbA1c, oxidative stress marker, antioxidant capacity, insulin resistance, lipid profile Secondary: Quality of life	After 2 months: HbA1c (%): no difference 7.494 ± 1.72 vs. 8.504 ± 2.059 vs. 8.504 ± 2.059 (p=0.1882) fasting glucose (mg/dl): lower in IG2 and CG: 111.3 (IQR 93.3-135.2) vs. 144 (114.8-201) vs. 113.3 (94-152.2) (p=0.017) Quality of life (SF 36): • Benefit of physical functioning and energy domains in IG2 vs. CG (p=0.0049, p=0.0253). • Benefit of role limitation to physical health and emotional improved in IG1 vs. CG (p=0.0267,p=0.0280) • no difference between groups in the other domains (emotional well-being, social functioning, pain and general health)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Rashad 2017 RCT	Egypt, urban	DM2, 50-62 yrs no insulin medication, allergies, recent thromboses or uncontrollable hypertension	n=34 43.3 % female age (yrs): 55.5±6.15 HbA1c (%):6.75±1.2 fasting glucose (mmol/l): 8.5±1.4 postprandial plasma glucose(mmol/l): 15.6±3.3 BMI (kg/m²):28.55±4 type of diabetes duration of diabetes (yrs): 6.1 ± 2.2	IG (n=17): Balanites aegyptiaca extract (400 mg)) vs. CG: (n=17) placebo capsules (potato maltodextrin) Duration: 8 wks	glycemic markers, lipid profile, FPG	Change over 8 wks: 2h postprandial plasma glucose: benefit for IG :26.88% decrease vs. CG 2.6% increase FPG (mmol/l): benefit for IG: 7.8 ± 0.9 vs. CG: 8.5 ± 1.1
Somanah 2012 NCT01248143 RCT	Mauritius, urban/rural 11/2010-03/2011	newly diagnosed DM, age 25–60 yrs fasting glucose range: 5.1–5.9 mmol/L no secondary complications, non-smoker or stopped for > 6 months , alcoholic consumption < 2 standard drinks/day, post-menopausal women without hormone replacement treatment, no glucose-lowering, cholesterol-lowering or anti-hypertension treatment	n=127 47% female age (yrs): range 25–60 HbA1c (%): 5.99±0.4 fasting glucose (mg/dL): 93.2±8.0 BMI (kg/m^2): 26.6 ± 3.7	IG (n=44): supplementation of a fermented papaya preparation (6g/d twice daily, over 12 wks), followed by a 2 week wash out period with the same amount of water vs. CG (n=56): consumed an equivalent amount of water Duration: 14wks	HbA1C fasting glucose, Lipid profile, diet score, blood pressure, alanine aminotransferase; aspartate aminotransferase, Ferritin, c-reactive protein, uric acid, microalbumin/urinary creatinine ratio	After 14 wks: HbA1c (%): no difference (p=0.448) fasting glucose (mg/dL): • remained relatively unchanged in boths genders: • males: 96.2±17.0 vs. 87.6±11.7 • females: 95.6±15.8 vs. 94.3±5.0
Strategies on treatment of DM related complications						

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Makaky 2020 NCT03783845 RCT	Egypt, urban/rural recruited 06/2015 to 03/2016	DM2 for >5 yrs, 40-70 yrs, HbA1c 7 to 9% at the last medical evaluation, no change in diabetes treatment over the previous 3 months, ≥ 6 permanent teeth excluding third molars, clinical attachment level and pocket depth ≥4 mm in >30 % of the sites, diagnosis of chronic periodontitis based on the presence of 4 teeth as a minimum with ≥ 1 site Pregnancy, alcoholism and smoking, Presence of any systemic disorders other than hypertension and diabetes, diabetic major complications, antimicrobial therapies or periodontal therapies in the last 6 months, allergy to metronidazole and amoxicillin	n=88 56.8 % females age (yrs): 52.6±6.8 HbA1c (%): 8.16±0.72	IG (n=44): immediate periodontal therapy: one-stage scaling and root planning, a combination of systemic antibiotics (amoxicillin 500 mg and metronidazole 400 mg 3x/day for 2 weeks), and oral hygiene instructions vs. CG(n=44): delayed periodontal therapy after 3 months Duration: 3 months	Primary: HbA1c Secondary: not named	After 3 months: HbA1c (%): benefit for IG: 7.27±0.5 vs. 8.34±0.64: MD -1.07 (-1.32 to -0.83)
El-Sharkawy 2016 NCT02794506 RCT	Egypt, urban 06/2014-03/2015.	DM2 >5 yrs, >20 teeth, chronic moderate or severe periodontitis with probing depth and clinical attachment level >5 mm, bleeding by probing, on oral hypogylcemic drug therapy > 6 months, no smoking, use of	n=50 34% female age (yrs): 50.5 ± 7.4 (38 to 63) HbA1c (%): 8.66 ±0.73 FPG (mg/dl): 183.5 ±12.547 BMI (kg/m²): 26.9± 3.1 duration of diabetes	IG (n=24): scaling and root planing (SRP)+ 400mg oral Propolis once daily vs. CG (n=26) scaling and root planing (SRP)+Placebo Duration: 6 months	Primary: HbA1c Secondary: FPG, serum N-(carboxymethyl) lysine, periodontal parameters	after 6 months HbA1c (%) Benefit for IG 7.75± 0.48 vs.8.5±0.73 (p<0.01) FPG(mg/dl) Benefit for IG

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		antibiotics, non-steroidal or anti-inflammatory drugs within the last 3 months, periodontal therapy ≤ 1 year, retinopathy grade 3/4, pregnancy, no contraceptive drugs	(yrs): 8.1 ± 3.9 hypertension: 4.5% neuropathy: 1.5% retinopathy: 0.5% nephropathy: 0%			
Ghoneim 2013 RCT	Egypt, 03/2010-03/2012	DM, duration ≥ 15 yrs, bilateral diabetic macular edema (≥ 6 months) no prior treatment with intravitreal corticosteroids, peribulbar steroid injection within ≤ 6 months, pars plana vitrectomy, history of glaucoma or steroid induced IOP elevation, ischemic maculopathy, foveal tracted, IOP≥ 23 mmHg	n=19 (38 eyes) 89.5 % female age (yrs): 52.3±11.4	IG (n=19): one eye with 8 mg triamcinolone acetonide vs. CG (n=19): other eye with4 mg of triamcinolone acetonide Duration: 6 months	Primary: Visual acuity Others: Intraocular pressure (IOP), IOP lowering drugs, complications	after 6 months: Complications: • no eyes with retinal detachment, vitreous haemorrhage, intraocular reaction or endophthalmitis. • one eye in IG developed posterior subcapsular cataract.
Nteleki 2015 RCT	South Africa, urban	DM2 with neuropathic or mixed (venous and arterial) ulcers; lower extremity ulcer; stable or worsening ulcer that has been present for ≥ 4 weeks no acute cellulitis, osteomyelitis, or gangrene, renal, hepatic, hematologic, neurologic, or immune disease not related to diabetes; presence of malignant disease not in remission for > 5 years; use of oral or parenteral	n=7 with 14 lower extremity ulcers 85 % male age (yrs): 62 duration of diabetes (yrs): 16.7	standard podiatric management and IG1 (n=2): phototherapy to the regional lymphatic nodes and ulcer(s) vs. IG2 (n=3): phototherapy on the ulcer vs. CG (n=2): placebo phototherapy Duration: 12 weeks	healing rate (area and perimeter of the ulcer)	after 3 months: Healing: • The rate of healing increased in all three groups, • 67% of ulcers received some form of phototherapeutic intervention, 40% of those ulcers resolved completely over 8 weeks no AEs

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		corticosteroids, immunosuppressive, or cytotoxic agents; known infection with human immunodeficiency virus or presence of AIDS; other leg ulcers				
Saeed 2013 RCT	Egypt, urban 11/2010-07/2012	DM, intractable diffuse diabetic macular edema without vitreomacular traction. central foveal thickness ≥300 µm no vitreomacular traction, active neovascularization of proliferative diabetic retinopathy, an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography, treatment for diabetic macular edema within ≤ 3 months, previous vitreoretinal surgery, other major ocular surgery within the previous 6 months, YAG capsulotomy within ≤2 months, macular pathology	n= 34 (34 eyes) 50% females age (yrs): 55.5 ± 8.9 duration of diabetes (yrs): 24±5.4	IG (n=15): vitrectomy with removal of the posterior hyaloid, at the end of the procedure injection of intravitreal triamcinolone acetonide (IVTA, 0.1 mL, 40 mg/mL) +bevacizumab (1.25 mg) +macular grid laser photocoagulation vs. CG (n=15); same intravitreal injection combination Duration: 12 months	primary: BCVA, central foveal thickness	Changes over 12 months Complications: • Changes in BCVA and central foveal thickness at 3, 6, and 12 *(P<* 0.01), better mean BCVA in IG at 12 months. • Better mean central foveal thickness in IG at 12 months. Major adverse events: development of cataracts (3/15 vs. 6/15) and elevation of intraocular pressure (7/15 vs. 2/15)
Tsobgny-Tsague 2018 NCT02745015 RCT	Cameroon, urban, tertiary care, 12/2014-	DM2, >11teeth, severe chronic periodontitis according to the 2012 CDC-AAP classification, no periodontal treatment,	n=34 56% female age (yrs): 51.4 ± 8.8 HbA1c (%):9.3 ± 1.3 BMI (kg/m²): 28.3± 5.4	IG (n=17): immediate ultrasonic scaling, scaling and root planning +subgingival 10% povidone iodine irrigation	Primary: change in HbA1c Secondary: Plaque index, gingival bleeding index, pocket depth, clinical attachment loss	Change over 3 months: HbA1c (%): Benefit with IG: 6.7 ± 2.0 % vs. 8.1 ± 2.6 %, MD: 2.2 (p=0.029) adverse events: 1 /15 patient reported tongue

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
	05/2015	alteration of DM treatment 6 mths prior to the study, onset of systemic diseases or an acute condition, use of immunosuppressive medications or others drugs or presence of conditions able to alter periodontitis clinical features	duration of diabetes (months): 55.5 ± 42.6 complications: neuropathy (%): 40 nephropathy (%): 7 retinopathy (%): 7 diabetic foot (%): 3	vs. CG(n=17): periodontal treatment 3 months later Duration: 3 months		irritation following chlorhexidine moth rinse in IG
Yakoot 2019 NCT01531517 07/2011-07/2013 RCT	Egypt, urban	Adult DM2 or DM1 patients, limb-threatening diabetic foot ulcerations no life-threatening extensive gangrenous lesions that needed immediate amputations; bad general condition; shock or unstable vital signs; critically ill with severe organ/system dysfunctions or advanced malignancy.	n=119 gender:44.5% female age (yrs): 54.7 ±8.4 type of diabetes: • DM1: 22.9% • DM2: 86.2%	conservative debridement of necrotic tissue and irrigation with warm normal saline and IG (n=61): local application of ointment composed of royal jelly and panthenol vs. CG (n=58): local application of Panthenol duration: 12months	primary: complete healing secondary: reduction of infection in the ulcer site, al reaction that may be due to study drug	after 12 months rate of complete healing (%): Benefit for IG: 32.4% vs. 12%; p=0.034

ADA: American Diabetes Association; BCVA: Best-corrected visual acuity; BMI: Body mass index; CG: Control group; CI: Confidence interval; CHC: Community health centre; DBP: Diastolic blood pressure; DM: diabetes mellitus; DM1: Type 1 diabetes; DM2: type 2 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG: intervention group; IQR: interquartile range; n: number of participants; NCD: Non-communicable disease; NPH: neutral protamine Hagedorn; MD: mean difference; MDa: adjusted mean difference; NCD: Non-communicable disease ;RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SAE: Serious adverse events; SBP: Systolic blood pressure; SCI: Diabetes Self-Care Inventory; SD: Standard-deviation; SMBG: self-monitoring of blood glucose; wks: weeks; yrs: years

Table 4: Characteristics and results of studies on patients with DM2

RCTs on pregnant DM patients

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value	**Study name** registration number Design
Strategies to increase physical activity						
Embaby 2016 RCT	Egypt, urban, 07/2014-02/2015	at increased risk for GDM due to obesity (BMI ≥ 30 kg/m^2), age:> 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2 no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease, cardiac, renal impairment and malignancy	n=40 100% female age (yrs): 29.2±3.8 BMI (kg/m²):28.7±1.3 fasting glucose (mmol/l): 6.5±0.9 fasting insulin (IU/l): 15.78±1.58	IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives. Duration: appr. 4 months	Fasting plasma glucose, Insulin level	Change to 37th week of gestation: FPG (mmol/l) Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001) Fasting insulin (IU/l): Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)
Other non-pharmacological therapies						
El-Shamy 2018 RCT	Egypt, urban 12/2016-05/2017	GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus no high-risk pregnancy, bad obstetric situations or diseases, smoking, oral sedatives	n=30 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): • fasting glucose: 129.05±0.6 • 2h postprandial: 146±1.65 BMI (kg/m²): 27±1.5	IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only Duration: 12 weeks	Primary: glycemic control, requirement for insulin, insulin resistance Secondary: neonatal outcomes	Change over 3 months: 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9 Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %

Utz 2018 NCT02979756 Cluster-RCT	Marocco, urban / rural, primary care, 11/2016-02/2018	Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM no DM2, DM1	20 health centres n= 215 age (yrs):27.6±6.6 urban (%): 38.5 rural (%): 61.5	20 clinics were randomized→ 10 in each group <u>IG (n=120):</u> first screening for GDM→positive tested women received counselling on nutrition and exercise <u>vs.</u> <u>CG (n=95):</u> routine practice	Primary: birthweight Secondary: maternal weight gain, glucose control, pregnancy complications.	Follow-up visits: 7.5±4.9 vs. 3.8±3.3 (p=0.001) FBG within the norm: better with IG <1/3 of all values: 7.6 vs. 32.6 % 1/3-2/3 of all values: 17.8 vs. 32.6 % >2/3 of all values: 74.6 vs. 34.8 % Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)
Pharmacological strategies						
Ashoush 2016 RCT	Egypt, urban, tertiary care 01/2014-11/2014	GDM, mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glycemic control despite adequate diet and exercise for ≥ 1 wk no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis	n=95 100% female age (yrs): 31.8±3 HbA1c (%): 5.75 ± 0.55 75g OGTT (mg/dl) • fasting: 106.05±4.6 • 1h:310.25±11.6 • 2h:176.65±9.4 BMI (kg/m²): 31.2±1.4	<u>IG (n = 47):</u> metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed) <u>vs.</u> <u>CG (n = 48):</u> <u>regular insulin + neutral protamine Hagedorn (3:7) (starting dose 0.7 units /kg*d, adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed)</u> <u>Duration: until delivery</u>	Primary: successful maternal glycemic control Secondary: maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit	Until delivery: fasting glucose during treatment (mg/dl): better with IG: • during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008) • during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029) maternal hypoglycaemia (%): no difference: 6.25 vs. 12.5 (p=0.254) neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p=0.791) Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001) neonatal congenital anomalies (%): 2.1 vs. 2.1 p= 0.747 headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy) neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514) Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)

Beyuo 2015 ACTRN12614000942651 RCT	Ghana, urban 01/2013-12/2013	pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy no T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin	n= 104 100% female age (yrs): 33.3±4.6 fasting glucose (mmol/l): 8 2HPG (mmol/l): 10.5 BMI (kg/m²): 3.1±6.6 type of diabetes: GDM (%): 65.9 DM2 (%): 34.0	IG (n=52): Metformin (starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary) vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg, titrated to achieve the glycemic targets, if necessary, admission to the ward and therapy with soluble insulin) Duration: until delivery	Primary: 2-hour post prandial blood glucose (2HPG) Secondary: fasting glucose, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.	Change from enrolment to delivery: glycemic control (mmol/l): fasting glucose: no difference: 6.42±0.98 vs. 6.62±1.57 (p=0.928) 1HPG: no difference: 8.95±1.27 vs. 9.62±1.44 (p=0.078) 2HPG: benefit for IG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)
Ibrahim 2014 NCT01915550 RCT	Egypt, urban 08/2011-04/2012	GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance No DM1, secondary diabetes or liver or renal impairment	n=90 100% female age (yrs): 29.8 ± 5.4 BMI (kg/m²):31.83 ± 3.23 Gestational age: 28.7 ± 3.7 wks GDM: 43.3 % Pre-existing DM: 56.7 % with median duration of 4 (1-15) yrs	IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose Patients switched to CG if treatment was not successful to control blood glucose concentrations CG (n=44): insulin dose was increased according to the standard protocol	Primary: maternal gylcemic control (fasting glucose ≤ 95 mg/dl and 2-HPG ≤ 120 mg/dl) Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes	gylcemic control: • better for CG: 76.1 vs. 100 % reached glycemic control (p=0.001) • 13 vs. 18.2 % had readmission for poor glycemic control • 6.5 vs. 22.7 % had bouts of maternal hypoglycaemia Complications: • 23.3 vs. 30.8 % had fetal macrosomia • 1 new-born in each group had congenital malformations • 7 vs. 38.5 % had neonatal hypoglycaemia • 18.6 vs. 41 % had NICU admission • 0 vs. 5.1 % had stillbirths • 11.6 vs. 25.6 % with respiratory distress syndrome

BMI: Body mass index; CG: Control group; CI: Confidence interval; DM: diabetes mellitus; DM2: type 2 diabetes; FPG: fasting plasma glucose; GDM: gestational diabetes; HbA1c: haemoglobin A1c; 1 / 2HPG: 1 / 2-hour post prandial blood glucose; IG: intervention group; n: number of participants; MD: mean difference; MDa: adjusted mean difference; OGTT: Oral glucose tolerance test; RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SD: Standard-deviation; wks: weeks; yrs: years

Table 5: Characteristics and results of studies on pregnant women with DM

R

isk of bias

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Abaza 2017	☺	☺	☹	☺	☹	☺	☺
Abdulrhman 2013	☺	😐	☹	☺	☺	☹	😐
Adibe 2013	☺	☺	☹	☹	☹	😐	☺
Adjei 2015	😐	😐	☹	☺	☺	😐	☹
Ali 2019	😐	😐	☹	😐	😐	😐	☹
Amendezo 2017	😐	😐	☹	☺	☹	☺	☹
Anderson 2001	😐	😐	☺	☺	😐	😐	☺
Anyanwu 2016	😐	😐	☹	😐	☹	😐	☺
Ashoush 2016	☺	☺	☹	😐	☺	😐	☺
Asuako 2017	😐	☺	☹	😐	☺	😐	☹
Beyuo 2015	😐	☺	☹	😐	☹	☹	☹
Chraibi 2017	😐	😐	☹	😐	☹	☺	☹
Debussche 2018	☺	☺	☹	😐	☺	☺	☺
Distiller 2014	😐	☺	☹	😐	☹	😐	☺
Elbarbary 2016	😐	😐	☹	😐	☹	😐	☹
Elbarbary 2018	☺	☺	☺	😐	☺	☺	☺
Elbarbary 2020	☺	☺	☺	☺	☺	☹	😐
El Gayar 2019	☺	☺	☺	☺	😐	😐	☹
El-Haggar 2015	😐	😐	☹	😐	😐	😐	☹
El-Makaky 2020	😐	☺	☹	☺	☺	😐	😐
El-Shamy 2018	☹	☹	😐	😐	☺	😐	☺
El-Sharkawy 2016	☺	☺	☺	☺	☺	☺	☹
El-Sheikh 2019	😐	😐	☹	😐	☹	😐	☹
Embaby 2016	😐	😐	☹	😐	☹	😐	☹
Essien 2017	☺	☺	😐	☺	☹	😐	☺
Fairall 2016	😐	☺	😐	😐	☺	☺	☺
Fayehun 2018	😐	☺	☹	☹	☺	😐	☺
Ghoneim 2013	☺	😐	☹	😐	😐	😐	☹
Hailu 2018	☺	😐	☹	☺	☹	😐	☹
Ibrahim 2014	☺	😐	☹	😐	☹	☺	☹
Krawinkel 2018	☺	😐	☹	☹	☹	☺	☺

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Labhardt 2011	☺	☺	☹	😐	☺	☺	☺
Maharaj 2016	😐	😐	☹	☺	😐	😐	☹
Malek 2015	😐	😐	☹	😐	☺	😐	😐
Malipa 2013	😐	😐	☹	☹	😐	😐	☹
Mash 2014	☺	😐	☹	☹	☹	☺	☺
Matter 2020	☺	☺	☺	☺	☺	☹	☺
Mohamad 2009	😐	😐	☹	😐	😐	😐	☹
Moustafa 2019	😐	😐	☹	😐	☹	😐	☹
Muchiri 2015	☺	☺	☹	☺	☺	😐	☹
Nteleki 2015	☹	😐	☹	😐	☺	😐	☹
Owolabi 2019	😐	☺	☹	☺	☺	☹	☹
Rashad 2017	☺	☺	☺	☺	☹	😐	☹
Ragheb 2020	☺	😐	☹	☹	☹	☺	☺
RezkAllah 2019	☺	☺	☹	☺	☺	☺	☺
Saeed 2013	😐	😐	☹	☹	☹	😐	☹
Salem 2010	😐	😐	☹	☹	😐	😐	☹
Sodipo 2017	☺	😐	☹	😐	☹	😐	☺
Somanah 2012	😐	😐	☹	😐	☹	☹	☹
Steyn 2013	☺	😐	☹	😐	☹	😐	☺
Takenga 2014	😐	😐	☹	😐	☺	😐	☹
Tawfik 2016	😐	☺	☺	☺	☹	😐	☺
Thuita 2020	😐	☺	☹	😐	☺	😐	☺
Tsobgny-Tsague 2018	☺	😐	☹	☺	☹	☺	☺
Utz 2018	☺	☺	☹	☺	☺	☹	☹
Van der Hoogt 2017	😐	😐	☹	😐	☹	😐	☹
Van Rooijen 2004	☺	☺	☹	☺	☺	😐	☹
Webb 2015	😐	😐	😐	☺	☹	☺	😐
Yakoot 2019	😐	☺	☹	☹	☺	☹	☹
Yan 2014	😐	😐	☹	😐	☺	😐	☹
☺: low, 😐: unclear, ☹: high risk of bias							

Table 6: Judgements on risk of bias

Supplement 2

Search strategies

Medline (Ovid)

Search on 19.11.2018, 1470 references, Update from 2018 to Current on 20.08.2020: 541 references

Nr.	Searches
1.	exp Diabetes Mellitus/
2.	Diabetes.tw
3.	**or/1-2**
4.	Africa.tw
5.	Exp Africa/
6.	Algeria$.tw or exp Algeria/
7.	Angol$.tw or exp Angola/
8.	Benin$.tw or exp Benin/
9.	Botswan$.tw or exp Botswana/
10.	Burkina Faso.tw or exp Burkina Faso/
11.	Burund$.tw or exp Burundi/
12.	Cameroon$.tw or exp Cameroon/
13.	Cape Verde.tw or exp Cape Verde/
14.	Central African Republic$.tw or exp Central African Republic/
15.	Chad$.tw or exp Chad/
16.	Comoros$.tw or exp Comoros/
17.	Cote d'Ivoire.tw or exp Cote d'Ivoire/
18.	Democratic Republic of Congo.tw or exp Democratic Republic of Congo
19.	Djibout$.tw or exp Djibouti/
20.	Egypt$.tw or exp Egypt/
21.	Equatorial Guinea$.tw or exp Equatorial Guinea/
22.	Eritrea$.tw or exp Eritrea/
23.	Ethiop$.tw or exp Ethiopia/
24.	Gabon$.tw or exp Gabon/
25.	Gambia$.tw or exp Gambia/
26.	Ghana$.tw or exp Ghana/
27.	Guinea$.tw or exp Guinea/
28.	Guinea-Bissau.tw or exp Guinea-Bissau/
29.	Kenya$.tw or exp Kenya/
30.	Lesoth$.tw or exp Lesotho/
31.	Liberia$.tw or exp Liberia/
32.	Libya$.tw or exp Libya/
33.	Madagascar$.tw or exp Madagascar/
34.	Malawi$.tw or exp Malawi/

Nr.	Searches
35.	Mali.tw or exp Mali/
36.	Mauritania$.tw or exp Mauritania/
37.	Mauritius$.tw or exp Mauritius/
38.	Morocc$.tw or exp Morocco/
39.	Mozambique$.tw or exp Mozambique/
40.	Namibia$.tw or exp Namibia/
41.	Niger.tw or exp Niger/
42.	Nigeria$.tw or exp Nigeria/
43.	Rwanda$.tw or exp Rwanda/
44.	(Sao Tome and Principe).tw
45.	Senegal$.tw or exp Senegal/
46.	Seychell$.tw
47.	Sierra Leone.tw or exp Sierra Leone/
48.	Somalia$.tw or exp Somalia/
49.	South Africa$.tw or exp South Africa.de
50.	South Sudan.tw or exp South Sudan/
51.	Sudan$.tw or exp Sudan/
52.	Swaziland$.tw or exp Swaziland/
53.	Tanzania$.tw or exp Tanzania/
54.	Togo$.tw or exp Togo/
55.	Tunisia$.tw or exp Tunisia/
56.	Uganda$.tw or exp Uganda/
57.	Zambia$.tw or exp Zambia/
58.	Zimbabwe$.tw or exp Zimbabwe/
59.	Somaliland$.tw or exp Somaliland/
60.	Sahrawi Arab Democratic Republic.tw.
61.	or/4-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	(randomized or randomised or randomly).ti,ab
65.	placebo.ti,ab.
66.	trial.ti,ab.
67.	groups.ti,ab.
68.	or/62-67
69.	3 and 61 and 68
70.	exp animals/ not humans.sh.
71.	69 not 70
72.	71 not (comment or editorial).pt.

CENTRAL

Search on 14.01.2019, 439 trials, Update from 2018 to Current on 20.08.2020: 244 trials

1	Africa, explode all trees
2	Algeria* or Angol* or Benin* or Botswan*
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)
4	Chad* or Comoros* or Cote d'Ivoire or Congo*
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor Diabetes, this term only
14	MESH descriptor Diabetes mellitus, explode all trees
15	Diabetes near 3 gestation*
16	Latent autoimmune diabetes in adults
17	Prediabetes
18	Insulin resistan*
20	HBA1C
21	Diabet* near 3 (angiopath* or foot orfeet or retinopath*)
22	Diabet* near 3 (cardiomyopathy* or coma or ketoacido* or neuropath*)
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
32	#12 and #23

CINAHL

Search on 20.08.2020: 19 results

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$

or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract

AND

diabetes in Abstract

AND

randomized or rct or randomized in Abstract

AND

In English

AND

Peer-reviewed

And

Humans

International Clinical Trials Registry Platform

Search on 9.-10.10.2019, update on 25.08.2020 (registration January 2019 to 31.08.2020)

http://apps.who.int/trialsearch/AdvSearch.aspx

1. Africa or African in the Title and diabetes or diabetic or HbA1c in the condition, Recruitment status: all**:** 90 records for 90 trials (9.10.2019)
2. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Central African Republic or Chad or Congo or Cite D'ivoire: 96 record for 63 trials
3. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia: 292 records for 159 trials
4. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Lybia: 22 records for 22 trials
5. diabetes or diabetic or HbA1c in the condition

Recruitment status: all

Countries of recruitment: Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique: 96 records for 34 trials

6. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Nigeria: 13 records for 13 trials

7. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Namibia or Niger or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Sudan or Sudan or Swaziland:

   11 records for 11 trials

8. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: South Africa: 1528 records for 429 trials:

9. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Togo or Tunesia or Ujanda or Zambia or Zimbabwe: 129 records for 50 trials

African Journals Online

https://www.ajol.info/index.php/index/search/search?query=%28diabetes+or+diabetic+or+hba1c%29+and+%28random+or+randomized+or+randomised%29&dateFromYear=2004&dateFromMonth=01&dateFromDay=1&dateToYear=2020&dateToMonth=10&dateToDay=14&authors=

Advanced search 14.10.2020
Titel: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
30 results

African Index Medicus Database

http://indexmedicus.afro.who.int/aim/opac_css/index.php?lvl=search_result&get_query=4

Advanced search 14.10.2020
Titel, Expression booléenne: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
122 results, no potentially eligible references

1 List of included and excluded studies

1.1 List of included studies

Abaza 2017

Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC public health. 2017;17(1):962.

Abaza H, Marschollek M, Schulze M. SMS Education for the Promotion of Diabetes Self-Management in Low & Middle Income Countries: A Randomized Controlled Trial in Egypt. Studies in Health Technology & Informatics. 2017;245:1209.

Abdulrhman 2013

Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. Journal of Medicinal Food. 2013;16(1):66-72.

Adibe 2013

Adibe MO, Ukwe CV, Aguwa CN. The Impact of Pharmaceutical Care Intervention on the Quality of Life of Nigerian Patients Receiving Treatment for Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):240-7.

Adibe MO, Aguwa CN, Ukwe CV. Cost-Utility Analysis of Pharmaceutical Care Intervention Versus Usual Care in Management of Nigerian Patients with Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):189-98.

Adjei 2015

Adjei DN, Agyemang C, Dasah JB, Kuranchie P, Amoah AG. The effect of electronic reminders on risk management among diabetic patients in low resourced settings. Journal of Diabetes & its Complications. 2015;29(6):818-21.

Ali 2019

Ali S, Ghanem Y, Sharaki O, Hewedy W, al. e. The impact of different regimens of vitamin d3 on glucose homeostasis in type 2 diabetic patients. Asian journal of pharmaceutical and clinical research. 2019;12(12):21- 6.

Amendezo 2017

Amendezo E, Walker Timothy D, Karamuka V, Robinson B, Kavabushi P, Ntirenganya C, et al. Effects of a lifestyle education program on glycemic control among patients with diabetes at Kigali University Hospital, Rwanda: A randomized controlled trial. Diabetes Research & Clinical Practice. 2017;126:129-37.

Anderson 2001

Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. Journal of the American College of Nutrition. 2001;20(3):212-8.

Anyanwu 2016

Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian Journal of Endocrinology and Metabolism. 2016;20(2):189-94.

Ashoush 2016

Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. Journal of obstetrics and gynaecology research. 2016;42(6):640- 7.

Asuako 2017

Asuako B, Moses MO, Eghan BA, Sarpong PA. Fasting plasma glucose and lipid profiles of diabetic patients improve with aerobic exercise training. Ghana Medical Journal. 2017;51(3):120-7.

Beyuo 2015

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Studies on patients with pre-DM

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	 Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Strategies to enhance physical activity						
RezkAllah 2019 ACTRN126170 00631303 RCT	Egypt, urban 07/2017-01/2018	Pre-DM, 25-45 yrs, BMI of 25–30 kg/m2, HbA1C 5.7–6.4%, fasting glucose 100–125 mg/dL, sedentary lifestyle No history of diabetes, cancer, prediabetic neuropathy, stroke, pulmonary embolism, or severe musculoskeletal problems restricting physical activity	n=60 45 % females age (yrs): 32.9±5.5 BMI (kg/m²): 28.3±1.4	IG2 (n=20): High-volume high intensity interval training, 40 min/session vs. IG1 (n=20): Low-volume high intensity interval training, 25 min/session Both with 90 % HR maximum, 3 times/week CG (n=20): No exercise intervention Duration: 12 weeks	Primary: HbA1c Other: fasting glucose	After 3 months HbA1c (%): Benefit for IG2 and IG1: Benefit for IG: 4.87±0.34 (-26 %) vs. 5.13±0.57 (-14.5 %) vs. 6.25±0.48 (+3.38 %) (p=0.0001) fasting glucose (mg/dL): Benefit for IG2 and IG1: 90.8±4.13 (-17.8 %) vs. 93.8±4.16 (-13.2 %) vs. 103.8±7.21 (+2.9 %) (p=0.0001)
Strategies on nutrition						
Krawinkel 2018 DRKS 00005131 Cross-over-RCT	Tanzania, urban 10/2013-03/2014	Individuals with pre-DM age (yrs): 30 -65, FPG 5.6-6.9 mmol/l (100–125 mg/dL) on 2 days or on one day + HbA1c 5.7-7.5 %, BMI 27–35 kg/m², BP 90/60-160/110 mmHg, waist circumference > 80/90 cm for women / men No chronic disease, taking regular intake of medication, identified glucose-6-phosphatase-dehydrogenase deficiency, heavy alcohol consumption, pregnancy,	n=52 55% female age (yrs): 47.5±8.7 HbA1c (%):5.85±0.43 FPG: (mmol/l): 5.34±0.49 BMI (kg/m²):29.6±2.2	IG/CG (n=30): started with bitter gourd supplementation (2,5 g) over 8 wks, followed by placebo over 8 wks vs. CG/IG (n=31): first placebo over 8 wks, followed by bitter gourd over 8 wks washout period: 4 wks Duration 8 weeks	Primary: FPG Secondary: HbA1c, Insulin, SBP, DBP, lipids	after 8 wks FPG (mmol/l): Benefit for IG/CG: MD 0.31 (0.08-0.54) HbA1c: (%): No differences (MD 0.05)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		lactation				

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DBP: Diastolic blood pressure; DM: diabetes mellitus; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants; MD: mean difference; RCT: randomized controlled trial; SBP: Systolic blood pressure; SD: Standard-deviation; wks: weeks; yrs: years

Table 2: Characteristics and results of studies on patients with pre-DM

Studies on patients with DM1

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	Population Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Malipa 2013 RCT	Zambia	DM1, 16-19 yrs	n=40 55% females 16-17 yrs: 35 % 18-19 yrs: 65 % Compliance: worse in IG 26.4 vs. 14.6 (p=0.001) Impact of diabetes: 20.5 Worries about diabetes: 20.5 Satisfaction with life: 20.5	IG (n=20): 1 meeting /wk over 8 wks CG (n=20); waiting list Duration: 8 wks	Compliance to treatment (Rating scale for compliance) Quality of life (impact and worries about diabetes, satisfaction with life)	After 2 months: Compliance: better in IG (11.0 vs. 30; p<0.001) Impact of diabetes: better in IG (16.8 vs. 24.2; p=0.045) Worries about diabetes: better in IG (14.32 vs. 26.68; p=0.001) Satisfaction with life: better in IG (28.5 vs. 12.5; p<0.001)
Strategies to enhance physical activity						
Salem 2010 RCT	Egypt, urban 02/2009-11/2009	DM1 for ≥3 years, 12-18 yrs, HbA1c ≥7.5 % for ≥6 months no significant diabetic complications limiting exercise like, uncontrolled hypertension, diabetic keto-acidosis, severe hypoglycemia within the past 3 months, patients on lipid lowering therapy	n=196 61.7 % female age (yrs): 14.78 ± 2.31 HbA1c (%): 8.7±1.7 duration of diabetes (yrs): 4.6 ± 1.9	IG2 (n=73): attended exercise sessions three times/week vs. IG 1 (n=75): attended exercise sessions once times/week vs. CG (n=48): no exercise Duration: 6 months	glycemic control, plasma lipids values, blood pressure, severity and frequency of hypoglycemia, anthropometric measurements and insulin dose	Change over 6 months: HbA1c (%): Benefit for IG2 and IG1: 7.8 ± 1.0 vs. 8.1 ± 1.1 vs. 8.9 ± 1.3% (p=0.2)
Strategies on nutrition						
Abdulrhman 2013 NCT01554566 Cross-over	Egypt, urban, tertiary care 01/2010 -	DM1, age > 2 yrs, HbA1c< 10 % no renal or hepatic impairment, coexisting	n=20 50 % females age (yrs): 11.3 ± 4.3 duration of diabetes (yrs): 4.7±4.5	IG/ CG (n=10): Honey consumption (0.5 ml/kg body weight per day) vs.	Primary: serum lipids, c-peptide Secondary: anthropometric measures (e.g. BMI), fasting and 2h-	After 12 weeks: (IG/CG vs. CG/IG): HbA1c (%): • Benefit with CG/IG: 6.7±0.9 vs. 5.9±0.8 (p<0.01) • no differences in change in period 1: -

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	10 / 2011	diseases or therapies that may affect body weight or serum lipids	HbA1c (%):7.21± 0.76 fasting glucose (mg/dl): 154.5±22.5	CG/IG (n=10): changed after 12 wks and received than honey Duration: 12 wks.	postprandial glucose, HBA1c, serum lipid profile	5.83 ± 13.66 vs. 2.94±8.82 (p=0.105) Fasting glucose (mg/dl): • benefit with CG/IG: 142.7 ±26.6 vs. 116.7±19.4 (p<0.01) benefit with IG/CG in period 1:-21.51 ± 10.84 vs. -0.08±5.14 (p=0.001)
Mohamad 2009 RCT	Egypt, urban	DM1, age 17 to 20 yrs no acute metabolic complications like diabetic ketoacidosis, hypoglycaemia, cardiovascular events, renal or acute infections	n=64 30 % female age (yrs): 19.9±6.8 HbA1c (%): 9.52±2.08 fasting glucose (mg/dl): 228.7±13.5 BMI (kg/m²): 18.82±3.01	IG (n=27): camel milk (500 ml) +usual care vs. CG (n=27): usual care for diabetes (i.e. diet, exercise, insulin mixtard) Duration: 16 weeks	Not specified: HbA1c, human C-peptide, lipid profile, serum insulin, anti-insulin antibodies, creatinine clearance, albumin extraction in 24 h urine, BMI, Diabetes QoL score, fasting glucose	After 16 wks HbA1c (%): Benefit for IG: 7.16±1.84 vs. 9.59±2.05 fasting glucose (mg/dl): benefit for IG: 227.2±17.7 vs. 98.9±16.2
van der Hoogt 2017 cross-over RCT	South Africa	DM1, age 4-17 yrs on insulin pump therapy, HbA1c>9,6% for ≥3months, BMI/age z.score -1 to < 3, total daily insulin use of >0,5 u/kg no remission of diabetes, smoking, coeliac disease, cystic fibrosis, diseases or medication that are associated with delayed gastric emptying or altered digestation, glucocorticoids, oral diabetic drugs, no acute illnesses	n=32 41% female age (yrs): 10.4±4.0 HbA1c (%): 8.2±0.8 duration of Diabetes (yrs): 3.5 (1.5-8.0)	IG1 (n=22): 1 home-based low fat and protein meal vs. IG2 (n=22): 1 high fat and protein meal with identical carbohydrate content two meals were consumed at dinner time (18:00) under parental supervision at least 1 day apart within one month Duration: 3months	primary: peak sensor glucose value post-meal, time to peak sensor glucose, time of first and largest correction bolus, total correction insulin, total meal insulin, additional insulin required ,area under the sensor glucose response curve (AUC) (≥ 8 mmol/L), duration of elevated post-prandial glucose	Change over 12 weeks Occurance of hypoglycaemic events: 7 (32 %) vs. 1 patients after IG1 vs. IG2
Medical device						
Elbarbary 2016 RCT	Egypt, urban 06/2014-07/2014	DM1, adolescents and adults who wished to fast the month of Ramadan with insulin pump for ≥6 months and attending the whole	n=73 68.3% female age (yrs): 15.6±2.7 HbA1c (%): 7.65±0.9 BMI (kg/m²):	Insulin pump therapy during Ramadan fasting IG (n=25): sensor with low glucose	Primary: hypoglycaemia Other: glucose value, number of 'full fasted days', emergency hospital visit for diabetes-related	After 1 months: Glucose value (mg/dl): 152.5±17.3 vs. 141±33.8 (p=0.9) Complications: Number of hypoglycaemic excursions:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		education session 2 months before fasting and committed to follow-up the given instructions no diabetic ketoacidosis, episodes of severe hypoglycaemia or symptoms of uncontrolled diabetes in the last 6 months, diabetic microvascular complications or macrovascular disease, pregnant women	24.56±3.5 duration of diabetes (yrs): 5.8±2.9 on pump therapy (yrs): 1.73±0.99	suspension activation vs. CG (n=35): sensor without low glucose suspension activation Duration:1 month	problem	3.68±1.62 vs. 6.7±2.1 (p=0.001) Number of hyperglycaemic excursions: 17.0±4.0 vs. 23.0±7.6 (p=0.001) No severe hypoglycaemic events, no episodes of diabetic ketoacidosis, no hyperglycaemic events associated with ketosis no deaths or device-related SAE
Pharmacological Strategies						
Elbarbary 2018 NCT0292825 RCT	Egypt, urban	DM1, age: 9 - 18 yrs, ≥ 5 yrs disease duration, active diabetic nephropathy in the form of microalbuminuria, HbA1c ≤ 8.5 % no infection, renal impairment due to other causes other than diabetes, other diabetic complications, hypersensitivity to carnosine	n=90 52.3 % female age (yrs): 12.85±3.1 HbA1c (%):7.85±1.95	IG (n=45): 1 g/d carnosine vs. CG (n=45): control/placebo group Patients in both groups received oral ACE-Is captopril 25 mg Duration: 12 wks	Primary: change in tubular damage marker Secondary: urinary albumin excretion (UAE), oxidative stress markers Safety: any AE	After 12 wks: HbA1c (%): • Benefit for IG: 7.4 ±1.3 vs. 8.3±2.4 • change -9.88±7.12 vs. 3.89±2.28 (p=0.005) No adverse reactions were reported
Elbarbary 2020 NCT03594240 RCT	Egypt, urban 03/2017-03/2018	DM1 on insulin therapy with > 5 yrs of disease duration, 12-18 yrs, active nephropathy, HbA1c< 8.5 %, no infections, renal impairment due to other causes than diabetes, other diabetic complications ,	n=80 55% female age (yrs): 15.4 ± 1.6 HbA1c (%):7.95±0.5 fasting glucose (mg/dl): 114.5±21.8 duration of diabetes (years): 8.65 ± 2.65	both groups received oral angiotensis-converting-enzyme inhibitors (captopril) IG (n=40) oral vitamin B complex (B1,B6,B12) once daily vs.	Primary: Cystatin C diet, physical activity, and metformin dosage	after 12 weeks HbA1c (%): Benefit for IG: 7.5±0.6 vs. 8.0±0.6 Fasting glucose (mg/dl): 107.7±14.1 vs. 116.4±17 (p=131)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	 Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		elevated liver enzymes, hyper-or hypothyroidism, hypertension, neoplasm, taking any vitamins or food supplements within 1 months before study start		CG (n=40): placebo Duration: 12 weeks		

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DM1: Type 1 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants ;RCT: randomized controlled trial; SD: Standard-deviation; wks: weeks; yrs: years

Table 3: Characteristics and results of studies on patients with DM1

RCTs mainly including patients with DM2

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Abaza 2017 NCT02868320 RCT	Egypt, urban, tertiary care, 03-07/2015	DM2, mobile phone, capable to read SMS or live with someone who could read	n=73 56 % females age (yrs): 51.5±9.2 majority had had diabetes for > 1 yr hypertension: 41.1 % on insulin: 19.2 % DM complication: 80.8 % HbA1c (%): 9.7±2.7	Diabetes awareness program: paper-based educations material plus IG (n=34): daily messages and weekly reminders addressing various diabetes care categories vs. CG (n=39): paper-based educations material Duration: 12 wks.	Primary: change in Hba1C Secondary: Random blood glucose levels, body weight, adherence of treatment and medication, diabetes self-efficacy and knowledge, rate of hospital/ER visits, frequency of measurements, regular exercise, patients confidence in healthcare provider and satisfaction, healthcare provider's reputation	After 3 months: HbA1c (%): • No differences: 8.73 ±1.98 vs. 8.84±2.40, MD_a: 0.290 (-0.402 to 0.983; p = 0.406) • Benefit with IG: 47 vs. 15 % achieved the targeted 1% drop (p = 0.003) Random blood glucose (mg/dl): • No difference: 181±65 vs. 201±87 (p=0.288) Treatment adherence (scores): • Benefit with IG in SCI 3.42±0.48 vs. 2.52±0.49 (p<0.001) and Morisky: 3.76±0.55 vs. 2.74±1.07 (p<0.001) Hospital /ER admission (%): No differences: 0 vs. 10.3 (p=0.118)
Adibe 2013 RCT	Nigeria, urban, tertiary care	DM2, age≥ 18 yrs with oral hypoglycemic and / or insulin therapy no pregnancy	n=220 58 % females age (yrs): 52.6±7.9 duration of diabetes (yrs): 4.7±2.5, 60.5% with diabetes > 5 yrs on insulin: 13.6 % hypertension: 60.5 %	IG (n=110): structured self-care education and training program by pharmacists and nurses vs. CG (n=110): usual / conventional care Duration: 12 months	Primary: incremental cost-utility ratio, net monetary benefit Other: quality of life	After 12 months: Quality of life: • Benefit with IG: 0.86 ± 0.12 vs. 0.64 ± 0.10 (p=0.0001) improved single attributes except "hearing" functioning of the patients Costs: • benefit of $0.76±0.15 vs. $0.64± 0.15 QALY/patient and year; MD: $ 0.12 (0.07 to 0.16) • incremental cost-utility ratio of $571 per QALY
Adjei 2015	Ghana, urban	DM	n=200 64.5% female	IG: (n=100): electronical reminder for	Primary: Compliance with appointment dates	After 6 months: Adherence to appointment schedules

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT			age (yrs): < 50 yrs: 63 % > 50 yrs: 37 % fasting glucose (mmol/l): 10.4±3.8	clinical appointments of patients + alert system for abnormal laboratory results vs. CG: (n=100): usual diabetes care, paper based method Duration: 6 months	Other: metabolic risk factors, BMI	(%) Benefit for IG: 97.8 vs. 89.4 (p=0.010) Fasting glucose (mmol/l): Benefit for IG: 8.04±2.14 vs. 8.85±2.63; MD 0.4 (-0.59 to -0.36, p=0.022)
Amendezo 2017 NCT02032108 RCT	Rwanda, urban, tertiary care	DM2>3mths, age>21yrs no pregnancy or severe co-morbid illnesses.	n=251 69.3% females age (yrs): 50.9 ±10.9 BMI (kg/m²): 27.9 (27.0-28.5) duration of diabetes : <10 yrs: 73.7%, >10 yrs: 16.3% HbA1c (%): 8.98±8.6-9.3	IG (n=115): standard care plus monthly lifestyle education sessions of 45 min duration vs. CG (n=108): standard care Duration: 12 months	Primary: difference in HbA1c Secondary: fasting glucose, systolic and diastolic blood pressure, BMI	after 12 months: HbA1c (%): Benefit for IG with median reductions of -1.70 (-2.09 to-1.31) vs. -0.52 (-0.95 to -0.10); MD: -0.72 (-1.14 to -0.30; p< 0.001) Fasting glucose (mmol/L): 6.9 (6.45 to 7.36) vs. 9.02 (8.18 to 9.87) (p<0.001)
Chraibi 2017 NCT01589653 RCT	Egypt, Indonesia, Morocco, Saudi Arabia, Vietnam 05/2012-07/2015	DM2 with diagnosis ≥ 12 months, age≥18 , currently being treated with NPH Insulin for ≥ 3 months + metformin (1000-1500 mg) for ≥ 2 months, HbA1c ≥ 7.0% ≤10%, BMI ≤ 40.0 kg/m² no treatment with thiazolidinedione, glucagon-like peptide-1 receptor agonists, pramlintide within the last 3 months , >1 IU/kg NPH insulin daily; previous use of premixed or bolus insulin, > 1 severe hypoglycemic episode during	n=155 74.9 % female age (yrs): 54.5 ±10.0 BMI (kg/m²): 29.05±4.9 HbA1c (%): 8.6 ±0.83 fasting glucose (mmol/L): 8.97 duration of diabetes (yrs): 9.5±5.8 African patients: • Egypt: 25.75 % • Morocco: 27.7 % Diabetic nephropathy / neuropathy / retinopathy (%): 3.2 / 16.1 / 3.2	IG (n=76): patient driven titration of Biphasic insulin aspart 30 twice daily, 3 clinic visits vs. CG (n=79): physician driven titration twice daily, 6 clinic visits Titration in both arms according to the titration protocol bases on self-measured plasma glucose values, measured twice daily on 3 preceding days, telephone contact whenever deemed	Primary: change in HbA1c Secondary: proportion of patients achieving the ADA target of HbA1c <7.0 % and the HbA1c target of <6.5 % after 20 weeks, FPG changes, hypoglycemic episodes,	Change over 5 months: HbA1c (%): • Decreased in both arms with non-inferiority between groups: MD -0.23 (-0.54 to 0.08) • More patients reached HbA1c <7.0%: 40.8 vs. 29.1 %, RR: 1.79 (0.87 to 3.65) and <6.5%: 25 vs. 19 %; RR: 1.52 (0.67 to 3.46) • More patients reached target HbA1c levels without severe or minor hypoglycemic episodes: <7.0%: 38 vs. 27.8 %, RR: 1.52 (0.61 to 3.79), <6.5%: 18 vs. 14.8 %; RR 1.13 (0.36 to 3.52) FPG (mmol/l): • Decreased in both arms with no difference between groups: 0.95±0.28

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		the previous 12 month, impaired kidney or hepatic function, proliferative retinopathy or maculopathy requiring treatment	Macroangiopathy (%): 5.2	necessary Duration: 20 weeks		vs. 0.67±0.28; MD: -0.28 (-1.07 to 0.52) Costs • Less frequent clinic visits to healthcare professionals in IG: 4.8±0.65 vs. 7.5±1.42 visits/patient Complications: • hypoglycemic episodes: no difference: 608.4 vs. 789.2 / 100 patient-years of exposure; RR: 0.74 (0.44; 1.23) treatment-emergent AEs: no difference: 324.2 vs. 302.2 events / 100 patient-years of exposure
Debussche 2018 NCT01485913 RCT	Mali, urban, secondary care, 07/2011-02/2013	DM2, age 30-80 yrs, HbA1c ≥ 8 %, no DM1, severe diabetes complications or concomitant illnesses that threatened their functional or vital prognosis	n=151 76.2% female age (yrs): 52.5±9.8 BMI (kg/m²):28.6±5.4	IG (n=76): peer-led structured patient education received culturally tailored structured patient education (3 courses of 4 sessions) delivered in the community by five trained peer educators vs. CG (n=75): conventional care alone Duration:1 yr	Primary: HbA1c Secondary: anthropometric indicators (weight and BMI, waist circumference), SBP, DBP, anti-diabetic and anti-hypertensive treatment, knowledge score, dietary practices	Change to 12 months HbA1c (%): • Benefit in IG: MD 1.05 % (-1.54;-0.56) vs. -0.15 % (-0.56; 0.26) (p = 0.006)
Essien 2017 PACTR201302 00047835 RCT	Nigeria, urban, tertiary care, 09/2013-05/2014	DM1 or DM2, age: ≥ 18 yrs, HbA1c> 8.5 %, able to engage in moderate exercise, no eye disease that would limit the ability to read	n=118 60.2 % female age (yrs): 52.7±10.5 BMI (kg/m²): 28.9±7.5 HbA1c (%):10.7±1.6 type of diabetes • DM1: 14.4 % • DM2: 85.6 %	IG: (n=59): intensive and systematic disease self-management education programme (invitation and encouragement by clinical staff to attend 12 structured teaching sessions) vs.	Primary: HbA1c	After 6 months: HbA1c (%): 8.4 (8 to 8.9) vs. 10.2 (9.8 to 10.7); MD_a: -1.8 (-2.4 to -1.2); (p < 0.0001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				CG (n=59): conventional disease-self-management education Duration: 6 months		
Fairall 2016 ISRCTN20283604 Cluster-RCT	South Africa, urban/rural, primary care, 03/2011 – 11 / 2011	age ≥ 18 yrs , clinics providing service for NCD Patients with DM, hypertension, chronic respiratory disease or depression, with self-reported hypoglycaemic (in case of DM)	n= 38 public sector primary care clinics, 4393 patients, n=1842 with DM 73 % female age (yrs):median, IQR): 52 (42-61) vs. 52 (44-62) BMI (kg/m²): 30±8 HbA1c (%):9 (4-17), in HbA1c in DM≥ 7 %: 77 %	IG (n=2166, 851 with DM): Nurses were trained to use a primary care programme to support and expand nurses`role in NCD care and contains a clinical management tool with enhances prescribing provisions vs. CG (n=2227, 991 with DM): Nurses continued to use the Lung Health and HIV/AIDS approach with usual training Duration: 14 months	Primary (for DM): treatment intensification (addition or increase in dose of metformin and/or sulphonylurea, insulin, ACE-inhibitor, aspirin, statin	over 14 months HbA1c (%): • <7 %: 41 vs. 38 %; RR 1.08 (0.77 to 1.52; p=0.638) • 7-10 %: 69 vs. 55 %; RR 1.30 (1.16 to 1.47; p<0.001) • >10 %: 71 vs. 73 %; RR 0.97 (0.81 to 1.16; p=0.703) Treatment intensification rates* (%): • 57% vs. 50%, RRa: 1.11 (0.99 to 1.26) (p=0.083) for patients with DM
Hailu 2018 NCT03185689 RCT	Ethiopia, urban, 02/2016-10/2017	DM2, age > 18 yrs no DM1 or GDM, pregnant women, severe cognitive or physical impairment, and terminally ill people	n=220 33 % female age (yrs): 54.5±10 BMI (kg/m²):25±4 HbA1c (%):10.5±4	IG (n= 116): Nurse-led disease-management education: 6 sessions, supported with illustrative pictures handbooks and fliers, customized to local conditions by trained nurses vs. CG (n=104): usual follow-up care Duration: 9 months	Primary: patients with target HbA1c (≤ 7 %) Secondary: systolic and diastolic blood pressure, fasting glycose, BMI, waist circumference	Change over 9 months: HbA1c (%): • No difference: 45 % vs. 50 % with target values (p=0.21), MD: 2.88% (-3.85 to -1.92) vs. 2.57% (-3.47 to -1.67) fasting glucose (mg/dl): • Benefit with IG: 36 % vs.25 % with target values, MD: -27 (-45 to -9; p=0.003)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Labhardt 2011 NCT00744458 Cluster-RCT	Cameroon rural, primary care, 08/2008-02/2010	newly detected adult patients with DM2 and /or hypertension in the catchment area of nurse-led health centres, staffed, equipped and trained to care for DM2 and hypertension	n=33 facilities, 221 patients 64% females age (yrs): 59.8±12.7 diabetes: 15.4 % Overweight (BMI 25-29.9 kg/m²): 28.5 % Obesity (BMI> 30 kg/m²): 20.4 %	IG 1 (11 centres, n=55): incentive group free treatment for 1 months for patients who regularly attended follow up visits vs. IG 2 (11 centres, n=77): letter group: reminder letters in case of a missed follow-up visit vs. CG (11 centres, n=89): no additional intervention Duration: 12 months	Primary: Patient retention at 1 yr (≥ 12 follow-up visits within 12 months) Secondary: Adherence with timely attendance of follow-up visit schemes and changes in blood pressure and blood glucose levels.	After 12 months: Retention rates (%): • Benefit for IG1 and IG2 vs.CG: 60 vs. 65 vs. 29 %; MD 34 (21 to 46) with no differences between IG1 and IG2; MD -5 (-22 to 12) Loss to follow-up: • Benefit for IG1 and IG2: IG1 vs. CG: HR 0.44 (0.27 to 0.72; p< 0.001) • IG2 vs. CG: HR 0.38 (0.24 to 0.61; p<0.001) Adherence (%): • Benefit for IG1 and IG2: 38 vs. 35 vs. 10; MD 26 (14 to 42), IG1 vs CG: MD 28(13 to 37); IG2 vs. CG: MD 25 (13 to 37) • no difference between IG1 and IG2: MD 3 (-14 to 20) FPG: No differences between groups
Mash 2014 Cluster RCT	South Africa, urban, primary care, 12/2010 -12/2012	DM2 with any therapy attending community health centres in the working class areas of Cape Town Metropole no DM1, dementia, mental illness or acute illness	n=34 public sector community health centres, 1570 patients 73.8% females age (yrs): 56.1±11.6 HbA1c (%): 9.1±2.3	IG (17 health centres, n=710): 4 monthly sessions lasting 60 min with group education about diabetes topics (understanding diabetes and medication, living a healthy lifestyle and preventing complications), delivered by a health promotion officer vs. CG (17 health centres, n=860): usual care: ad hoc advice during consultations and	Primary: improvement of diabetes self-care activities (5 % weight loss, and a 1 % reduction in HbA1c level) Secondary: improved diabetes specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol levels, quality of life	After 12 months: HbA1c (%): No differences: 8.4±2.0 vs. 8.8±2.2; MD_a: 0.01 (-0.27 to 0.28; p=0.967) Adherence (self-care activities): No differences in scores of physical activity, use of diet plan or medication, foot care or frequency of smoking Quality of life: No differences in physical functioning, role or social functioning, mental or general health and pain Costs: Incremental cost effectiveness ratio: 1862 Dollar/ QALY gained

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				occasional educational talks in waiting room Duration: 12 months		
Muchiri 2015 RCT	South Africa, rural, primary care, 04/2010-11/2011	DM2, age 40-70 yrs attending community health centres, HbA1c≥ 8 %, blood sugar levels ≥ 10 mmol/l, duration of diabetes ≥ 1 yr no insulin therapy, pregnant women, full time employed	n=82 86.6 % female age (yrs): 59±7.4 BMI(kg/m²): 30.9±6.9 HbA1c (%): 11.1±2.0 duration of diabetes (yrs): 6	IG (n=41): education materials+ 8 weekly group educational sessions about diabetes and nutrition, follow-up sessions+vegetable gardening CG (n=41): education materials Duration: 12 months	Primary: HbA1c Secondary: Other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c, dietary behaviours	over 12 months HbA1c (%): • no difference: 9.8±1.92 vs. 10.4±1.92; MD −0.63 (-0.26 to 1.50; p=0.16)
Owolabi 2019 PACTR201810599931422 RCT	South Africa urban/rural, primary care 07/2018-04/2019	DM, age ≥18 yrs, DM diagnosed at least in the last 6 months, currently receiving treatment at the selected clinics, on stable medication for ≥ 3 months prior to recruitment, uncontrolled glycaemic control, in possession of a mobile phone, able to retrieve and read SMSs and willing to receive SMSs health or mental conditions that could interfere with the study, pregnant or planning to get pregnant within the next 6 months, debilitated or handicapped in such a way that obtaining anthropometric measurements could be	n=216 84.3 % females age (yrs): 60.6±11.6 DM2 (%): 94 Treated with oral pills (%): 75.5 Duration of DM (yrs): 9.1±7.4 Duration of DM treatment (yrs): 8.8±7.2 Hypertension (%): 83.0 Random blood glucose (mmol/L): 14.34±3.9 BMI(kg/m²): 32.2±6.2	IG (n=108): daily SMS text-messaging SMS at an agreed time of the day, according to their needs, care plan and goal with motivational and support messages, advice on lifestyle behaviours (e.g. diets, physical activity, smoking cessation, medication and appointment reminders) vs. CG (n=108): usual diabetes care Duration: 6 months	Primary: Morning random blood sugar Secondary: co-morbid outcomes (hypertension and obesity), obtained through blood pressure measurement, anthropometric measurements (body weight, BMI) acceptability, feasibility	Over 6 months: Blood glucose levels (mmol/L): -1.58±5.29 vs. -1.95±4.69; MD 0.51(-0.8 to 1.82), MD_a 0.26 (-0.81 to 1.32)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		challenging				
Sodipo 2017 RCT	Nigeria, primary care, 03/2013-11/2013	DM2 ≥ 18 yrs. on antidiabetic medication no patients with emergencies, chronic complications such as nephropathy, neuropathy etc., those already using glucometer	n=120 gender: 50% female age (yrs): 59±10.95 HbA1c (%): 8.7±2.45 fasting glucose (mg/dl): 152±60.9 duration of diabetes (yrs): 50%> 3yrs	IG (n=60): Self-monitoring of blood glucose before and after meals 3 days a week for 12 weeks CG (n=60); non SMBG Duration: 12 wks	HbA1C, fasting glucose	after 3 months: HbA1c (%): No difference: 7.2±2.0 vs.7.7±2.0 (p= 0.174) fasting glucose (mg/dl): No difference: 123.2±35.1 vs. 137.6±50.1 (p=0.087)
Steyn 2013 Cluster-RCT	South Africa, urban, primary care, 1999-2000	public sector primary health care clinics (CHC) with ≥ 25 diabetes and ≥ hypertension patients age ≥15yrs, a documented attendee at the particular CHC with ≥ 4 visits during the previous year for hypertension or diabetes who received treatment for these conditions at each visit no patients being unable to answer a questionnaire	18 community health centres n=1096, of them n= 456 with DM age (yrs): 58.3 ± 11 gender:74 % females BMI (kg/m$^{2)}$: 30.7 ± 6.2 Type of Diabetes: • DM1: 5.8% • DM2: 91.35% uncertain DM type: 2.85%	IG (9 clinics, n=229): introduction of structured clinical record with guidelines prompts after training of doctors in their use and suggestions to incorporate them in regular patient records, contact over 1 year vs. CG (9 clinics, n= 227): usual care with passively disseminated guidelines Duration: 1 year	primary: HbA1C in the diabetes group secondary: uncontrolled glycaemia (HbA1c ≥7%) in the diabetes group.	After 3 months: HbA1c (%): IG: 8.8% vs. 8.8%; MDa -1.0 (-1.1 to -0.9) HbA1c ≥7% (%): no relevant difference: 64.1 vs. 62.6; MD 0.90 (0.53 to 1.53)
Takenga 2014 RCT	Congo, urban	DM2, 35-75 yrs	n=40 20 % females age (yrs): 53.3 ± 10.1 HbA1c (%): 8.63	IG (n=20): self-management of diabetes with Mobil DIAB (telemedical approach) vs. CG (n=20): conventional therapy without telemedical system	primary: HbA1c	after 2 months: HbA1c (%): Benefit for IG: 6.73±1.59 vs. vs. 8.6±1.35 (MD -1.87 (-2.91 to -0.83)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				Duration: 60 days		
Tawfik 2016 RCT	Egypt, urban, primary care, 05/2015-09/2015	DM2 for ≥ 1 yr, 40-79 yrs attending an outpatient clinic no patients who were already using a similar medication chart, severe or terminal health conditions, or patients with behavioural health issue that could make it difficult to understand the communication	n=255 53.7 % females age (yrs): 55.7±8.35 HbA1c (%): 8.14±1.3 duration of diabetes (yrs): 8.3±1.3	IG (n=127): comprehensive cardiovascular risk communication vs. CG (n=128): standard usual care Duration: 3 months	Primary: HbA1c Secondary: Cardiovascular risk perception, diabetes self-care, cardiovascular risk scores	After 3 months: HbA1c (%): Benefit for IG: 7.5±0.8 vs. 8.12±0.9; MD -0.62 (-0.85 to -0.39) controlled HbA1c (%): 32.7 vs. 29.9
Thuita 2020 PACTR201910518676391 RCT	Kenya Secondary care recruitment 08/2016 - 10/2016	DM2, 20-79 yrs with regular attendance of an outpatient clinic Pregnancy, complications such as renal failure, congestive heart failure, or stroke	n=153 59.5 % females age (yrs). 56±11.6 Family history of DM (%): 46.6 Poor glycaemic control (%) with HbA1c>7%: 77.8 DM for 1-5 yrs (%): 58.2 % Years with DM: 6.7±6.9 Oral medications (%): 82.4 BMP (kg/m2): 27±4.6 HbA1c (%): 8.49±1.9 fasting glucose (mmol/l): 11.0±3.3	IG2 (n=51): nutrition education programme for 2 hrs /week with peer-to-peer support vs. IG1 (n=51): Education programme vs. CG (n=51): Standard care Duration: 8 weeks	Primary: metabolic syndrome prevalence (MetS) Other: anthropometry and clinical data, blood pressure, blood glucose and lipid profile, physical activity levels, food intake	After 6 months: Metabolic syndrome prevalence: lower with IG2: Harmonized criteria:52.1 vs.69.4 vs. 91.3 (p<0.001) WHO: 58.3 vs. 77.6 vs. 89.1 (p=0.003) HbA1c (%): Mean change: no differences -2.04±2.70 vs. 1.48±2.73 vs. -0.73±2.71 High HbA1c: no differences: 47.9 vs. 29.0 vs. 34.8 % fasting glucose (mmol/l): no differences: -2.59±0.66 vs. -2.95±0.64 vs. -1.55±0.68 high fasting glucose: 79.2 vs. 83.7 vs. 91.3 %

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	Population Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Webb 2015 NCT01275040 Cluster RCT	South Africa, urban, primary care, 06/2010-03/2011	primary health care clinics, patients with clinical diagnosis of DM2 or DM1 for ≥5yrs, age ≥ 18 yrs	n= 12 primary health care clinics n= 599 gender:68.5 % female age (yrs): 57.8±10.5 HbA1c (%): 8.73±2.3 HbA1c ≥ 7 %: 73 % BMI (kg/m$^{2)}$: 30.8±6.7 Typ of diabetes: • DM1: 3.7 %, • DM2: 70.3 % • unknown: 26 % duration of Diabetes: • < 5 yrs: 47.3 % • 5-10 yrs: 22.0 % • > 10 yrs: 20.2 % • unknown: 10.5 %	IG (n=328): mobile screening team visits primary care clinic and provides education and active screening for diabetic complications (foot, kidney, cardiac and renal complications) vs. CG(n=273): no mobile screening team, routine care with similar education for patients. and health care workers Duration: 1 yr	Primary: HbA1c, detected neuropathy, nephropathy and retinopathy, HbA1c categories Secondary: detected complications, referred patients for complication assessment or care, blood pressure and lipid control, costs, LDL cholesterol, creatinine	after 12 months HbA1c (%): no difference: 8.54±2.11 vs. 8,76 ±2.2, MD-0.22 (-0.64, 0.20) screening rate for complications: in IG 60% increase of screening in all complication indicator groups, in both groups testing of HbA1c and renal complications (serum-creatinine) increased , but no significant difference , screening for eye complications, only increased significantly in IG no significant difference in the proportion of actions taken beween IG and CG (p=0.83)
Strategies to enhance physical activity						
Asuako 2017 RCT	Ghana, urban, tertiary care, 08/2015-03/2016	DM, age: 20-68 yrs, ambulant patients, without diabetes complications with < 150 minutes /wk of moderate physical activity no SBP > 140 or DBP> 90 mmHg, bilateral or unilateral lower or upper limbs amputation, use of insulin pump	n=12 83% female age (yrs): 83% were 46-55 yrs. BMI (kg/m²):25.4±4.5 fasting glucose (mmol/l):9.33 ± 5.7 type of diabetes: DM1: 17 % DM2: 83 % duration of diabetes (yrs): • 1-5 yrs: 25 % • 6-10 yrs: 50 % • 10 yrs: 25 %	IG (n=7): walking aerobic exercise sessions without treadmills (3/week) vs. CG (n=5): only activity of daily living Both continued regular medical/clinical routines Duration: 8 weeks	FPG, Lipid profile, body weight, BMI	Change over 2 months: FPG (mmol/l): Benefit for IG: 6.27 ± 0.91 vs. 8.00 ± 0.96; MD 1.73 (-1.88 to -1.59; p<0.001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Fayehun 2018	Nigeria, urban 06/2014-11/2014	DM2, age 18-64 yrs, Diagnosed ≥ 12 months, non-insulin dependent, on dietary control ± hypoglycemic agents, able to walk without limitations no pregnant women, smokers, prescription of medications that might impair ability to walk	n= 46 63 % female age (yrs): 54±7.7 (33-64) BMI (kg/m²): 22.4±3.3 HbA1c (%): 6.6 (5.3-9.0) duration of diabetes (yrs):<7 yrs: 70 %, >7 yrs 30 %	IG (n=23): Goal to accumulate 10000 steps per day vs. CG (n=23): normal activity habits Duration: 10 weeks	Primary: HbA1c Secondary: step count	Change over 2.5 months: HbA1c (%): Benefit for IG: 6.26 (6.19 to 6.33) vs. 6.82 (6.69 to 6.95); MD_a: -0.74 (-1.32 to -0.02; p=0.015)
Maharaj 2016 RCT	Nigeria, rural 07/2013-06/2014	DM2, non- insulin dependent, blood glucose levels 6 - 13 mmol/l no cardiac, abdominal or spinal surgery ≤ 6 months, history of fractures of lower limbs, spine, weakness, deformities, loss of sensation in the feet, retinopathy, nephropathy	n=90 52 % females age (yrs): 39.4 ± 8.6 (30-58) BMI (kg/m²): 27.7±5.8 HbA1c (%): 8.79±2.11 duration of diabetes (yrs): 2.5±2.1	IG (n=45): rebound exercise 3 times/week for 20-30 min, moderate intensity of 40-60 % of HR maximum vs. CG (n=45): watched videos and read health magazines Duration: 9 weeks	Primary: HbA1c , FPG, BMI Other: Heart and respiratory rates, blood pressure, oxygen saturation	After 9 weeks HbA1c (%): Benefit for IG: 7.12±1.19 vs. 8.36±1.25; MD_a: 0.904 (0.832 to 0.984; p=0.017) FPG (mmol/l): Benefit for IG: 6.92±1.21 vs. 8.73±1.23; MD_a: 0.787 (0.7345- 0.841; p=0.002)
van Rooijen 2004 RCT	South Africa, urban 03/2002-11/2002	black women with DM2, age 40-65yrs, duration of DM ≥12 months no chest pain on effort, possible previous myocardial infarction and intermittent claudication, cerebro-vascular incidents, arthritis, retinopathy	n=158 gender:100 % females age (yrs): 54-55 HbA1c (%): 9.35	IG (n=80): education+ incremental daily home exercise, use of daily physical activity records+6 fortnightly supervised aerobic exercise classes vs. CG(n=77): education+ relaxation exercise Duration: 12wks	Primary: HbA1c, BMI Secondary: walking distance (6 min walk)	Change over 3 months: HbA1c (%): no difference: 8.99±2.59 vs. 8.26±1.97
Yan 2014	Mozambique,	DM2, male, age 40-70 yrs, diagnosis for ≥ 12 months	n=41 100% male	IG (n=31): low or vigorous intensity	plasma glucose, HbA1c	Change over 3 months: HbA1c (%):

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	urban	no known diseases other than DM2 and hypertension, no diagnosed cardiovascular diseases	age(yrs): 54±2.5 HbA1c: 8.6±0.7 plasma glucose (mmol/l): 9.65±1.2 BMI ($kg/m^{2)}$: 27.1 ± 1.0	exercise 3-5 times/week vs. CG(n=10): walked 1 hour per day as part of their daily lifestyle Duration:12 wks		reduction in both groups with no differences between groups: 7.7±0.4 vs. 7.7±0.8 Plasma glucose (mmol/l): 9.6 ± 0.7 vs. 11.1 ± 1.3
Pharmacological strategies						
Distiller 2014 RCT	South Africa	DM2 for ≥ 1 year with total insulin requirement of >200 U/d for ≥ 3 months, BMI > 30 kg/m^2, HbA1c> 7,5 %, on long-term metformin therapy (1.7–2.5 g/d) no pregnant or with childbearing potential, endocrinopathy, chronic inflammatory or systematic autoimmune disorder, CVD, active carcinoma, chronic illness, renal dysfunction, gastroparesis, no corticosteroids, DPP-4 inhibitors, exenatide, liraglutide, no anticipated change in other concomitant medication or insulin resistence	n=28 50% female age (yrs): 51.7 (36-71) HbA1c (%): 8.95 (7.6-11.3) BMI (kg/m^2): 40.8 (31.2-47)	IG (n=14): regular Insulin (500 U/ml) + metformin + exenatide (5 µg orally twice a day for 1 month and titrated to 10 µg) vs. CG (n=14): regular Insulin (500 U/ml) +metformin Duration: 6 months	Primary: HbA1c Secondary: Body weight, insulin dose, hypoglycemia	Change to 6 months: HbA1c (%): Significant improvement in both groups 8.7→7.7(p=0.002) vs. 9.2→7.5 (p=0.0001) With no difference between groups (MD: 0.28; p=0.80) Complications: Mild hypoglycaemia: 5 vs. 2 persons with 20 vs. 5 events (p ≤ 0.001)
El-Haggar 2015 RCT	Egypt, urban 01/2013-04/2014	DM2, age: 45-55 yrs, obese (BMI≥30 kg/m^2), with duration 5-10 yrs, treated with glimepiride alone no Inflammatory disease,	n=48 79 % female age (yrs): 50.1±4.6 HbA1c (%): 7.83±0.87 fasting glucose (mg/dl): 193±50	IG1 (n=16): glimepiride (3 mg/d) + 2 (1 mg twice/d) vs. IG2 (n=16): glimepiride (3 mg/d) +	not specified: glycemic markers, metabolic markers, adiponectin, interleukin-6, leukotriene B4, mast cell tryptase, lipid panel,	Changes over 12 weeks: HbA1c (%): • Highest benefit for IG1: 7.1±0.86 vs. 8.2±0.82 vs. 8.7±0.93 (p< 0.05) fasting glucose (mg/dl): • Highest benefit for IG1: 199±38 vs.

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		severe hepatic or renal disease, epilepsy pregnant/lactating females	BMI (kg/m²): 37.6±4.6 duration of diabetes (yrs): 7.7 ±2.6	ketotifen (1 mg once/d) vs. CG (n=16): glimepiride (3 mg/d) alone Duration: 12 weeks	BMI	207.7± 47.6 (p< 0.05)
Malek 2015 RCT	Egypt, Algeria, Tunesia, South Africa 03/2010-05/2012	DM2, age ≥ 18 yrs, currently treated with suboptimal dose of oral anti-diabetic drugs; HbA1c 7-11 % (under metformin-monotherapy) and ≤ 10 % (under combination therapy), BMI≤40 kg/m² no allergies or contraindications to the product, pregnant or breastfeeding, impaired hepatic or renal function, cardiovascular history, uncontrolled hypertension, proliferative retinopathy, macular oedema	n=403 age (yrs): 52.8±9.6 59.8 % female HbA1c (%): 8.65 BMI (kg/m²): 29.7±4.5 duration of diabetes (yrs): 7.5±5.1	Stepwise individual insulin intensification of IG (n=200): basal-bolus insulin analogues (insulin detemir +Insulin aspart) vs. CG (n=203): thrice daily biphasic insulin aspart depending on HbA1c-values over 50 wks	Primary: HbA1c Secondary: patients achieving HbA1c < 7.0 %, prandial plasma glucose	Change over 50 weeks: HbA1c (%): Non-inferiority: 7.4 vs. 7.3; MD 0.1 (-0.1 to 0.3 (full-analysis set), MD 0.2 (-0.1 to 0.4 (per protocol) 40.3% and 44.9% achieved HbA1c<7.0% Hypoglycaemia (events/patient year): 9.4 vs. 9.8 Serious adverse events: 6.5 vs. 3.4 % with 1 treatment-related SAE in CG Adverse events: 58.5 vs. 63.1%
Strategies on food supplementation						

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Ali 2019 RCT	Egypt Urban, tertiary care 09/2017 – 04/2018	DM2, oral antidiabetic agents with no change of type and dosage of antidiabetic agents in the past 3 months, ≥ 30 years insulin-dependence, pregnancy, lactation, use of Ca, multivitamins, Vitamin D supplements, use of drugs that affect Vitamin D status, dietary Ca intake > 1500 mg/d, hypo- or hyperthyroidism, smoking, use of antiepileptic drugs, sarcoidosis, tuberculosis, potentially terminal illness, inflammatory bowel disease, liver or kidney disease, malignancy	n=85 age (yrs): 54.6 ±2.8 68 % females BMI (kg/m²): 28.6±3.3 Diabetic duration (yrs): 4.4±2.1 fasting glucose (mg(dL): 168±54.4 fasting serum insulin (µIU/mL): 18.1±8.3 HbA1c(%):8.8±1.8	oral antidiabetic agents as usual + IG 1 (n=22): continuous oral Vitamin D3 (4000 IU/ d) vs. IG 2 (n=22): intermittent regimen of Vitamin D3 (50 000 IU/ week) vs. IG 3 (n=21): single IM injection of 300 000 IU of Vitamin D3 at the start of the study vs. CG (n=20): only oral antidiabetic agents Duration: 3 months	Not specified: serum creatinine, blood urea nitrogen, total and ionized Ca, serum phosphorus, fasting glucose, fasting serum insulin, 25(OH)D3 levels, HbA1c	After 3 months: fasting glucose (mg(dL): higher decrease in IG1 and IG2: -20.9±18.1 vs. -23.0±37.9 vs. -3.5±6.9 vs. 1.0±5.6 (p<0.001) fasting serum insulin (µIU/mL): higher decrease in IG1 and IG2: -4.44±5.2 vs.-5.88±4.6 vs. -1.55±9.4 vs. 0.10±1.0 (p< 0.001) HbA1c (%):higher decrease in IG1 and IG2: -0.81±0.77 vs. -0.82±0.87 vs. -0.34±1.47 vs. 0.05±0.08 (p<0.001)
Anderson 2001 RCT	Tunesia, urban	DM2 ≥ 5y, age< 65 yrs, fasting glucose > 8 mmol/l and HbA1C > 7.5 % no pregnant or lactating women, receiving trace element supplements in past 3 months, with gastric or diuretic treatment, acute renal, acute infection or recent surgery	n=110 age (yrs): 53.2 ±16.8 BMI (kg/m²): 29.1±1.0 HbA1c (%):8.82±3.25 fasting glucose (mmol/l): 11.45±0. 83 duration of diabetes (months): 73.6±66	IG 1 (n=27): Zinc (30 mg/d) vs. IG 2 (n=27): Chromium (400 µg/d) vs. IG 3 (n=27): Zinc (30 mg /d) + Chromium (400 µg /d) vs. CG (n=29): placebo Duration: 6 months	Not specified: HbA1C, fasting glucose plasma concentrations of zinc, copper, selenium, urinary chromium and zinc, Plasma thiobarbituric acid reactive substances, copper-zinc-superoxid dismutase, selenium - glutathione peroxidase	Change over 6 months: HbA1c (%): 7.7±1.6 vs. 7.4±1.4 vs. 8.1±1.6 CG: not reported
Anyanwu 2016	Nigeria, urban	DM2, age 35-65 yrs on oral antidiabetics with vitamin D	n=42 57.6 % female	IG (n=21): Vitamin D3 supplements	Primary: HbA1c Other: fasting glucose,	Changes over 12 wks: HbA1c (%):

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT .		deficiency and poor glycemic control (HbA1c > 6.5 %) no patients on insulin, pregnancy, renal insufficiency, chronic liver disease or alanine transferase > 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state	age (yrs): 51.8±2.05 HbA1c (%): 7.88 fasting glucose (mg/dl): 152.8±56.5	(3000 IU/d) vs. CG(n=21): placebo Duration: 12 weeks	levels of serum Vitamin D, calcium, albumin, phosphate, creatinine, and alanine transaminase	• MD (IG vs. CG): -0.66 (-0.161 to 0.29) vs 0.38 (-0.08 to 0.84); • MD: -1.04 (-2.09 to 0.01) • change from poor glycemic control (HbA1c>6.5 %) to normal HbA1c (%): benefit for IF: 33.3 vs. -9.1 (p<0.05) fasting glucose (mg/dl): 137.2±33.6 vs. 154±67.5 patient adherence (tablet counts, %): 62.2 vs. 59.9
El Gayar 2019 **RCT**	Egypt, urban, outpatients 01/2017-01/2018	DM2 for < 6 months, 30-60 yrs, HbA1c level < 9%, BMI≥30 kg/m^2 no insulin therapy, any injectable or oral antidiabetic medication other than metformin, no smoking, consumption of alcohol or narcotic drugs, no acute illnesses at the baseline or during the study, no pregnancy or lactation, autoimmune disorder, cardiac or renal diseases, thyroid, chronic inflammatory diseases, peptic ulcer, regular consumption of ginger or other herbal drugs, hypersensitivity to ginger, consumption of lipid lowering drugs or oral contraceptive pills or any supplements 2 months before starting the study	n=80 49 % female age (yrs): 46.2 ± 9.1 HbA1c (%): 8.04±0.5 fasting glucose (mg/dl): 176.9±18.3 Fasting serum insulin (mIU/L): 19.3±3.3 BMI (kg/m²): 32.3±1.4	diet, physical activity, and metformin IG (n=40): ginger powder supplementation (600 mg/capsule, 3 capsules/d) vs. CG (n=40): Placebo Duration: 8 weeks	Not specified: glycemic status, lipid profile and beta-cell function	After 8 wks: HbA1c (%): decrease in both groups to 6.94±0.38 vs. 7.26±0.45 Fasting serum insulin (mIU/L): decrease in both groups to 12.86±2.59 vs. 13.21±2.08 fasting glucose (mg/dl): decrease in both groups to 120.88±9.06 vs. 151.70±13.23

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Sheikh 2019 RCT	Egypt, urban	DM2 on glimepiride alone, age ≥30 yrs no insulin sensitizers, steroids, NSAIDs, warfarin or lipid lowering medications, thyroid hormones, valproic acid or suffered from: acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism epilepsy, pregnant and breast-feeding women	n= 72 67 % female age (yrs): 50.6±8.7 HbA1c (%):9.76±1 fasting glucose (mg/dl):194.84±20.8 BMI (kg/m²): 34.4±5.45	IG (n=38): glimepiride 2 mg twice daily + L-carnitine 1 gm twice daily vs. CG (n=34): glimepiride dose 2 mg twice daily Duration: 6 months	HbA1c, fasting glucose, PPBG, fasting insulin, extracellular part of insulin regulated aminopeptidase, tumor necrosis factor-alpha, visfatin and lipid panel, BMI and homeostasis model assessment of insulin resistance	Change over 6 months: HbA1c (%): Benefit for IG: 7.41±0.5 vs. 9.5±0.78 (p<0.001) fasting glucose (mg/dl): Benefit for IG: 179.6±9.3 vs. 192.41±27.4 (p=0.018)
Matter 2020 NCT03851055 RCT	Egypt, urban, outpatients 08/2017 to 08/2018	DM, treated with insulin, 10 to 18 yrs, transfusion dependent beta-thalassemia major no other hemoglobinopathies (e.g. a-thalassemia or sickle thalassemia, disorders that may affect glucose homeostasis other than b-TM, autoimmune diseases, collagen diseases, hypo- or hyperthyroidism, infections, or tumours, or those who were taking any vitamins or food supplements < 1 month before the study and participating in a previous investigational drug study within 3 mo preceding screening	n=80 52.5% females age (yrs): 16.3±1.4 (range 12-18) fasting glucose (mg/dL): 144.5±22.4	diet schedule with optimal macronutrient distribution and pharmacologic treatment IG (n=40): zinc gluconate (2x20 mg/d) vs. CG (n=40): placebo Duration: 3 months	Primary: fasting glucose Secondary: fructosamine, fasting C-peptide, and HOMA-IR safety: any AEs (e.g. nausea, vomiting, abdominal pain, diarrhea, constipation, and reduction of appetite)	After 12 wks: fasting glucose (mg/dL): higher decrease with IG to 116.9±4.6 vs. 144.5±22.9 (p<0.001) HbA1c (%): higher in IG (no results reported) no side effects were reported
Moustafa	Egypt,	DM2, newly diagnosed	n=62	IG (n=29, 21 analysed):	Glycemic control,	After 3 months:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
2019 RCT	urban, outpatients recruitment 02/2016-03/2018	(within a time duration ≤6 months), 18–60 yrs other antidiabetic medications, pregnant and lactating women, major organ dysfunction (hepatic failure, active hepatitis, liver cirrhosis or renal complications), changed their standard medications during the 12 weeks of the study	72% females HbA1c(%): 7.51±1.4 fasting glucose (mg/dl): 154.4±51.6 BMI(kg/m^2): 33.9±6.1 family history of DM (%): 78.5 retinopathy/altered vision (%): 53 GDM (%): 9.2	nigella sativa oil capsules (3x 450 mg/d) vs. CG (n=33, 23 analysed): metformin (2000 mg/d) Duration: 3 months	oxidative stress markers, biochemical parameters, weight/BMI/waist circumference, total antioxidant capacity TAC	HbA1c (%): no difference: 7.01±0.83 vs. 6.55±0.72 fasting glucose (mg/dl): no difference: 119.8±23.7 vs. 120.7±25.4 Complications: no differences in occurrence of chills, sweating, tachycardia, lethargy/ weakness, polydipsia, polyuria, dry skin, polyphagia, blurred vision, foot problems, or tingling/numbness foot problems lower in IG: 4.8% vs. 33.3%, (p = 0.025).
Ragheb 2020 NCT03437902 RCT	Egypt, urban, outpatients care 02/2019-05/2018	DM2, receiving standard oral hypoglycemic agents, ≥ 35 yrs, no history of overt vascular disease, renal or hepatic failure or antioxidant supplementation or insulin therapy, no change of oral hypoglycemic drugs	n=70 age (yrs): 54.9±8.4 70 % females BMI (kg(m^2): 32.5±5.7 HbA1c(%): 8.50±1.86 fasting glucose (mg/dl): 142.8±52.6	IG2 (n=20): Rutin (60) + vitamin C (160 mg) 3x daily vs. IG1 (n=20): Vitamin C (500 mg) 1x daily vs. CG (n=13); only usual oral antidiabetic treatment Duration: 8 weeks	Primary: HbA1c, oxidative stress marker, antioxidant capacity, insulin resistance, lipid profile Secondary: Quality of life	After 2 months: HbA1c (%): no difference 7.494 ± 1.72 vs. 8.504 ± 2.059 vs. 8.504 ± 2.059 (p=0.1882) fasting glucose (mg/dl): lower in IG2 and CG: 111.3 (IQR 93.3-135.2) vs. 144 (114.8-201) vs. 113.3 (94-152.2) (p=0.017) Quality of life (SF 36): • Benefit of physical functioning and energy domains in IG2 vs. CG (p=0.0049, p=0.0253). • Benefit of role limitation to physical health and emotional improved in IG1 vs. CG (p=0.0267,p=0.0280) • no difference between groups in the other domains (emotional well-being, social functioning, pain and general health)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Rashad 2017 RCT	Egypt, urban	DM2, 50-62 yrs no insulin medication, allergies, recent thromboses or uncontrollable hypertension	n=34 43.3 % female age (yrs): 55.5±6.15 HbA1c (%):6.75±1.2 fasting glucose (mmol/l): 8.5±1.4 postprandial plasma glucose(mmol/l): 15.6±3.3 BMI (kg/m²):28.55±4 type of diabetes duration of diabetes (yrs): 6.1 ± 2.2	IG (n=17): Balanites aegyptiaca extract (400 mg)) vs. CG: (n=17) placebo capsules (potato maltodextrin) Duration: 8 wks	glycemic markers, lipid profile, FPG	Change over 8 wks: 2h postprandial plasma glucose: benefit for IG :26.88% decrease vs. CG 2.6% increase FPG (mmol/l): benefit for IG: 7.8 ± 0.9 vs. CG: 8.5 ± 1.1
Somanah 2012 NCT01248143 RCT	Mauritius, urban/rural 11/2010-03/2011	newly diagnosed DM, age 25–60 yrs fasting glucose range: 5.1–5.9 mmol/L no secondary complications, non-smoker or stopped for > 6 months , alcoholic consumption < 2 standard drinks/day, post-menopausal women without hormone replacement treatment, no glucose-lowering, cholesterol-lowering or anti-hypertension treatment	n=127 47% female age (yrs): range 25–60 HbA1c (%): 5.99±0.4 fasting glucose (mg/dL): 93.2±8.0 BMI (kg/m²): 26.6 ± 3.7	IG (n=44): supplementation of a fermented papaya preparation (6g/d twice daily, over 12 wks), followed by a 2 week wash out period with the same amount of water vs. CG (n=56): consumed an equivalent amount of water Duration: 14wks	HbA1C fasting glucose, Lipid profile, diet score, blood pressure, alanine aminotransferase; aspartate aminotransferase, Ferritin, c-reactive protein, uric acid, microalbumin/urinary creatinine ratio	After 14 wks: HbA1c (%): no difference (p=0.448) fasting glucose (mg/dL): • remained relatively unchanged in boths genders: • males: 96.2±17.0 vs. 87.6±11.7 • females: 95.6±15.8 vs. 94.3±5.0
Strategies on treatment of DM related complications						

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Makaky 2020 NCT03783845 RCT	Egypt, urban/rural recruited 06/2015 to 03/2016	DM2 for >5 yrs, 40-70 yrs, HbA1c 7 to 9% at the last medical evaluation, no change in diabetes treatment over the previous 3 months, ≥ 6 permanent teeth excluding third molars, clinical attachment level and pocket depth ≥4 mm in >30 % of the sites, diagnosis of chronic periodontitis based on the presence of 4 teeth as a minimum with ≥ 1 site Pregnancy, alcoholism and smoking, Presence of any systemic disorders other than hypertension and diabetes, diabetic major complications, antimicrobial therapies or periodontal therapies in the last 6 months, allergy to metronidazole and amoxicillin	n=88 56.8 % females age (yrs): 52.6±6.8 HbA1c (%): 8.16±0.72	IG (n=44): immediate periodontal therapy: one-stage scaling and root planning, a combination of systemic antibiotics (amoxicillin 500 mg and metronidazole 400 mg 3x/day for 2 weeks), and oral hygiene instructions vs. CG(n=44): delayed periodontal therapy after 3 months Duration: 3 months	Primary: HbA1c Secondary: not named	After 3 months: HbA1c (%): benefit for IG: 7.27±0.5 vs. 8.34±0.64: MD -1.07 (-1.32 to -0.83)
El-Sharkawy 2016 NCT02794506 RCT	Egypt, urban 06/2014-03/2015.	DM2 >5 yrs, >20 teeth, chronic moderate or severe periodontitis with probing depth and clinical attachment level >5 mm, bleeding by probing, on oral hypogylcemic drug therapy > 6 months, no smoking, use of	n=50 34% female age (yrs): 50.5 ± 7.4 (38 to 63) HbA1c (%): 8.66 ±0.73 FPG (mg/dl): 183.5 ±12.547 BMI (kg/m²): 26.9± 3.1 duration of diabetes	IG (n=24): scaling and root planing (SRP)+ 400mg oral Propolis once daily vs. CG (n=26) scaling and root planing (SRP)+Placebo Duration: 6 months	Primary: HbA1c Secondary: FPG, serum N-(carboxymethyl) lysine, periodontal parameters	after 6 months HbA1c (%) Benefit for IG 7.75± 0.48 vs.8.5±0.73 (p<0.01) FPG(mg/dl) Benefit for IG

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		antibiotics, non-steroidal or anti-inflammatory drugs within the last 3 months, periodontal therapy ≤ 1 year, retinopathy grade 3/4, pregnancy, no contraceptive drugs	(yrs): 8.1 ± 3.9 hypertension: 4.5% neuropathy: 1.5% retinopathy: 0.5% nephropathy: 0%			
Ghoneim 2013 RCT	Egypt, 03/2010-03/2012	DM, duration ≥ 15 yrs, bilateral diabetic macular edema (≥ 6 months) no prior treatment with intravitreal corticosteroids, peribulbar steroid injection within ≤ 6 months, pars plana vitrectomy, history of glaucoma or steroid induced IOP elevation, ischemic maculopathy, foveal tracted, IOP≥ 23 mmHg	n=19 (38 eyes) 89.5 % female age (yrs): 52.3±11.4	IG (n=19): one eye with 8 mg triamcinolone acetonide vs. CG (n=19): other eye with4 mg of triamcinolone acetonide Duration: 6 months	Primary: Visual acuity Others: Intraocular pressure (IOP), IOP lowering drugs, complications	after 6 months: Complications: • no eyes with retinal detachment, vitreous haemorrhage, intraocular reaction or endophthalmitis. • one eye in IG developed posterior subcapsular cataract.
Nteleki 2015 RCT	South Africa, urban	DM2 with neuropathic or mixed (venous and arterial) ulcers; lower extremity ulcer; stable or worsening ulcer that has been present for ≥ 4 weeks no acute cellulitis, osteomyelitis, or gangrene, renal, hepatic, hematologic, neurologic, or immune disease not related to diabetes; presence of malignant disease not in remission for > 5 years; use of oral or parenteral	n=7 with 14 lower extremity ulcers 85 % male age (yrs): 62 duration of diabetes (yrs): 16.7	standard podiatric management and IG1 (n=2): phototherapy to the regional lymphatic nodes and ulcer(s) vs. IG2 (n=3): phototherapy on the ulcer vs. CG (n=2): placebo phototherapy Duration: 12 weeks	healing rate (area and perimeter of the ulcer)	after 3 months: Healing: • The rate of healing increased in all three groups, • 67% of ulcers received some form of phototherapeutic intervention, 40% of those ulcers resolved completely over 8 weeks no AEs

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		corticosteroids, immunosuppressive, or cytotoxic agents; known infection with human immunodeficiency virus or presence of AIDS; other leg ulcers				
Saeed 2013 RCT	Egypt, urban 11/2010-07/2012	DM, intractable diffuse diabetic macular edema without vitreomacular traction. central foveal thickness ≥300 µm no vitreomacular traction, active neovascularization of proliferative diabetic retinopathy, an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography, treatment for diabetic macular edema within ≤ 3 months, previous vitreoretinal surgery, other major ocular surgery within the previous 6 months, YAG capsulotomy within ≤2 months, macular pathology	n= 34 (34 eyes) 50% females age (yrs): 55.5 ± 8.9 duration of diabetes (yrs): 24±5.4	IG (n=15): vitrectomy with removal of the posterior hyaloid, at the end of the procedure injection of intravitreal triamcinolone acetonide (IVTA, 0.1 mL, 40 mg/mL) +bevacizumab (1.25 mg) +macular grid laser photocoagulation vs. CG (n=15); same intravitreal injection combination Duration: 12 months	primary: BCVA, central foveal thickness	Changes over 12 months Complications: • Changes in BCVA and central foveal thickness at 3, 6, and 12 *(P*< 0.01), better mean BCVA in IG at 12 months. • Better mean central foveal thickness in IG at 12 months. Major adverse events: development of cataracts (3/15 vs. 6/15) and elevation of intraocular pressure (7/15 vs. 2/15)
Tsobgny-Tsague 2018 NCT02745015 RCT	Cameroon, urban, tertiary care, 12/2014-	DM2, >11teeth, severe chronic periodontitis according to the 2012 CDC-AAP classification, no periodontal treatment,	n=34 56% female age (yrs): 51.4 ± 8.8 HbA1c (%):9.3 ± 1.3 BMI (kg/m²): 28.3± 5.4	IG (n=17): immediate ultrasonic scaling, scaling and root planning +subgingival 10% povidone iodine irrigation	Primary: change in HbA1c Secondary: Plaque index, gingival bleeding index, pocket depth, clinical attachment loss	Change over 3 months: HbA1c (%): Benefit with IG: 6.7 ± 2.0 % vs. 8.1 ± 2.6 %, MD: 2.2 (p=0.029) adverse events: 1 /15 patient reported tongue

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
	05/2015	alteration of DM treatment 6 mths prior to the study, onset of systemic diseases or an acute condition, use of immunosuppressive medications or others drugs or presence of conditions able to alter periodontitis clinical features	duration of diabetes (months): 55.5 ± 42.6 complications: neuropathy (%): 40 nephropathy (%): 7 retinopathy (%): 7 diabetic foot (%): 3	vs. CG(n=17): periodontal treatment 3 months later Duration: 3 months		irritation following chlorhexidine moth rinse in IG
Yakoot 2019 NCT01531517 07/2011-07/2013 RCT	Egypt, urban	Adult DM2 or DM1 patients, limb-threatening diabetic foot ulcerations no life-threatening extensive gangrenous lesions that needed immediate amputations; bad general condition; shock or unstable vital signs; critically ill with severe organ/system dysfunctions or advanced malignancy.	n=119 gender:44.5% female age (yrs): 54.7 ±8.4 type of diabetes: • DM1: 22.9% • DM2: 86.2%	conservative debridement of necrotic tissue and irrigation with warm normal saline and IG (n=61): local application of ointment composed of royal jelly and panthenol vs. CG (n=58): local application of Panthenol duration: 12months	primary: complete healing secondary: reduction of infection in the ulcer site, al reaction that may be due to study drug	after 12 months rate of complete healing (%): Benefit for IG: 32.4% vs. 12%; p=0.034

ADA: American Diabetes Association; BCVA: Best-corrected visual acuity; BMI: Body mass index; CG: Control group; CI: Confidence interval; CHC: Community health centre; DBP: Diastolic blood pressure; DM: diabetes mellitus; DM1: Type 1 diabetes; DM2: type 2 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG: intervention group; IQR: interquartile range; n: number of participants; NCD: Non-communicable disease; NPH: neutral protamine Hagedorn; MD: mean difference; MDa: adjusted mean difference; NCD: Non-communicable disease ;RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SAE: Serious adverse events; SBP: Systolic blood pressure; SCI: Diabetes Self-Care Inventory; SD: Standard-deviation; SMBG: self-monitoring of blood glucose; wks: weeks; yrs: years

Table 4: Characteristics and results of studies on patients with DM2

RCTs on pregnant DM patients

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value	**Study name** registration number Design
Strategies to increase physical activity						
Embaby 2016 RCT	Egypt, urban, 07/2014-02/2015	at increased risk for GDM due to obesity (BMI ≥ 30 kg/m²), age:> 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2 no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease, cardiac, renal impairment and malignancy	n=40 100% female age (yrs): 29.2±3.8 BMI (kg/m²):28.7±1.3 fasting glucose (mmol/l): 6.5±0.9 fasting insulin (IU/l): 15.78±1.58	IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives. Duration: appr. 4 months	Fasting plasma glucose, Insulin level	Change to 37th week of gestation: FPG (mmol/l) Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001) Fasting insulin (IU/l): Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)
Other non-pharmacological therapies						
El-Shamy 2018 RCT	Egypt, urban 12/2016-05/2017	GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus no high-risk pregnancy, bad obstetric situations or diseases, smoking, oral sedatives	n=30 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): • fasting glucose: 129.05±0.6 • 2h postprandial: 146±1.65 BMI (kg/m²): 27±1.5	IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only Duration: 12 weeks	Primary: glycemic control, requirement for insulin, insulin resistance Secondary: neonatal outcomes	Change over 3 months: 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9 Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %

Utz 2018 NCT02979756 Cluster-RCT	Marocco, urban / rural, primary care, 11/2016-02/2018	Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM no DM2, DM1	20 health centres n= 215 age (yrs):27.6±6.6 urban (%): 38.5 rural (%): 61.5	20 clinics were randomized→ 10 in each group IG (n=120): first screening for GDM→positive tested women received counselling on nutrition and exercise vs. CG (n=95): routine practice	Primary: birthweight Secondary: maternal weight gain, glucose control, pregnancy complications.	Follow-up visits: 7.5±4.9 vs. 3.8±3.3 (p=0.001) FBG within the norm: better with IG <1/3 of all values: 7.6 vs. 32.6 % 1/3-2/3 of all values: 17.8 vs. 32.6 % >2/3 of all values: 74.6 vs. 34.8 % Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)
Pharmacological strategies						
Ashoush 2016 RCT	Egypt, urban, tertiary care 01/2014-11/2014	GDM, mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glycemic control despite adequate diet and exercise for ≥ 1 wk no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis	n=95 100% female age (yrs): 31.8±3 HbA1c (%): 5.75 ± 0.55 75g OGTT (mg/dl) • fasting: 106.05±4.6 • 1h:310.25±11.6 • 2h:176.65±9.4 BMI (kg/m²): 31.2±1.4	IG (n = 47): metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed) vs. CG (n = 48): regular insulin + neutral protamine Hagedorn (3:7) (starting dose 0.7 units /kg*d, adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed) Duration: until delivery	Primary: successful maternal glycemic control Secondary: maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit	Until delivery: fasting glucose during treatment (mg/dl): better with IG: • during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008) • during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029) maternal hypoglycaemia (%): no difference: 6.25 vs. 12.5 (p=0.254) neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p=0.791) Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001) neonatal congenital anomalies (%): 2.1 vs. 2.1 p= 0.747 headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy) neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514) Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)

Beyuo 2015 ACTRN12614000942651 RCT	Ghana, urban 01/2013-12/2013	pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy no T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin	n= 104 100% female age (yrs): 33.3±4.6 fasting glucose (mmol/l): 8 2HPG (mmol/l): 10.5 BMI (kg/m²): 3.1±6.6 type of diabetes: GDM (%): 65.9 DM2 (%): 34.0	IG (n=52): Metformin (starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary) vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg, titrated to achieve the glycemic targets, if necessary, admission to the ward and therapy with soluble insulin) Duration: until delivery	Primary: 2-hour post prandial blood glucose (2HPG) Secondary: fasting glucose, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.	Change from enrolment to delivery: glycemic control (mmol/l): fasting glucose: no difference: 6.42±0.98 vs. 6.62±1.57 (p=0.928) 1HPG: no difference: 8.95±1.27 vs. 9.62±1.44 (p=0.078) 2HPG: benefit for IG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)
Ibrahim 2014 NCT01915550 RCT	Egypt, urban 08/2011-04/2012	GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance No DM1, secondary diabetes or liver or renal impairment	n=90 100% female age (yrs): 29.8 ± 5.4 BMI (kg/m²):31.83 ± 3.23 Gestational age: 28.7 ± 3.7 wks GDM: 43.3 % Pre-existing DM: 56.7 % with median duration of 4 (1-15) yrs	IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose Patients switched to CG if treatment was not successful to control blood glucose concentrations CG (n=44): insulin dose was increased according to the standard protocol	Primary: maternal gylcemic control (fasting glucose ≤ 95 mg/dl and 2-HPG ≤ 120 mg/dl) Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes	gylcemic control: • better for CG: 76.1 vs. 100 % reached glycemic control (p=0.001) • 13 vs. 18.2 % had readmission for poor glycemic control • 6.5 vs. 22.7 % had bouts of maternal hypoglycaemia Complications: • 23.3 vs. 30.8 % had fetal macrosomia • 1 new-born in each group had congenital malformations • 7 vs. 38.5 % had neonatal hypoglycaemia • 18.6 vs. 41 % had NICU admission • 0 vs. 5.1 % had stillbirths • 11.6 vs. 25.6 % with respiratory distress syndrome

BMI: Body mass index; CG: Control group; CI: Confidence interval; DM: diabetes mellitus; DM2: type 2 diabetes; FPG: fasting plasma glucose; GDM: gestational diabetes; HbA1c: haemoglobin A1c; 1 / 2HPG: 1 / 2-hour post prandial blood glucose; IG: intervention group; n: number of participants; MD: mean difference; MDa: adjusted mean difference; OGTT: Oral glucose tolerance test; RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SD: Standard-deviation; wks: weeks; yrs: years

Table 5: Characteristics and results of studies on pregnant women with DM

R

isk of bias

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Abaza 2017	☺	☺	☹	☺	☹	☺	☺
Abdulrhman 2013	☺	😐	☹	☺	☺	☹	😐
Adibe 2013	☺	☺	☹	☹	☹	😐	☺
Adjei 2015	😐	😐	☹	☺	☺	😐	☹
Ali 2019	😐	😐	☹	😐	😐	😐	☹
Amendezo 2017	😐	😐	☹	☺	☹	☺	☹
Anderson 2001	😐	😐	☺	☺	😐	😐	☺
Anyanwu 2016	😐	😐	☹	😐	☹	😐	☺
Ashoush 2016	☺	☺	☹	😐	☺	😐	☺
Asuako 2017	😐	☺	☹	😐	☺	😐	☹
Beyuo 2015	😐	☺	☹	😐	☹	☹	☹
Chraibi 2017	😐	😐	☹	😐	☹	☺	☹
Debussche 2018	☺	☺	☹	😐	☺	☺	☺
Distiller 2014	😐	☺	☹	😐	☹	😐	☺
Elbarbary 2016	😐	😐	☹	😐	☹	😐	☹
Elbarbary 2018	☺	☺	☺	😐	☺	☺	☺
Elbarbary 2020	☺	☺	☺	☺	☺	☹	😐
El Gayar 2019	☺	☺	☺	☺	😐	😐	☹
El-Haggar 2015	😐	😐	☹	😐	😐	😐	☹
El-Makaky 2020	😐	☺	☹	☺	☺	😐	😐
El-Shamy 2018	☹	☹	😐	😐	☺	😐	☺
El-Sharkawy 2016	☺	☺	☺	☺	☺	☺	☹
El-Sheikh 2019	😐	😐	☹	😐	☹	😐	☹
Embaby 2016	😐	😐	☹	😐	☹	😐	☹
Essien 2017	☺	☺	😐	☺	☹	😐	☺
Fairall 2016	😐	☺	😐	😐	☺	☺	☺
Fayehun 2018	😐	☺	☹	☹	☺	😐	☺
Ghoneim 2013	☺	😐	☹	😐	😐	😐	☹
Hailu 2018	☺	😐	☹	☺	☹	😐	☹
Ibrahim 2014	☺	😐	☹	😐	☹	☺	☹
Krawinkel 2018	☺	😐	☹	☹	☹	☺	☺

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Labhardt 2011	☺	☺	☹	😐	☺	☺	☺
Maharaj 2016	😐	😐	☹	☺	😐	😐	☹
Malek 2015	😐	😐	☹	😐	☺	😐	😐
Malipa 2013	😐	😐	☹	☹	😐	😐	☹
Mash 2014	☺	😐	☹	☹	☹	☺	☺
Matter 2020	☺	☺	☺	☺	☺	☹	☺
Mohamad 2009	😐	😐	☹	😐	😐	😐	☹
Moustafa 2019	😐	😐	☹	😐	☹	😐	☹
Muchiri 2015	☺	☺	☹	☺	☺	😐	☹
Nteleki 2015	☹	😐	☹	😐	☺	😐	☹
Owolabi 2019	😐	☺	☹	☺	☺	☹	☹
Rashad 2017	☺	☺	☺	☺	☹	😐	☹
Ragheb 2020	☺	😐	☹	☹	☹	☺	☺
RezkAllah 2019	☺	☺	☹	☺	☺	☺	☺
Saeed 2013	😐	😐	☹	☹	☹	😐	☹
Salem 2010	😐	😐	☹	☹	😐	😐	☹
Sodipo 2017	☺	😐	☹	😐	☹	😐	☺
Somanah 2012	😐	😐	☹	😐	☹	☹	☹
Steyn 2013	☺	😐	☹	😐	☹	😐	☺
Takenga 2014	😐	😐	☹	😐	☺	😐	☹
Tawfik 2016	😐	☺	☺	☺	☹	😐	☺
Thuita 2020	😐	☺	☹	😐	☺	😐	☺
Tsobgny-Tsague 2018	☺	😐	☹	☺	☹	☺	☺
Utz 2018	☺	☺	☹	☺	☺	☹	☹
Van der Hoogt 2017	😐	😐	☹	😐	☹	😐	☹
Van Rooijen 2004	☺	☺	☹	☺	☺	😐	☹
Webb 2015	😐	😐	😐	☺	☹	☺	😐
Yakoot 2019	😐	☺	☹	☹	☺	☹	☹
Yan 2014	😐	😐	☹	😐	☺	😐	☹
☺: low, 😐: unclear, ☹: high risk of bias							

Table 6: Judgements on risk of bias

Supplement 2

Search strategies

Medline (Ovid)

Search on 19.11.2018, 1470 references, Update from 2018 to Current on 20.08.2020: 541 references

Nr.	Searches
1.	exp Diabetes Mellitus/
2.	Diabetes.tw
3.	**or/1-2**
4.	Africa.tw
5.	Exp Africa/
6.	Algeria$.tw or exp Algeria/
7.	Angol$.tw or exp Angola/
8.	Benin$.tw or exp Benin/
9.	Botswan$.tw or exp Botswana/
10.	Burkina Faso.tw or exp Burkina Faso/
11.	Burund$.tw or exp Burundi/
12.	Cameroon$.tw or exp Cameroon/
13.	Cape Verde.tw or exp Cape Verde/
14.	Central African Republic$.tw or exp Central African Republic/
15.	Chad$.tw or exp Chad/
16.	Comoros$.tw or exp Comoros/
17.	Cote d'Ivoire.tw or exp Cote d'Ivoire/
18.	Democratic Republic of Congo.tw or exp Democratic Republic of Congo
19.	Djibout$.tw or exp Djibouti/
20.	Egypt$.tw or exp Egypt/
21.	Equatorial Guinea$.tw or exp Equatorial Guinea/
22.	Eritrea$.tw or exp Eritrea/
23.	Ethiop$.tw or exp Ethiopia/
24.	Gabon$.tw or exp Gabon/
25.	Gambia$.tw or exp Gambia/
26.	Ghana$.tw or exp Ghana/
27.	Guinea$.tw or exp Guinea/
28.	Guinea-Bissau.tw or exp Guinea-Bissau/
29.	Kenya$.tw or exp Kenya/
30.	Lesoth$.tw or exp Lesotho/
31.	Liberia$.tw or exp Liberia/
32.	Libya$.tw or exp Libya/
33.	Madagascar$.tw or exp Madagascar/
34.	Malawi$.tw or exp Malawi/

Nr.	Searches
35.	Mali.tw or exp Mali/
36.	Mauritania$.tw or exp Mauritania/
37.	Mauritius$.tw or exp Mauritius/
38.	Morocc$.tw or exp Morocco/
39.	Mozambique$.tw or exp Mozambique/
40.	Namibia$.tw or exp Namibia/
41.	Niger.tw or exp Niger/
42.	Nigeria$.tw or exp Nigeria/
43.	Rwanda$.tw or exp Rwanda/
44.	(Sao Tome and Principe).tw
45.	Senegal$.tw or exp Senegal/
46.	Seychell$.tw
47.	Sierra Leone.tw or exp Sierra Leone/
48.	Somalia$.tw or exp Somalia/
49.	South Africa$.tw or exp South Africa.de
50.	South Sudan.tw or exp South Sudan/
51.	Sudan$.tw or exp Sudan/
52.	Swaziland$.tw or exp Swaziland/
53.	Tanzania$.tw or exp Tanzania/
54.	Togo$.tw or exp Togo/
55.	Tunisia$.tw or exp Tunisia/
56.	Uganda$.tw or exp Uganda/
57.	Zambia$.tw or exp Zambia/
58.	Zimbabwe$.tw or exp Zimbabwe/
59.	Somaliland$.tw or exp Somaliland/
60.	Sahrawi Arab Democratic Republic.tw.
61.	or/4-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	(randomized or randomised or randomly).ti,ab
65.	placebo.ti,ab.
66.	trial.ti,ab.
67.	groups.ti,ab.
68.	or/62-67
69.	3 and 61 and 68
70.	exp animals/ not humans.sh.
71.	69 not 70
72.	71 not (comment or editorial).pt.

CENTRAL

Search on 14.01.2019, 439 trials, Update from 2018 to Current on 20.08.2020: 244 trials

1	Africa, explode all trees
2	Algeria* or Angol* or Benin* or Botswan*
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)
4	Chad* or Comoros* or Cote d'Ivoire or Congo*
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor Diabetes, this term only
14	MESH descriptor Diabetes mellitus, explode all trees
15	Diabetes near 3 gestation*
16	Latent autoimmune diabetes in adults
17	Prediabetes
18	Insulin resistan*
20	HBA1C
21	Diabet* near 3 (angiopath* or foot orfeet or retinopath*)
22	Diabet* near 3 (cardiomyopathy* or coma or ketoacido* or neuropath*)
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
32	#12 and #23

CINAHL

Search on 20.08.2020: 19 results

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$

or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract
AND
diabetes in Abstract
AND
randomized or rct or randomized in Abstract
AND
In English
AND
Peer-reviewed
And
Humans

International Clinical Trials Registry Platform

Search on 9.-10.10.2019, update on 25.08.2020 (registration January 2019 to 31.08.2020)
http://apps.who.int/trialsearch/AdvSearch.aspx

1. Africa or African in the Title and diabetes or diabetic or HbA1c in the condition, Recruitment status: all**:** 90 records for 90 trials (9.10.2019)
2. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Central African Republic or Chad or Congo or Cite D'ivoire: 96 record for 63 trials
3. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia: 292 records for 159 trials
4. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Lybia: 22 records for 22 trials
5. diabetes or diabetic or HbA1c in the condition

Recruitment status: all

Countries of recruitment: Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique: 96 records for 34 trials

6. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Nigeria: 13 records for 13 trials

7. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Namibia or Niger or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Sudan or Sudan or Swaziland:

   11 records for 11 trials

8. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: South Africa: 1528 records for 429 trials:

9. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Togo or Tunesia or Ujanda or Zambia or Zimbabwe: 129 records for 50 trials

African Journals Online

https://www.ajol.info/index.php/index/search/search?query=%28diabetes+or+diabetic+or+hba1c%29+and+%28random+or+randomized+or+randomised%29&dateFromYear=2004&dateFromMonth=01&dateFromDay=1&dateToYear=2020&dateToMonth=10&dateToDay=14&authors=

Advanced search 14.10.2020
Titel: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
30 results

African Index Medicus Database

http://indexmedicus.afro.who.int/aim/opac_css/index.php?lvl=search_result&get_query=4

Advanced search 14.10.2020
Titel, Expression booléenne: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
122 results, no potentially eligible references

1 List of included and excluded studies

1.1 List of included studies

Abaza 2017

Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC public health. 2017;17(1):962.

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Randomized controlled trials on prevention, diagnosis, and treatment of diabetes in African countries - a systematic review

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ABSTRACT

Objectives The epidemiological transition from infectious to chronic diseases leads to novel challenges in African health systems. The prevalence of diabetes mellitus (DM) is increasing dramatically. Undiagnosed and undertreated DM leads to numerous complications including end-organ damage and death. Our objectives were to collect the best locally generated evidence on DM interventions, identify knowledge gaps, and determine underexplored research areas.

Design A systematic review and meta-analysis of randomized controlled trials.

Participants and setting African patients in primary, secondary and tertiary prevention, diagnosis and treatment DM type 1 (DM1), type 2 (DM2) and gestational DM (GDM).

Outcome All-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs.

Data sources Articles published in MEDLINE Ovid, CENTRAL, CINAHL, African Journals Online and African Index Medicus and the International Clinical Trials Registry Platform in English language without time restrictions. The systematic search was last updated in October 2020.

Results Out of 3736 identified publications, we included 60 eligible studies conducted in 15 countries, 75 % were conducted in urban health care settings, including 10,112 participants. We included eight studies on DM1, six on GDM, two on pre-DM, 37 on mainly DM2 including seven on DM related complications. The design of the studied intervention was heterogeneous with a focus on educational strategies. The other studies investigated the efficacy of nutritional strategies including food supplementations, pharmacological strategies and strategies to enhance physical activity. Seven studies included interventions on DM-related complications.

Conclusions: Research activities increased in recent years, but available evidence is still not representative for all African countries. There is a big lack of evidence in primary health care and rural settings, implementation research, pharmacological interventions, especially in poorer countries. Nevertheless, the identified studies offer a variety of effective interventions that can inform medical care and future research.

PROSPERO registration number: CRD42019122785.

Keywords: Diabetes mellitus, Africa, systematic review, randomized-controlled trial

Strengths and limitations of this systematic review

- This systematic review includes studies at the highest level of evidence to provide an overview of the best available interventions to prevent, diagnose and treat DM in the African context.
- Inclusion criteria are restricted to randomized controlled trials conducted in African countries published in English language with no restrictions on time of publication.
- We performed a systematic search in four international databases and updated the search in October 2020.
- The main aim of our systematic review is to provide an overview of interventions for DM. Meta-analyses are restricted to regularly reported results on HbA1c as strong clinical outcome indicator of an efficient DM management.
- Limited external validity due to the origin from few countries and urban areas, results concentrate on glycemic control due to short follow-up periods.

INTRODUCTION

Diabetes mellitus (DM) and other non-communicable diseases (NCDs) are responsible for a double burden in African countries due to the epidemiological transition from communicable to non-communicable diseases and resulting disabilities and deaths (1-3). In Africa, around 19.4 million adults are living with DM. Prevalence rates range from 4.7 % in Sub Saharan Africa (SSA) to 12.2 % in the Middle East and North Africa region (4). Due to the increasing prevalence of risk factors such as obesity and westernized lifestyle, the prevalence of DM is expected to increase by 96 % in SSA until 2045 (4). Currently, about 50 to 60 % of adults living with DM in African countries are undiagnosed (4, 5). Low awareness as well as genetic differences and lifestyle habits result in very heterogeneous prevalence rates of DM between different countries in Africa as well as rural and urban regions (6, 7). Undiagnosed and undertreated DM can result in organ damage, and lead to complications like cardiovascular diseases, peripheral neuropathy, retinopathy and diabetic foot (7, 8). Moreover, these factors attribute to substantial financial costs for households and governments (9). Recently, almost one fifth of COVID-19 deaths in African countries occurred among DM patients (10).

The United Nations 2030 Agenda aims to reduce the burden of premature mortality from NCD including DM through improvement in prevention and treatment (11). Proven and effective actions to prevent or delay the onset of DM base on the empowerment of the population, patients and health care providers (12). Measures on DM include early detection in primary health-care settings, lifestyle modifications including diet, physical activity and, if necessary, medication. Primary prevention programs include lifestyle measures to reduce consumption of sugar-sweetened beverages, mandatory detailed labels on food packaging as well as education and awareness campaigns to increase physical activity are crucial since onset of DM can be detained (13). Moreover, health systems must ensure technical and financial resources as well as training of healthcare staff to recognize the symptoms of DM, to perform and interpret diagnostic tests and provide adequate treatment and care (4). Since DM patients need regular specialist assessment, a functioning referral system is necessary (14). Concerning pharmacotherapy, prioritization of metformin, gliclazide and human insulin is recommended (15). Glucometers, needles and test strips should be provided for people with DM (4).

Only a fraction of patients in African countries have access to the same treatment as recommended in high-income countries (16, 17). At the moment, most guideline recommendations in LMIC are based on studies conducted in high-income Western countries (18). These general management strategies have to be adjusted to local

contexts in African countries including environmental, cultural and social aspects like the relatively young age of patients, co-infections, long distances to health-care facilities, traditional beliefs, decision making in the families and socioeconomic status. Furthermore, there is a huge genetic diversity on the African continent (19, 20) .

The purpose of this review was to collect the best locally generated evidence, regarding preventive, diagnostic and therapeutic intervention on DM, as the lack of evidence is one of the major challenges to prevent and control DM in African countries. Therefore, we aimed to address existing knowledge gaps and identify unexplored research areas in the African context. This may support the formulation of local evidence-based strategies to systematically strengthen clinical and preventive capacities of healthcare systems in African countries.

METHODS

We prospectively registered a protocol of this systematic review in the PROSPERO International Prospective Register of systematic reviews (CRD42019122785). This systematic review follows the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (21) and the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (22).

Inclusion criteria and exclusion criteria

This systematic review includes studies conducted in African countries on the efficacy of interventions for prevention, diagnosis and treatment of patients with DM including prediabetes, type 1 (DM1), type 2 (DM2) and gestational DM (GDM). Primary outcome was defined to be all-cause mortality. Secondary outcomes included glycemic control (HbA1c, fasting serum or plasma glucose, insulin resistance, oral glucose tolerance test), quality of life, treatment adherence, hospital admissions, complications of DM and resulting costs (see Table 1 for detailed inclusion criteria).

We included full-text publications on randomized controlled trials (RCTs) (e.g. individual RCTs, cluster-RCTs and randomized cross-over trials) according to the Consolidated Standards of Reporting Trials (CONSORT) (23) published in English language. We excluded international multicenter studies with less than 50 % of sites in African countries to ensure that the study location was in Africa.

Design and setting	RCTs, mainly conducted in African countries (at least 50 % African countries in international studies)
Population	African patients in primary, secondary or tertiary prevention with a clinical diagnosis of • Prediabetes • Diabetes mellitus type 1 (DM1, due to autoimmune β-cell destruction) • Diabetes mellitus type 2 (DM2, due to a progressive loss of adequate β-cell insulin secretion)

	• Gestational diabetes (diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation) As described by the authors
Interventions	All interventions to of prevent, diagnose and treat diabetes
Comparison	Placebo or standard care Another intervention or the same intervention with a different dose or timing
Outcome	Primary: all-cause mortality Secondary: • glucose control (HbA1c, oral glucose tolerance test, insulin resistance, fasting serum or blood glucose) • complications • quality of life • hospital admission • treatment adherence Additional: costs at longest follow-up
Publications	Full-text publications according to CONSORT
CONSORT: Consolidated Standards of Reporting Trials; DM: Diabetes mellitus; DM1: Type 1 diabetes; DM2: Type 2 diabetes; GDM: Gestational diabetes; HbA1c: hemoglobin A1c; RCT: randomized controlled trial	

Table 1: Inclusion and exclusion criteria

Systematic search

We performed a systematic search in electronic bibliographic databases (MEDLINE Ovid, CENTRAL, International Clinical Trials Registry Platform of the WHO) as planned in the protocol and added a search in CINAHL andc regional electronic databases (African Journals Online and African Index Medicus) (see Online Supplemental File 1 material). All searches were performed without time constrictions. The last search was conducted in October 2020. Search strings were based on Medical Subject Headings (MeSH) and terms on DM, Africa, a list of all 54 African countries and terms related to RCTs. All references retrieved from the literature search were exported into a reference manager software (EndNote) (24). Duplicate references were identified in case of congruence of authors, title, year and journal and thusly deleted. The search strategy is available in the supplementary file.

Study selection and data extraction.

Two authors independently checked titles and abstracts based on the inclusion criteria (Table 1). The full texts of all potentially eligible papers were assessed for final inclusion. All disagreements were resolved by discussion until consensus was obtained (21). All reported information on the following were extracted and checked by another author:

- publications, registration and design,
- time and place (country, urban/ rural setting and health care setting)

- study population (inclusion and exclusion criteria, sample size and baseline characteristics on age, gender, type and length of DM, body mass index (BMI) and gylcemic control at baseline)
- intervention and control groups with the number of randomized participants per group and duration of the interventions
- outcomes (classified into primary, secondary, non-specified) and
- results on pre-planned outcomes within the longest follow up period with intervention effects with their 95 % confidence intervals (CI) and level of significance.

The study names were defined by the surname of the first author and the year of the first full-text publication of the results. We compared study and patient characteristics across studies to ensure that each included study represents a unique publication of study data. In cross-over RCTs, only data from the first period were used (25).

Quality assessment and risk of bias

Risk of bias was judged based on seven specific categories (sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) of the Cochrane risk of bias tool as 'low', 'high' or 'unclear' (22). Judgments were done by two of the authors and all discrepancies were resolved by discussion.

Judgments on blinding and incomplete outcome data were based on the primary outcome of included studies. Selective outcome reporting was defined as low when the study protocol with pre-defined primary and secondary outcomes was available and high when any result of pre-planned outcomes was missing. Incomplete outcome data was judged as high when more than 10% of randomized participants dropped out from analyses. Other sources of bias were judged as high risk of bias including missing reporting of sample size calculation, no description of a primary endpoint, and relevant differences of main baseline characteristics between intervention and control groups (22).

Data synthesis

The results of all pre-defined outcomes were described. Effect sizes on HbA1c for the longest follow-up period were visualized in forest plots using RevMan (26). Negative mean differences (MDs) describe lower HbA1c in the intervention compared to the control group. Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant. Heterogeneity was interpreted based on the

I^2 statistics as not important (I^2 < 30 %), moderate (30-60 %) and substantial (I^2> 60 %) (22).

Protocol registration

We registered a protocol of this systematic review on the PROSPERO website: https://www.crd.york.ac.uk/prospero/ under the registration number: CRD42019122785.

Patient and Public Involvement

There is no patient involved

RESULTS

A total of 2865 references were identified from electronic databases and 871 additional trials from the Clinical Trials Registry Platform were checked. We evaluated 185 potentially eligible full-text publications and included 60 eligible studies in 68 publications in this review (Figure 1 and Supplementary file).

Figure 1: PRISMA flow chart describing the process of study selection

Setting

In total 60 studies, which were conducted in 64 study centers of 15 African countries; North Africa (33 studies from four countries), West Africa (10 studies from three countries), East Africa (seven studies from 7 countries), Central Africa (three studies from two countries) and Southern Africa (11 studies only from South Africa) were included. Two studies (Malek 2015 and Chraibi 2017) were conducted in more than one African country and partially conducted in non-African countries. Chraibi (2017) was conducted in Egypt, Morocco, South Arabia and Vietnam. Malek (2015) included four study centers in Algeria, Tunisia, Egypt and South Africa. Those additional study centers are presented in brackets behind the country names in Figure 2. Egypt, South Africa and Nigeria are the three study centers included most often in this review (Figure 2 and supplemenary Table 1 available in the supplement).

Figure 2: Geographical regions, countries, and type of DM of the included studies

Seventy-five percent of the studies (45/60) were set in urban areas, 5 % (3/60) were in rural areas only. The setting of the remaining 20 % (12/60 studies) was mixed or remained unclear. The majority, 83 % (50/60) of the studies, were conducted in secondary and tertiary health care centers, while 17 % (10/60) took place in primary care settings.

Though the search had no time restrictions, the oldest eligible study (Anderson 2001) was published in 2001. More than 60 % of the studies were published since 2015, and 22 % of them had been published in 2019 or 2020 (see supplementary Table 1 available in the supplement).

Design

Fifty parallel-group studies randomized individual participants with DM. Six cluster-randomized studies (Fairall 2016, Labhardt 2011, Mash 2014, Steyn 2013, Utz 2018,

Webb 2015) randomly assigned health care facilities to intervention and control groups. In three randomized cross-over studies (Abdulrhman 2013, Krawinkel 2018, van der Hoogt 2017) each participant received different interventions in a random sequence, and in one study (Ghoneim 2013) each patient received two different treatment doses for each eye based on a random allocation of eyes and doses.

Interventions for patients with pre-DM

Two studies randomized a total of 112 overweight or obese patients (BMI 25–35 kg/m^2) with pre-DM (HbA1c 5.7-7.5 %) and a mean age of 32.9 and 47.5 years (see supplementary Table 1: Characteristics and results of studies on patients with pre-DM available in the supplement). These studies stated the efficacy regarding glycemic control of low and high volume, high-intensity interval training strategies (RezkAllah 2019), and the consumption of bitter gourd to improve glucose control (Krawinkel 2018).

Interventions for patients with DM1

A total of 8 studies were conducted including 595 patients diagnosed with DM1 (Abdulrhman 2013, Elbarbary 2016, Elbarbary 2018, Elbarbary 2020, Malipa 2013, Mohamad 2009, Salem 2010, van der Hoogt 2017) (see supplementary Table 2 Characteristics and results of studies on patients with DM1 available in the supplement). They mainly included children, adolescents, and young adults with a mean age between 10.4-19.9 years. The mean duration of DM ranged from 3.5 to 8.6 years and the mean baseline HbA1c from 7.21 to 9.52 %. The studies investigated heterogeneous strategies. Malipa 2013 showed the efficacy of weekly meetings to improve treatment compliance, reduce impact and worries about DM and improve general life satisfaction in adolescents. Salem 2010 evaluated the efficacy of two exercise programs to reduce cardiovascular risk with no relevant effect on glucose control. Three studies investigated different nutritional strategies and stated the beneficial effects of honey (Abdulrhman 2013) and camel milk (Mohamad 2009) on glucose control. Meals with low fat and protein (van der Hoogt 2017) caused less frequent hypoglycemic events. Elbarbary 2016 showed the efficacy of a low-glucose suspension algorithm during Ramadan to reduce the number of hypo- and hyperglycemic excursions. Two studies on food supplementation stated improved glycemic control with carnosine (Elbarbary 2018), but no benefit from a vitamin B complex (Elbarbary 2020).

Interventions for patients with DM2

A total of 44 studies were conducted including 8881 patients suffering from DM2 or different diabetic illnesses (see supplementary Table 3: Characteristics and results of studies on patients with DM2 availble in the supplement). Most studies included patients with a mean age between 50 and 60 years, only four studies included younger patients (Adjei 2015, El Gayar 2019, Matter 2020, Maharaj 2016). Most studies included more females than males. These studies presented a wide variety of patients in different stages of DM2 and general conditions. They ranged from newly diagnosed DM (El Gayar 2019, Labhardt 2011, Mostafa 2019, Owolabi 2019, Somanah 2012), non-insulin dependency or oral insulin therapy (Adibe 2013, Ali 2019, Fayehun 2018, Maharaj 2016, Malek 2015, Ragheb 2020) to durations of over 10 years with severe DM related complications (Abaza 2017, Nteleki 2015, Tsobigny-Tsague 2018, El-Shakawy 2016, Ghoneim 2013, Saeed 2013, Yakoot 2019). Thus, mean baseline HbA1c ranged from 6.75% to 11.1%. Most studies included high proportions of overweight and obese participants with mean BMIs ranging from 22.4 to 40.8 kg/m².

Educational strategies

A total of 19 studies with 6942 patients and follow-up periods between 2-14 months investigated the impact of educational strategies on diabetes treatment. These included providing information about lifestyle modification measures, dietary recommendations, drug-based therapy, DM-related complications and self-management. Training sessions were provided based on group-based educational sessions or individual treatment plans by nursing staff or pharmacists and complemented by lectures, discussion services, brochures, newsletters, computer programs, electronic communication devices and tele-monitoring systems. Three of these studies were led by nurses (Adibe 2013, Hailu 2018, Labhardt 2011) and two cluster-randomized studies trained nurses to expand their role in the treatment of patients with NCDs (Fairall 2016) or aimed to improve guideline implementation in the treatment of patients with DM (Steyn 2013).

Three studies (Abaza 2017, Adjei 2015, Labhardt 2011) reported results on treatment adherence. All strategies lead to improved adherence, measured by improved perception of patients to treatment recommendations (Abaza 2017) or higher regularity of appointment schedules (Adjei 2015, Labhardt 2011). Two studies (Adibe 2013, Mash 2014) reported results on costs with lower costs for patients receiving educational strategies. Two studies reported fewer admissions to different health-care facilities (hospital or emergency room and clinic visits) (Abaza 2017, Chraibi 2017).

Results on quality of life were reported in two studies with follow-up periods over 12 months and conflicting results. A structured self-care education program by pharmacists and nurses (Adibe 2013) improved quality of life, but no benefit was shown after group education by trained professionals (Mash 2014).

The majority of the educational strategies resulted in lower mean HbA1c levels in the intervention groups with a clinically relevant mean decrease of -0.66 % (95 %-CI -0.94 to -0.39) and substantial heterogeneity between results of different studies (I^2=64 %) (Figure 3).

Figure 3: Results of educational strategies on HbA1c levels or changes of HbA1c levels of patients with DM2

Strategies to enhance physical activity

Five studies with 359 participants evaluated the efficacy of different strategies to enhance physical activity on glucose control. Strategies included counselling, setting goals and training sessions with different intensities or both over periods between 8-12 weeks.

Two studies were successful in lowering HbA1c where patients were given goals to accumulate 10,000 steps per day (Fayehun 2018) or patients were allocated to rebound exercise (Maharaj 2016). A third study investigated the effects of aerobic exercise training and was able to decrease fasting plasma glucose (27).

Two other exercise interventions failed to reduce HbA1c by incremental exercises compared to relaxation (Van Rooijen 2004) or higher intensity of exercises (Yan 2014) (Figure 4). Results were not pooled due to considerable heterogeneity with different directions of treatment effects.

Figure 4: Results of strategies to enhance physical activity on HbA1c levels of patients with DM2

Pharmacological strategies

Three studies with 479 participants tested the efficacy of pharmacological treatment strategies on glucose control of patients with DM2. El-Haggar 2015 found ketotifen and glimepiride an effective dual therapy. Malek 2015 described the non-inferiority of once-

daily basal-bolus insulin analogues and thrice daily insulin therapy. Distiller 2014 did not find an additional improvement with exenatide in addition to insulin and metformin therapy on glycemic control.

Strategies on food supplementations

Several different food supplementations were tested in 10 studies including 762 participants. Vitamin D3 supplementation had a positive effect on glycemic control in two studies (Ali 2019, Anyanwu 2016). Four studies tested the effect of plant-based substances. Ginger powder and balantines aegyptiaca (desert date) extract regimes supported glucose control (El Gayar 2019, Rashad 2017). Nigella sativa (black cumin) oil capsules slightly improved glucose control but were inferior to metformin (Moustafa 2019). A regime based on fermented papaya did show beneficial results (Somanah 2012). Anderson 2001 and Matter 2020 showed positive effects of zinc/ chromium in chronic DM and zinc supplementation in diabetic beta-thalassemia major patients. The addition of rutin and vitamin C did not improve the results of oral antidiabetics (Ragheb 2020). The addition of l-carnitine improved diabetic control achieved by glimepiride treatment (El-Sheikh 2019).

Strategies on the treatment of DM related complications

Seven studies with 351 participants and follow-up periods between 3-12 months evaluated different strategies to treat possibly DM-related complications including periodontitis (3 studies), foot ulcerations (2 studies) and macular edema (2 studies).
El-Makaky 2020 and Tsobgny-Tsague 2018 described the benefit of immediate vs. delayed non-surgical periodontal interventions on glucose control and El-Sharkawy 2016 stated the effectiveness of propolis as an additive in periodontitis treatment. Two studies stated a benefit of combined phototherapy and podiatric management (Nteleki 2015) and an additional local ointment application of royal jelly and panthenol (Yakoot 2019) on the healing of lower extremity ulcers. Ghoneim 2013 and Saeed 2013 tested different diabetic macular edema treatment strategies. Both studies described generally positive treatment effects but also considerable adverse events including rise of intra ocular pressure and glaucoma.

Interventions for patients with DM in a pregnant woman

Six studies included a total of 574 pregnant women at increased risk for gestational DM (GDM) (Embaby 2016), with newly diagnosed GDM (Utz 2018, El-Shamy 2018, Ashoush 2016) or with newly diagnosed GDM or pre-existing DM (Beyuo 2015, Ibrahim 2014) between the 20th and 34th week of pregnancy. The mean age ranged from 24.2-

33.3 years (see supplementary Table 4: Characteristics and results of studies on pregnant women with DM available in the supplements).

Three studies (Ashoush 2016, Beyuo 2015, Ibrahim 2014) with 289 participants examined metformin as an additional medication to insulin in comparison to insulin therapy only. Effects on glycemic control of metformin supported therapy ranged from a relevant decrease (Ashoush 2016) to no effect on fasting plasma glucose, but beneficial effect on two hour plasma glucose in a 75 g OGTT (Beyuo 2015) in women without insulin resistance.Adding metformin to insulin therapy of pregnant women with insulin resistant diabetes was associated with several benefits concerning the time of hospital stay, reduced occurrence of maternal or neonatal hyperglycemia, less neonatal intensive care unit (NICU) admissions and reduced cases of respiratory distress syndrome (Ibrahim 2014).

The other studies (285 participants) investigated non-pharmacological interventions. The tested interventions were aerobic exercise program (treadmill walking) (Embaby 2016), acupressure (El-Shamy 2018) and screening for GDM, followed by nutritional and exercise counseling for positive tested women (Utz 2018). The aerobic exercise program resulted in a relevant reduction of fasting plasma glucose until delivery (Embaby 2016). The acupressure intervention did not manage to show a benefit regarding glycemic control (El-Shamy 2018). Screening, counselling and intensive follow-up were able to improve glycemic control and reduce the number of newborns with macrosomia (Utz 2018).

Potential biases

None of the included studies was categorized as low risk of bias in all seven domains only (see supplementary Table 5: Judgement on risk of bias available in the supplements).

The most common restriction on study quality was found in the domain performance bias due to a lack of blinding of participants and personnel in 48 studies. Detection bias due to blinding of the outcome assessors was judged as high or unclear in 38 studies. 14 studies with high risk of bias due to no blinding of participants and personnel, reported adequate methods to ensure blinding of the outcome assessors.

Another frequent problem was an incomplete analyses of outcome data in 26 studies defined as a loss to follow-up over 10 % of randomized participants or per-protocol analyses.

In 23 studies a protocol was available. Risk of bias due to selective outcome reporting was judged as low in 15 studies. High risk of bias, meaning lack of reporting of results

of some pre-planned outcomes was judged in eight studies (Abdulrhman 2013, Beyuo 2015, Elbarbary 2020, Matter 2020, Owolabi 2019, Somanah 2012, Utz 2018 Yakoot 2019).

In the domain sequence generation, two studies were assessed as high risk. El- Nteleki 2015 randomized only seven patients into three different treatment groups. Shamy 2018 used a non-probability sampling method on the basis of the hospital admission code and was subsequently judged as high risk in domains sequence generation and allocation concealment.

In 31 studies, we identified further methodological limitations including missing reporting of information on sample-size calculation, definition of primary and secondary target criteria, relevant differences regarding baseline characteristics or reporting of intermediate results only.

DISCUSSION

This systematic review describes interventions from 60 studies to summarize the available randomized trials on to prevention, diagnosis and treatment of DM with a total of 12,113 participants from 15 African countries. Several promising interventions were identified that can be used in settings with limited resources or involved locally available materials. Despite a trend of increasing research activity in recent years, many areas of diabetes research in African countries are still underexplored leaving knowledge gaps that should be tackled in the future.

Scarcity of randomized DM trials in African countries

While 60 included randomized trials are not nothing it also means an average only slightly higher than one randomized DM study per country for all types of diabetes that has ever been conducted and published. Only two studies on pre-diabetic interventions have been conducted, despite a clear need and aim to tackle early to avoid the future DM burden that is expected to arise (17). Implementation research, considered important in addressing know-do gaps in real-world settings, especially in primary care settings are still very rare (28). Implementing evidence-based care while observing, evaluating und publishing it's result deems crucial in the massive challenge of creating diabetes care infrastructure for millions of diabetes patients. Nevertheless, forty-three of the 60 studies have been conducted since 2015 demonstrating at positive trend of research activity.

Rural vs. urban, primary vs. secondary care and geographic disparities

Three out of four studies were set in urban areas and only 5 % (3/60) were set in rural areas only. Despite decreasing population shares over the last decades, still almost 60 % of people in Sub-Saharan Africa are living in rural areas with rising absolute numbers (currently about 667 million) (29). Despite diabetes being considered to be associated with westernized lifestyle more prevalent in urban areas, prevalence rates in rural areas are still high, in some parts even higher (30, 31).

Moreover, the majority (83 %) of the studies were conducted in secondary and tertiary health care centers, leaving less than one fifth in primary care settings were most routine and day-to-day diabetes care should be carried out to support people in their everyday life with this chronic long-term illness to prevent long-term consequences.

Another considerable aspect is the geographical distribution of the conducted studies. Almost half (46%) of the included trial were conducted in Egypt, the country ranking 2nd on the African Infrastructure Development Index 2018 with the highest prevalence in

Northern Africa (32). South Africa, ranking fourth on the index, contributed another share of 18% (11 studies) (7). Almost three quarters of the studies were set in the top ten ranking countries on that list, all Northern and Southern Africa leaving huge blank spaces in Central, Western and Eastern Africa including countries with high prevalences including Kenya and Zimbabwe and pointing to both the infrastructural necessities of research as well as the structural development that is still ahead before to increase research activity (33). The broad majority of included studies was conducted in urban settings, this is likely due to the better health care infrastructure and thusly the increased practicability of research. Health care workers, including doctors and nurses, seem to prefer providing services in urban areas leading to an even higher deficit of health care access in rural areas. The consequence is limited generalizability of the results on the needs of the rural population.

Screening strategies to diagnose DM and its complications

The rate of undiagnosed patients with DM is estimated to be between 3.9 % in SSA (34) and 12 % in North Africa (35). This might be related to genetic disparities in the development level of the health care system and awareness in the general population (19). The high rates of undiagnosed DM highlight a high need for research on and implementation of DM screening strategies in the African context. We identified two studies (36-38) investigating primary care strategies to detect and manage women with GDM (36) and screen diabetic patients for complications (39). The observed GDM prevalence of 23.7% among pregnant Moroccan women underlines the importance of regular screening and management to enable early interventions at a primary care level (36). A diabetic population receiving primary care found a high rate of complications including retinopathy, maculopathy, neuropathy, nephropathy, possible infarction and severe erectile dysfunction (37-39).

Intervention for patients with pre-DM for primary prevention of DM

We identified two studies patients (40, 41) with elevated blood glucose levels below diagnosis criteria of DM improving glucose levels via interval training bitter gourd, a plant with antidiabetic properties that is consumed in many Asian as well as some African countries. Both studies offer effective strategies, but further research is necessary, exemplarily on early educational strategies, as a measure of patient empowerment and early tackling of DM (42).

Educational strategies for patients and health-care providers

Education is essential for effective diabetes control. It must be accomplished at, personal (patient empowement), community (raise the awereness of the disease and its risk factors) and health care provider level (training of medical staff to diagnose, monitor and treat it correctely) to manage the rising burden of diabetes (43).

Due to complex challenges for DM patients and health care providers, educational campaigns are necessary to support health care providers and empower patients to manage their disease-associated decisions, lifestyle habits and medication use. Best benefits are proposed to be achieved by continuous individualized education, guided by patients' concerns, preferences and needs (12, 44).

Several studies on DM2 (45-57), DM1 (58) and GDM (36) investigated long-term interventions to support patient empowerment based on improved knowledge, motivation, and capacity to take control of their disease (12). Three studies trialed nurse-led (46, 52, 53, 59) and 2 studies investigated strategies to train healthcare providers in the management of patients with DM (60, 61). Improvement of patient empowerment improved adherence and glucose control, fewer admissions to healthcare facilities and lower costs. Only two studies reported on the quality of life with heterogeneous results (46, 59, 62).

Currently, the COVID-19 pandemic has forced all nations to implement alternative, oftentimes digital strategies including tele-monitoring and teleconsultation to continue care of NCDs (63). The application of telemedicine in DM management showed beneficial results (55, 64). Lifestyle focused messages might be an effective low-cost option to keep patients motivated to adhere to healthy lifestyles and further research seems advisable (65).

All included studies were adapted to local contexts and the trialed strategies hold the promise of adaptability to health care systems in other African and LMIC. Moreover, the tasks of nurses in NCD care could be reshaped and expanded in countries with comparably few physicians in order to improve DM diagnostics, treatment and education.

Strategies to increase physical activity

As in the literature (GDM (66), DM1 (67, 68) and DM2 (69, 70)), exercise therapy generally showed positive effects (DM2 (27, 71-74), DM1 (75), GDM (76)) on glycemic control. Exemplarily, four weeks by setting the goal to accumulate 10,000 steps per day significantly reduced HbA1C levels (71). Due to limited follow up periods, it is advisable to target long-term adherence to these strategies in future research.

Pharmacological strategies

Currently, the available research on pharmacological interventions for DM is sparse in Africa. We identified only six studies (3 on DM2 (77-79), 3 on GDM (80-82)) testing pharmacological interventions as a central part of DM care (83) despite known differences between African and European Americans (19). This might be attributable to our criteria excluding international studies with less than 50% of the sites in African countries (e.g. (84-89)). Many major multi centric pharmacological studies only have few study centers in Africa. Nevertheless, in-depth research into differing effectiveness of diabetic medications is still lacking.

reported the usability and safety of a basal-bolus insulin regime with stepwise intensification in an African setting The efficacy of basal-bolus insulin regimes, as an easy to handle, practical DM treatment option was successfully tested by Malek 2015 (79) and has been previously described in other settings (90, 91). Further research should consider regional contexts like availability of medication, practicability of the medication (e.g. insulin needs proper storage (92, 93)) lifestyle habits and genetic aspects (94, 95). Consideration of findings on African American cohorts seems advisable (96, 97).

Strategies on nutrition and food supplementations

Nutritional and food supplementation interventions can successfully be used supporting pharmacological care or in early and pre-DM stages improving glycemic control, lipid profiles and management of DM-related complications (98-110). In this review, nutritional interventions (40, 111-113), including long-term consumption of honey (111), camel milk (112) and a low fat and protein content of meals (113) with positive effects on metabolic control. Camel milk, traditionally used for treatment of DM in arid areas of Africa and Asia, improves glycemic control, reduces insulin requirement and limits diabetic complications (114). Rashad 2017 (115) stated the beneficial effects of balanites aegyptiaca (desert date) extract on glycemic control. This evergreen tree is common in arid regions in Africa and was traditionally used in Egyptian traditional medicine (116).

Several food supplementations (zinc-gluconate (117) and zinc-chromium (118) supplementations, ginger powder (119), Nigella sativa oil capsules (120), L-carnitine (121), L-carnosine (122) as well as vitamin B, C or D supplementation (62, 123-125)) had positive effects on glycemic control.

Strategies on the treatment of DM related complications

Three studies tested the role of periodontitis treatment in diabetic patients (126-128). Tsobgny-Tsague et al. (128) and El-Makaky et al. (126) described the importance of early treatment start, resulting in favorable patient outcomes in periodontal health and glucose control. El-Sharkawy et al. (127) found propolis to be a favorable addition to planing and scaling. In an Ethiopian cohort, only 21% of DM patients received oral health screening (129). The WHO regards oral health as a crucial component of health care with 12-14 % of 35 to 44-year-old Africans suffering from periodontitis (130).

Treatment options for diabetic wounds were tested in two studies (131, 132). Phototherapy in addition to usual care was first trialed in an African cohort of patients suffering from diabetic foot ulcers, showing beneficial wound healing outcomes. Similar results were described in other settings (133). The addition of propolis to usual care regimes showed improved wound healing. These findings are supported by studies from other settings (134, 135).

Strength and limitations

The external validity of this systematic review is limited by the focus on a limited number of countries and urban health care setting. The included studies were set in 15 of the 54 African countries with a focus on the North African region, especially Egypt. Egypt is the country with the highest known prevalence of DM in the African continent (4, 7). This might be related to economic expansion and urbanization, but also due to specific dietary issues (e.g. white bread, polished rice, trans fats), reduced physical activity due to prohibition of exercise in public places, shortage of exercise facilities, poor physical education in schools. Poor diet and physical inactivity are causing a high rate of overweight and obesity among the Egyptian population (136).

Our pre-planned primary outcome was mortality which was not reported in any of the included studies. Since DM is a chronic disease with a slow progression and long-term development of organ damage, the survival time is higher than the follow-up time of most of the studies. The included studies looked at long-term treatment strategies rather than treatment for acute hypo- or hyperglycemic events that can lead to acutely fatal events. Nevertheless, long-term glucose control, being represented by the HbA1c value is one of the strongest clinical-outcome indicators of efficient DM management and health outcomes (137). It is easy to measure and serves as a representation of the individual's average blood glucose levels in the previous 3 months (137). Furthermore, it is up to discussion if improvement of glycemic control based on blood glucose measures like HbA1C are necessary the best strategic in LMIC or if diabetes

complications are more effectively prevented by targeting bloodpressure or blood lipids (138).

Next, this review does not include non-randomized study types including prospective cohort trials or qualitative research, probable not taking into account the evidence that has been accumulated. Nevertheless, our aim was to search for randomized trials, since these study types, if conducted well, have a high evidence quality, allowing to minimize biases. Moreover, many of the studies included had a high risk of bias.

This systematic review includes studies as the highest level of evidence to investigate the benefits and harms of interventions (139). We included studies published in the English language without time restrictions. Language bias was shown to be unlikely. Despite the high linguistic diversity on the African continent, the languages mostly spoken are English, Arabic, and French (140). Eventually, we did not exclude any study due to the publication language, but we might have missed studies from journals that are not listened in searched databases.

CONCLUSION

This systematic review shows an increasing number of studies due to the rising prevalence and awareness of DM in African countries. However, the number of high-quality studies is still low and emphasizes knowledge gaps and underexplored research areas. Available studies are not representative of all African regions and were mainly conducted in urban areas of higher developed countries. Especially primary care settings and implementation research are underrepresented.

An improvement of the prognosis of DM patients in Africa requires adequate technical and financial resources, training of healthcare staff and the implementation of comprehensive strategies to improve early diagnostics, adherence to medical treatment and subsequent regular checks. The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances.

Ethics approval

No ethical approval is necessary

Authors contribution

Sandholzer-Yilmaz AS developed the concept of the review, performed the initial systematic search in the International Trials Registry, screened the references, extracted study data in 2019, wrote a draft of the manuscript and worked in the

coauthors comments on the final version of the manuscript and finally submitted the manuscript.

Kroeber ES updated the systematic search, added a search in 2 regional databases, screened the updated search results and extracted the updated data and wrote the final version of the manuscript.

Unverzagt S has expertise in systematic reviews and is the guarantor of the methodological quality of the systematic review, developed the review concept has registered the protocol, performed the systematic search in 2 databases, screened all references, checked the initial as well as the updated data extraction and wrote the final version of this manuscript.

Ayele W provided expertise on the needs of evidence in the African context, developed the review concept, discussed the protocol and critically read and commented on the manuscript.

Frese T and provided expertise on primary care, developed the review concept, critically read and commented on the manuscript.

Kantelhardt EJ provided expertise on the needs of evidence in the African context, developed the review concept, critically read and commented on the manuscript.

Sandholzer-Yilmaz AS and Kroeber ES are joint first authors of this manuscript.

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Competing interests statement

The authors declare no competing interests.

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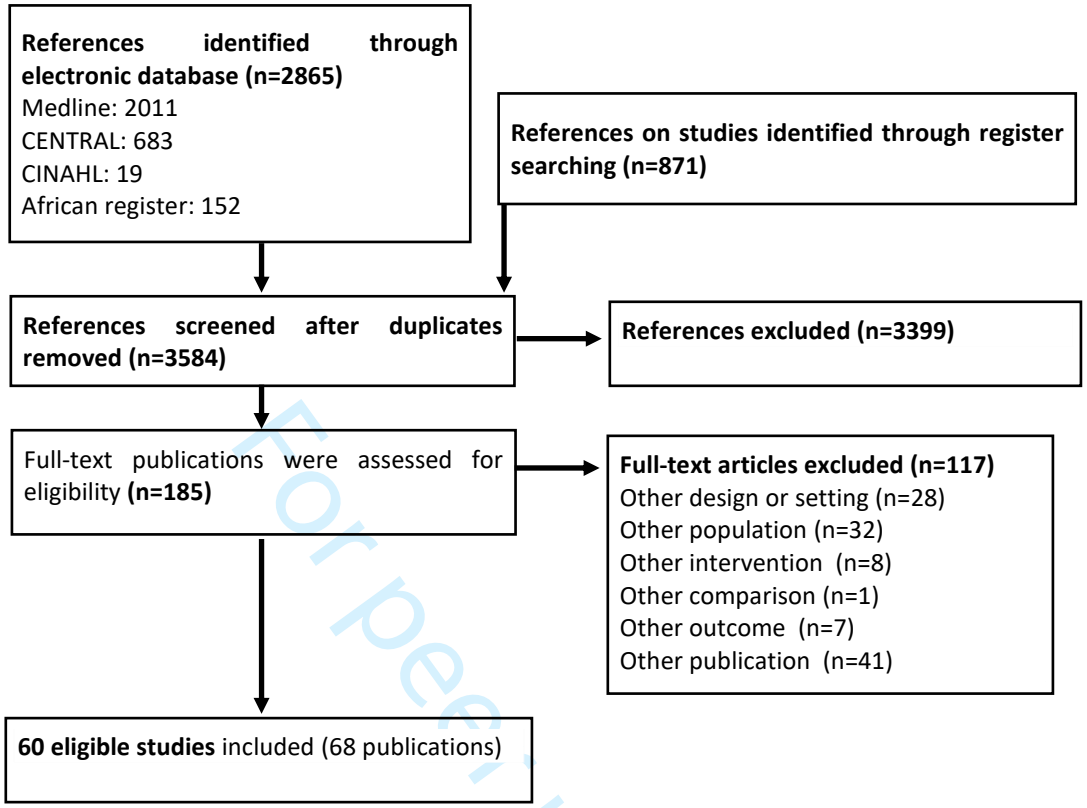
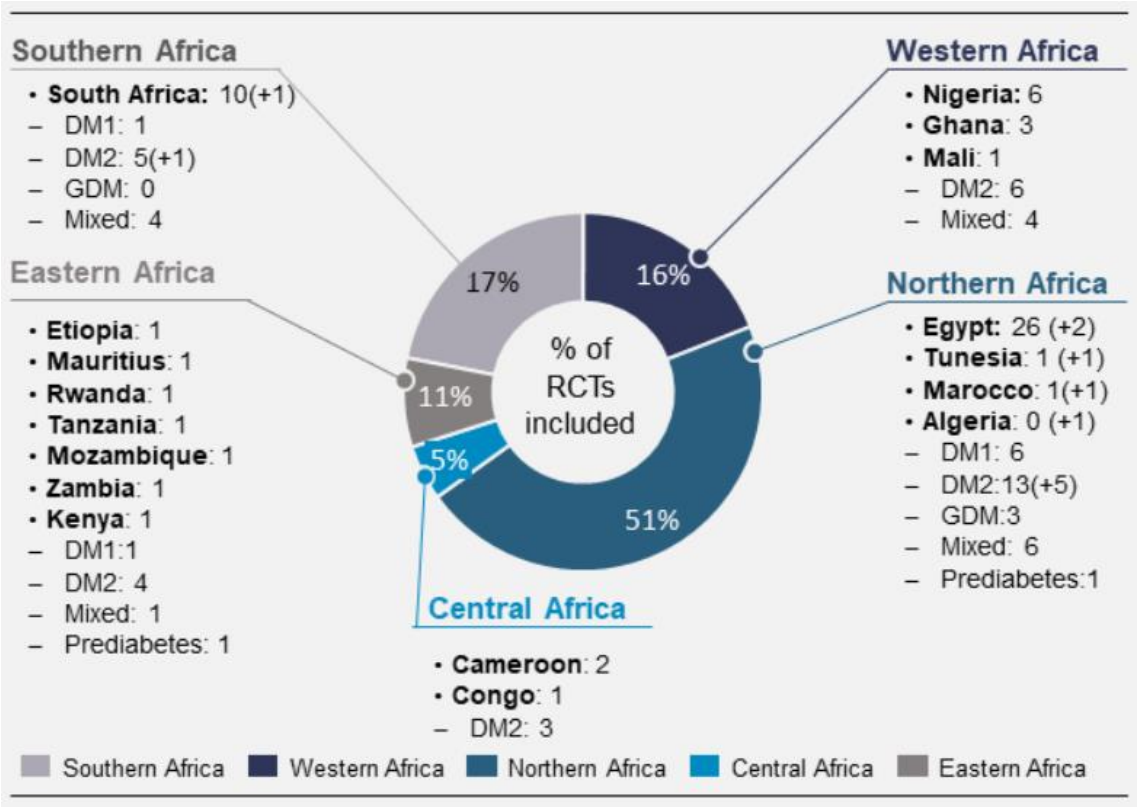
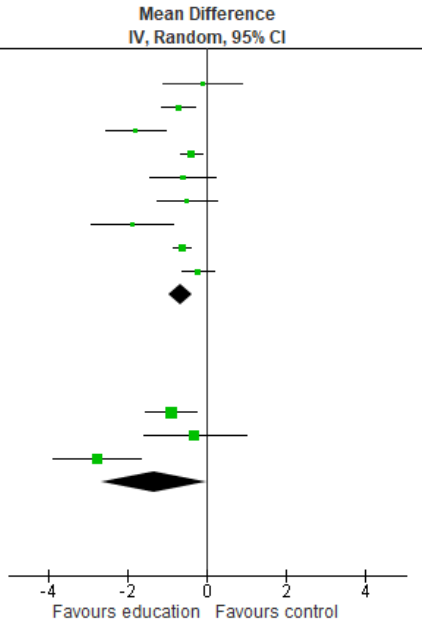
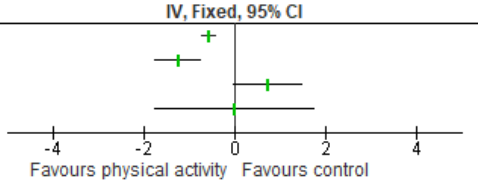




Study or Subgroup	Education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 End of follow-up								
Abaza 2017 (Egypt)	8.73	1.98	34	8.84	2.4	39	5.7%	-0.11 [-1.12, 0.90]
Amendezo 2017 (Rwanda)	7.49	1.48	115	8.21	1.72	108	14.3%	-0.72 [-1.14, -0.30]
Essien 2017 (Nigeria)	8.4	1.67	53	10.2	2.19	51	8.4%	-1.80 [-2.55, -1.05]
Mash 2014 (South Africa)	8.4	2	391	8.8	2.2	475	17.5%	-0.40 [-0.68, -0.12]
Muchiri 2016 (South Africa)	9.8	1.92	41	10.4	1.92	41	7.4%	-0.60 [-1.43, 0.23]
Sodipo 2017 (Nigeria)	7.2	2	55	7.7	2	52	8.3%	-0.50 [-1.26, 0.26]
Takenga 2014 (Congo)	6.73	1.59	17	8.6	1.35	14	5.4%	-1.87 [-2.91, -0.83]
Tawfik 2016 (Egypt)	7.5	0.8	107	8.12	0.9	107	18.6%	-0.62 [-0.85, -0.39]
Webb 2015 (South Africa)	8.54	2.11	225	8.76	2.22	191	14.4%	-0.22 [-0.64, 0.20]
Subtotal (95% CI)			**1038**			**1078**	**100.0%**	**-0.66 [-0.94, -0.39]**
Heterogeneity: Tau² = 0.10; Chi² = 21.97, df = 8 (P = 0.005); I² = 64%								
Test for overall effect: Z = 4.66 (P < 0.00001)								
1.1.2 Change until end of follow-up								
Debussche 2018 (Mali)	-1.05	2.09	70	-0.15	1.75	70	38.0%	-0.90 [-1.54, -0.26]
Hailu 2018 (Ethiopia)	-2.88	4.28	78	-2.57	3.59	64	29.7%	-0.31 [-1.60, 0.98]
Thuita 2020 (Kenya)	-2.04	2.7	48	0.73	2.71	46	32.4%	-2.77 [-3.86, -1.68]
Subtotal (95% CI)			**196**			**180**	**100.0%**	**-1.33 [-2.65, -0.01]**
Heterogeneity: Tau² = 1.08; Chi² = 10.57, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 1.98 (P = 0.05)								



Study or Subgroup	Physical education Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fayehun 2018 (Nigeria)	6.26	0.17	23	6.82	0.32	23	-0.56 [-0.71, -0.41]
Maharaj 2016 (Nigeria)	7.12	1.19	45	8.36	1.25	45	-1.24 [-1.74, -0.74]
van Rooijen 2004 (South Africa)	8.99	2.59	75	8.26	1.97	74	0.73 [-0.01, 1.47]
Yan 2014 (Mozambique)	7.7	2.23	31	7.7	2.53	10	0.00 [-1.75, 1.75]



Studies on patients with pre-DM

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Strategies to enhance physical activity						
RezkAllah 2019 ACTRN126170 00631303 RCT	Egypt, urban 07/2017-01/2018	Pre-DM, 25-45 yrs, BMI of 25–30 kg/m2, HbA1C 5.7–6.4%, fasting glucose 100–125 mg/dL, sedentary lifestyle No history of diabetes, cancer, prediabetic neuropathy, stroke, pulmonary embolism, or severe musculoskeletal problems restricting physical activity	n=60 45 % females age (yrs): 32.9±5.5 BMI (kg/m²): 28.3±1.4	IG2 (n=20): High-volume high intensity interval training, 40 min/session vs. IG1 (n=20): Low-volume high intensity interval training, 25 min/session Both with 90 % HR maximum, 3 times/week CG (n=20): No exercise intervention Duration: 12 weeks	Primary: HbA1c Other: fasting glucose	After 3 months HbA1c (%): Benefit for IG2 and IG1: Benefit for IG: 4.87±0.34 (-26 %) vs. 5.13±0.57 (-14.5 %) vs. 6.25±0.48 (+3.38 %) (p=0.0001) fasting glucose (mg/dL): Benefit for IG2 and IG1: 90.8±4.13 (-17.8 %) vs. 93.8±4.16 (-13.2 %) vs. 103.8±7.21 (+2.9 %) (p=0.0001)
Strategies on nutrition						
Krawinkel 2018 DRKS 00005131 Cross-over-RCT	Tanzania, urban 10/2013-03/2014	Individuals with pre-DM age (yrs): 30 -65, FPG 5.6-6.9 mmol/l (100–125 mg/dL) on 2 days or on one day + HbA1c 5.7-7.5 %, BMI 27–35 kg/m^2, BP 90/60-160/110 mmHg, waist circumference > 80/90 cm for women / men No chronic disease, taking regular intake of medication, identified glucose-6-phosphatase-dehydrogenase deficiency, heavy alcohol consumption, pregnancy,	n=52 55% female age (yrs): 47.5±8.7 HbA1c (%):5.85±0.43 FPG: (mmol/l): 5.34±0.49 BMI (kg/m²):29.6±2.2	IG/CG (n=30): started with bitter gourd supplementation (2,5 g) over 8 wks, followed by placebo over 8 wks vs. CG/IG (n=31): first placebo over 8 wks, followed by bitter gourd over 8 wks washout period: 4 wks Duration 8 weeks	Primary: FPG Secondary: HbA1c, Insulin, SBP, DBP, lipids	after 8 wks FPG (mmol/l): Benefit for IG/CG: MD 0.31 (0.08-0.54) HbA1c: (%): No differences (MD 0.05)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		lactation				

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DBP: Diastolic blood pressure; DM: diabetes mellitus; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants; MD: mean difference; RCT: randomized controlled trial; SBP: Systolic blood pressure; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 1: Characteristics and results of studies on patients with pre-DM

Studies on patients with DM1

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Malipa 2013 RCT	Zambia	DM1, 16-19 yrs	n=40 55% females 16-17 yrs: 35 % 18-19 yrs: 65 % Compliance: worse in IG 26.4 vs. 14.6 (p=0.001) Impact of diabetes: 20.5 Worries about diabetes: 20.5 Satisfaction with life: 20.5	IG (n=20): 1 meeting /wk over 8 wks CG (n=20); waiting list Duration: 8 wks	Compliance to treatment (Rating scale for compliance) Quality of life (impact and worries about diabetes, satisfaction with life)	After 2 months: Compliance: better in IG (11.0 vs. 30; p<0.001) Impact of diabetes: better in IG (16.8 vs. 24.2; p=0.045) Worries about diabetes: better in IG (14.32 vs. 26.68; p=0.001) Satisfaction with life: better in IG (28.5 vs. 12.5; p<0.001)
Strategies to enhance physical activity						
Salem 2010 RCT	Egypt, urban 02/2009-11/2009	DM1 for ≥3 years, 12-18 yrs, HbA1c ≥7.5 % for ≥6 months no significant diabetic complications limiting exercise like, uncontrolled hypertension, diabetic keto-acidosis, severe hypoglycemia within the past 3 months, patients on lipid lowering therapy	n=196 61.7 % female age (yrs): 14.78 ± 2.31 HbA1c (%): 8.7±1.7 duration of diabetes (yrs): 4.6 ± 1.9	IG2 (n=73): attended exercise sessions three times/week vs. IG 1 (n=75): attended exercise sessions once times/week vs. CG (n=48): no exercise Duration: 6 months	glycemic control, plasma lipids values, blood pressure, severity and frequency of hypoglycemia, anthropometric measurements and insulin dose	Change over 6 months: HbA1c (%): Benefit for IG2 and IG1: 7.8 ± 1.0 vs. 8.1 ± 1.1 vs. 8.9 ± 1.3% (p=0.2)
Strategies on nutrition						
Abdulrhman 2013 NCT01554566 Cross-over	Egypt, urban, tertiary care 01/2010 -	DM1, age > 2 yrs, HbA1c< 10 % no renal or hepatic impairment, coexisting	n=20 50 % females age (yrs): 11.3 ± 4.3 duration of diabetes (yrs): 4.7±4.5	IG/ CG (n=10): Honey consumption (0.5 ml/kg body weight per day) vs.	Primary: serum lipids, c-peptide Secondary: anthropometric measures (e.g. BMI), fasting and 2h-	After 12 weeks: (IG/CG vs. CG/IG): HbA1c (%): • Benefit with CG/IG: 6.7±0.9 vs. 5.9±0.8 (p<0.01) • no differences in change in period 1: -

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	10 / 2011	diseases or therapies that may affect body weight or serum lipids	HbA1c (%):7.21± 0.76 fasting glucose (mg/dl): 154.5±22.5	CG/IG (n=10): changed after 12 wks and received than honey Duration: 12 wks.	postprandial glucose, HBA1c, serum lipid profile	5.83 ± 13.66 vs. 2.94±8.82 (p=0.105) Fasting glucose (mg/dl): benefit with CG/IG: 142.7 ±26.6 vs. 116.7±19.4 (p<0.01) benefit with IG/CG in period 1:-21.51 ± 10.84 vs. -0.08±5.14 (p=0.001)
Mohamad 2009 RCT	Egypt, urban	DM1, age 17 to 20 yrs no acute metabolic complications like diabetic ketoacidosis, hypoglycaemia, cardiovascular events, renal or acute infections	n=64 30 % female age (yrs): 19.9±6.8 HbA1c (%): 9.52±2.08 fasting glucose (mg/dl): 228.7±13.5 BMI (kg/m²): 18.82±3.01	IG (n=27): camel milk (500 ml) +usual care vs. CG (n=27): usual care for diabetes (i.e. diet, exercise, insulin mixtard) Duration: 16 weeks	Not specified: HbA1c, human C-peptide, lipid profile, serum insulin, anti-insulin antibodies, creatinine clearance, albumin extraction in 24 h urine, BMI, Diabetes QoL score, fasting glucose	After 16 wks HbA1c (%): Benefit for IG: 7.16±1.84 vs. 9.59±2.05 fasting glucose (mg/dl): benefit for IG: 227.2±17.7 vs. 98.9±16.2
van der Hoogt 2017 cross-over RCT	South Africa	DM1, age 4-17 yrs on insulin pump therapy, HbA1c>9,6% for ≥3months, BMI/age z.score -1 to < 3, total daily insulin use of >0,5 u/kg no remission of diabetes, smoking, coeliac disease, cystic fibrosis, diseases or medication that are associated with delayed gastric emptying or altered digestation, glucocorticoids, oral diabetic drugs, no acute illnesses	n=32 41% female age (yrs): 10.4±4.0 HbA1c (%): 8.2±0.8 duration of Diabetes (yrs): 3.5 (1.5-8.0)	IG1 (n=22): 1 home-based low fat and protein meal vs. IG2 (n=22): 1 high fat and protein meal with identical carbohydrate content two meals were consumed at dinner time (18:00) under parental supervision at least 1 day apart within one month Duration: 3months	primary: peak sensor glucose value post-meal, time to peak sensor glucose, time of first and largest correction bolus, total correction insulin, total meal insulin, additional insulin required ,area under the sensor glucose response curve (AUC) (≥ 8 mmol/L), duration of elevated post-prandial glucose	Change over 12 weeks Occurance of hypoglycaemic events: 7 (32 %) vs. 1 patients after IG1 vs. IG2
Medical device						
Elbarbary 2016 RCT	Egypt, urban 06/2014-07/2014	DM1, adolescents and adults who wished to fast the month of Ramadan with insulin pump for ≥6 months and attending the whole	n=73 68.3% female age (yrs): 15.6±2.7 HbA1c (%): 7.65±0.9 BMI (kg/m²):	Insulin pump therapy during Ramadan fasting IG (n=25): sensor with low glucose	Primary: hypoglycaemia Other: glucose value, number of 'full fasted days', emergency hospital visit for diabetes-related	After 1 months: Glucose value (mg/dl): 152.5±17.3 vs. 141±33.8 (p=0.9) Complications: Number of hypoglycaemic excursions:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		education session 2 months before fasting and committed to follow-up the given instructions no diabetic ketoacidosis, episodes of severe hypoglycaemia or symptoms of uncontrolled diabetes in the last 6 months, diabetic microvascular complications or macrovascular disease, pregnant women	24.56±3.5 duration of diabetes (yrs): 5.8±2.9 on pump therapy (yrs): 1.73±0.99	suspension activation vs. CG (n=35): sensor without low glucose suspension activation Duration:1 month	problem	3.68±1.62 vs. 6.7±2.1 (p=0.001) Number of hyperglycaemic excursions: 17.0±4.0 vs. 23.0±7.6 (p=0.001) No severe hypoglycaemic events, no episodes of diabetic ketoacidosis, no hyperglycaemic events associated with ketosis no deaths or device-related SAE
Pharmacological Strategies						
Elbarbary 2018 NCT0292825 RCT	Egypt, urban	DM1, age: 9 - 18 yrs, ≥ 5 yrs disease duration, active diabetic nephropathy in the form of microalbuminuria, HbA1c ≤ 8.5 % no infection, renal impairment due to other causes other than diabetes, other diabetic complications, hypersensitivity to carnosine	n=90 52.3 % female age (yrs): 12.85±3.1 HbA1c (%):7.85±1.95	IG (n=45): 1 g/d carnosine vs. CG (n=45): control/placebo group Patients in both groups received oral ACE-Is captopril 25 mg Duration: 12 wks	Primary: change in tubular damage marker Secondary: urinary albumin excretion (UAE), oxidative stress markers Safety: any AE	After 12 wks: HbA1c (%): • Benefit for IG: 7.4 ±1.3 vs. 8.3±2.4 • change -9.88±7.12 vs. 3.89±2.28 (p=0.005) No adverse reactions were reported
Elbarbary 2020 NCT03594240 RCT	Egypt, urban 03/2017-03/2018	DM1 on insulin therapy with > 5 yrs of disease duration, 12-18 yrs, active nephropathy, HbA1c< 8.5 %, no infections, renal impairment due to other causes than diabetes, other diabetic complications ,	n=80 55% female age (yrs): 15.4 ± 1.6 HbA1c (%):7.95±0.5 fasting glucose (mg/dl): 114.5±21.8 duration of diabetes (years): 8.65 ± 2.65	both groups received oral angiotensis-converting-enzyme inhibitors (captopril) IG (n=40) oral vitamin B complex (B1,B6,B12) once daily vs.	Primary: Cystatin C diet, physical activity, and metformin dosage	after 12 weeks HbA1c (%): Benefit for IG: 7.5±0.6 vs. 8.0±0.6 Fasting glucose (mg/dl): 107.7±14.1 vs. 116.4±17 (p=131)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	 Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		elevated liver enzymes, hyper-or hypothyroidism, hypertension, neoplasm, taking any vitamins or food supplements within 1 months before study start		CG (n=40): placebo Duration: 12 weeks		

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DM1: Type 1 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants ;RCT: randomized controlled trial; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 2: Characteristics and results of studies on patients with DM1

RCTs mainly including patients with DM2

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Abaza 2017 NCT02868320 RCT	Egypt, urban, tertiary care, 03-07/2015	DM2, mobile phone, capable to read SMS or live with someone who could read	n=73 56 % females age (yrs): 51.5±9.2 majority had had diabetes for > 1 yr hypertension: 41.1 % on insulin: 19.2 % DM complication: 80.8 % HbA1c (%): 9.7±2.7	Diabetes awareness program: paper-based educations material plus IG (n=34): daily messages and weekly reminders addressing various diabetes care categories vs. CG (n=39): paper-based educations material Duration: 12 wks.	Primary: change in Hba1C Secondary: Random blood glucose levels, body weight, adherence of treatment and medication, diabetes self-efficacy and knowledge, rate of hospital/ER visits, frequency of measurements, regular exercise, patients confidence in healthcare provider and satisfaction, healthcare provider's reputation	After 3 months: HbA1c (%): • No differences: 8.73 ±1.98 vs. 8.84±2.40, MD_a: 0.290 (-0.402 to 0.983; p = 0.406) • Benefit with IG: 47 vs. 15 % achieved the targeted 1% drop (p = 0.003) Random blood glucose (mg/dl): • No difference: 181±65 vs. 201±87 (p=0.288) Treatment adherence (scores): • Benefit with IG in SCI 3.42±0.48 vs. 2.52±0.49 (p<0.001) and Morisky: 3.76±0.55 vs. 2.74±1.07 (p<0.001) Hospital /ER admission (%): No differences: 0 vs. 10.3 (p=0.118)
Adibe 2013 RCT	Nigeria, urban, tertiary care	DM2, age≥ 18 yrs with oral hypoglycemic and / or insulin therapy no pregnancy	n=220 58 % females age (yrs): 52.6±7.9 duration of diabetes (yrs): 4.7±2.5, 60.5% with diabetes > 5 yrs on insulin: 13.6 % hypertension: 60.5 %	IG (n=110): structured self-care education and training program by pharmacists and nurses vs. CG (n=110): usual / conventional care Duration: 12 months	Primary: incremental cost-utility ratio, net monetary benefit Other: quality of life	After 12 months: Quality of life: • Benefit with IG: 0.86 ± 0.12 vs. 0.64 ± 0.10 (p=0.0001) improved single attributes except "hearing" functioning of the patients Costs: • benefit of $0.76±0.15 vs. $0.64± 0.15 QALY/patient and year; MD: $ 0.12 (0.07 to 0.16) • incremental cost-utility ratio of $571 per QALY
Adjei 2015	Ghana, urban	DM	n=200 64.5% female	IG: (n=100): electronical reminder for	Primary: Compliance with appointment dates	After 6 months: Adherence to appointment schedules

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT			age (yrs): < 50 yrs: 63 % > 50 yrs: 37 % fasting glucose (mmol/l): 10.4±3.8	clinical appointments of patients + alert system for abnormal laboratory results vs. CG: (n=100): usual diabetes care, paper based method Duration: 6 months	Other: metabolic risk factors, BMI	(%) Benefit for IG: 97.8 vs. 89.4 (p=0.010) Fasting glucose (mmol/l): Benefit for IG: 8.04±2.14 vs. 8.85±2.63; MD 0.4 (-0.59 to -0.36, p=0.022)
Amendezo 2017 NCT02032108 RCT	Rwanda, urban, tertiary care	DM2>3mths, age>21yrs no pregnancy or severe co-morbid illnesses.	n=251 69.3% females age (yrs): 50.9 ±10.9 BMI (kg/m²): 27.9 (27.0-28.5) duration of diabetes : <10 yrs: 73.7%, >10 yrs: 16.3% HbA1c (%): 8.98±8.6-9.3	IG (n=115): standard care plus monthly lifestyle education sessions of 45 min duration vs. CG (n=108): standard care Duration: 12 months	Primary: difference in HbA1c Secondary: fasting glucose, systolic and diastolic blood pressure, BMI	after 12 months: HbA1c (%): Benefit for IG with median reductions of -1.70 (-2.09 to-1.31) vs. -0.52 (-0.95 to -0.10); MD: -0.72 (-1.14 to -0.30; p< 0.001) Fasting glucose (mmol/L): 6.9 (6.45 to 7.36) vs. 9.02 (8.18 to 9.87) (p<0.001)
Chraibi 2017 NCT01589653 RCT	Egypt, Indonesia, Morocco, Saudi Arabia, Vietnam 05/2012-07/2015	DM2 with diagnosis ≥ 12 months, age≥18 , currently being treated with NPH Insulin for ≥ 3 months + metformin (1000-1500 mg) for ≥ 2 months, HbA1c ≥ 7.0% ≤10%, BMI ≤ 40.0 kg/m^2 no treatment with thiazolidinedione, glucagon-like peptide-1 receptor agonists, pramlintide within the last 3 months , >1 IU/kg NPH insulin daily; previous use of premixed or bolus insulin, > 1 severe hypoglycemic episode during	n=155 74.9 % female age (yrs): 54.5 ±10.0 BMI (kg/m²): 29.05±4.9 HbA1c (%): 8.6 ±0.83 fasting glucose (mmol/L): 8.97 duration of diabetes (yrs): 9.5±5.8 African patients: • Egypt: 25.75 % • Morocco: 27.7 % Diabetic nephropathy / neuropathy / retinopathy (%): 3.2 / 16.1 / 3.2	IG (n=76): patient driven titration of Biphasic insulin aspart 30 twice daily, 3 clinic visits vs. CG (n=79): physician driven titration twice daily, 6 clinic visits Titration in both arms according to the titration protocol bases on self-measured plasma glucose values, measured twice daily on 3 preceding days, telephone contact whenever deemed	Primary: change in HbA1c Secondary: proportion of patients achieving the ADA target of HbA1c <7.0 % and the HbA1c target of <6.5 % after 20 weeks, FPG changes, hypoglycemic episodes,	Change over 5 months: HbA1c (%): • Decreased in both arms with non-inferiority between groups: MD -0.23 (-0.54 to 0.08) • More patients reached HbA1c <7.0%: 40.8 vs. 29.1 %, RR: 1.79 (0.87 to 3.65) and <6.5%: 25 vs. 19 %; RR: 1.52 (0.67 to 3.46) • More patients reached target HbA1c levels without severe or minor hypoglycemic episodes: <7.0%: 38 vs. 27.8 %, RR: 1.52 (0.61 to 3.79), <6.5%: 18 vs. 14.8 %; RR 1.13 (0.36 to 3.52) FPG (mmol/l): • Decreased in both arms with no difference between groups: 0.95±0.28

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		the previous 12 month, impaired kidney or hepatic function, proliferative retinopathy or maculopathy requiring treatment	Macroangiopathy (%): 5.2	necessary Duration: 20 weeks		vs. 0.67±0.28; MD: -0.28 (-1.07 to 0.52) Costs • Less frequent clinic visits to healthcare professionals in IG: 4.8±0.65 vs. 7.5±1.42 visits/patient Complications: • hypoglycemic episodes: no difference: 608.4 vs. 789.2 / 100 patient-years of exposure; RR: 0.74 (0.44; 1.23) treatment-emergent AEs: no difference: 324.2 vs. 302.2 events / 100 patient-years of exposure
Debussche 2018 NCT01485913 RCT	Mali, urban, secondary care, 07/2011-02/2013	DM2, age 30-80 yrs, HbA1c ≥ 8 %, no DM1, severe diabetes complications or concomitant illnesses that threatened their functional or vital prognosis	n=151 76.2% female age (yrs): 52.5±9.8 BMI (kg/m²):28.6±5.4	IG (n=76): peer-led structured patient education received culturally tailored structured patient education (3 courses of 4 sessions) delivered in the community by five trained peer educators vs. CG (n=75): conventional care alone Duration:1 yr	Primary: HbA1c Secondary: anthropometric indicators (weight and BMI, waist circumference), SBP, DBP, anti-diabetic and anti-hypertensive treatment, knowledge score, dietary practices	Change to 12 months HbA1c (%): • Benefit in IG: MD 1.05 % (-1.54;-0.56) vs. -0.15 % (-0.56; 0.26) (p = 0.006)
Essien 2017 PACTR201302 00047835 RCT	Nigeria, urban, tertiary care, 09/2013-05/2014	DM1 or DM2, age: ≥ 18 yrs, HbA1c> 8.5 %, able to engage in moderate exercise, no eye disease that would limit the ability to read	n=118 60.2 % female age (yrs): 52.7±10.5 BMI (kg/m²): 28.9±7.5 HbA1c (%):10.7±1.6 type of diabetes • DM1: 14.4 % • DM2: 85.6 %	IG: (n=59): intensive and systematic disease self-management education programme (invitation and encouragement by clinical staff to attend 12 structured teaching sessions) vs.	Primary: HbA1c	After 6 months: HbA1c (%): 8.4 (8 to 8.9) vs. 10.2 (9.8 to 10.7); MD_a: -1.8 (-2.4 to -1.2); (p < 0.0001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				CG (n=59): conventional disease-self-management education Duration: 6 months		
Fairall 2016 ISRCTN20283604 Cluster-RCT	South Africa, urban/rural, primary care, 03/2011 – 11 / 2011	age ≥ 18 yrs , clinics providing service for NCD Patients with DM, hypertension, chronic respiratory disease or depression, with self-reported hypoglycaemic (in case of DM)	n= 38 public sector primary care clinics, 4393 patients, n=1842 with DM 73 % female age (yrs):median, IQR): 52 (42-61) vs. 52 (44-62) BMI (kg/m²): 30±8 HbA1c (%):9 (4-17), in HbA1c in DM≥ 7 %: 77 %	IG (n=2166, 851 with DM): Nurses were trained to use a primary care programme to support and expand nurses`role in NCD care and contains a clinical management tool with enhances prescribing provisions vs. CG (n=2227, 991 with DM): Nurses continued to use the Lung Health and HIV/AIDS approach with usual training Duration: 14 months	Primary (for DM): treatment intensification (addition or increase in dose of metformin and/or sulphonylurea, insulin, ACE-inhibitor, aspirin, statin	over 14 months HbA1c (%): • <7 %: 41 vs. 38 %; RR 1.08 (0.77 to 1.52; p=0.638) • 7-10 %: 69 vs. 55 %; RR 1.30 (1.16 to 1.47; p<0.001) • >10 %: 71 vs. 73 %; RR 0.97 (0.81 to 1.16; p=0.703) Treatment intensification rates* (%): • 57% vs. 50%, RRa: 1.11 (0.99 to 1.26) (p=0.083) for patients with DM
Hailu 2018 NCT03185689 RCT	Ethiopia, urban, 02/2016-10/2017	DM2, age > 18 yrs no DM1 or GDM, pregnant women, severe cognitive or physical impairment, and terminally ill people	n=220 33 % female age (yrs): 54.5±10 BMI (kg/m²):25±4 HbA1c (%):10.5±4	IG (n= 116): Nurse-led disease-management education: 6 sessions, supported with illustrative pictures handbooks and fliers, customized to local conditions by trained nurses vs. CG (n=104): usual follow-up care Duration: 9 months	Primary: patients with target HbA1c (≤ 7 %) Secondary: systolic and diastolic blood pressure, fasting glycose, BMI, waist circumference	Change over 9 months: HbA1c (%): • No difference: 45 % vs. 50 % with target values (p=0.21), MD: 2.88% (-3.85 to -1.92) vs. 2.57% (-3.47 to -1.67) fasting glucose (mg/dl): • Benefit with IG: 36 % vs.25 % with target values, MD: -27 (-45 to -9; p=0.003)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Labhardt 2011 NCT00744458 Cluster-RCT	Cameroon rural, primary care, 08/2008-02/2010	newly detected adult patients with DM2 and /or hypertension in the catchment area of nurse-led health centres, staffed, equipped and trained to care for DM2 and hypertension	n=33 facilities, 221 patients 64% females age (yrs): 59.8±12.7 diabetes: 15.4 % Overweight (BMI 25-29.9 kg/m^2): 28.5 % Obesity (BMI> 30 kg/m^2): 20.4 %	IG 1 (11 centres, n=55): incentive group free treatment for 1 months for patients who regularly attended follow up visits vs. IG 2 (11 centres, n=77): letter group: reminder letters in case of a missed follow-up visit vs. CG (11 centres, n=89): no additional intervention Duration: 12 months	Primary: Patient retention at 1 yr (≥ 12 follow-up visits within 12 months) Secondary: Adherence with timely attendance of follow-up visit schemes and changes in blood pressure and blood glucose levels.	After 12 months: Retention rates (%): • Benefit for IG1 and IG2 vs.CG: 60 vs. 65 vs. 29 %; MD 34 (21 to 46) with no differences between IG1 and IG2; MD -5 (-22 to 12) Loss to follow-up: • Benefit for IG1 and IG2: IG1 vs. CG: HR 0.44 (0.27 to 0.72; p< 0.001) • IG2 vs. CG: HR 0.38 (0.24 to 0.61; p<0.001) Adherence (%): • Benefit for IG1 and IG2: 38 vs. 35 vs. 10; MD 26 (14 to 42), IG1 vs CG: MD 28(13 to 37); IG2 vs. CG: MD 25 (13 to 37) • no difference between IG1 and IG2: MD 3 (-14 to 20) FPG: No differences between groups
Mash 2014 Cluster RCT	South Africa, urban, primary care, 12/2010 -12/2012	DM2 with any therapy attending community health centres in the working class areas of Cape Town Metropole no DM1, dementia, mental illness or acute illness	n=34 public sector community health centres, 1570 patients 73.8% females age (yrs): 56.1±11.6 HbA1c (%): 9.1±2.3	IG (17 health centres, n=710): 4 monthly sessions lasting 60 min with group education about diabetes topics (understanding diabetes and medication, living a healthy lifestyle and preventing complications), delivered by a health promotion officer vs. CG (17 health centres, n=860): usual care: ad hoc advice during consultations and	Primary: improvement of diabetes self-care activities (5 % weight loss, and a 1 % reduction in HbA1c level) Secondary: improved diabetes specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol levels, quality of life	After 12 months: HbA1c (%): No differences: 8.4±2.0 vs. 8.8±2.2; MD_a: 0.01 (-0.27 to 0.28; p=0.967) Adherence (self-care activities): No differences in scores of physical activity, use of diet plan or medication, foot care or frequency of smoking Quality of life: No differences in physical functioning, role or social functioning, mental or general health and pain Costs: Incremental cost effectiveness ratio: 1862 Dollar/ QALY gained

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				occasional educational talks in waiting room Duration: 12 months		
Muchiri 2015 RCT	South Africa, rural, primary care, 04/2010-11/2011	DM2, age 40-70 yrs attending community health centres, HbA1c≥ 8 %, blood sugar levels ≥ 10 mmol/l, duration of diabetes ≥ 1 yr no insulin therapy, pregnant women, full time employed	n=82 86.6 % female age (yrs): 59±7.4 BMI(kg/m²): 30.9±6.9 HbA1c (%): 11.1±2.0 duration of diabetes (yrs): 6	IG (n=41): education materials+ 8 weekly group educational sessions about diabetes and nutrition, follow-up sessions+vegetable gardening CG (n=41): education materials Duration: 12 months	Primary: HbA1c Secondary: Other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c, dietary behaviours	over 12 months HbA1c (%): • no difference: 9.8±1.92 vs. 10.4±1.92; MD −0.63 (-0.26 to 1.50; p=0.16)
Owolabi 2019 PACTR201810599931422 RCT	South Africa urban/rural, primary care 07/2018-04/2019	DM, age ≥18 yrs, DM diagnosed at least in the last 6 months, currently receiving treatment at the selected clinics, on stable medication for ≥ 3 months prior to recruitment, uncontrolled glycaemic control, in possession of a mobile phone, able to retrieve and read SMSs and willing to receive SMSs health or mental conditions that could interfere with the study, pregnant or planning to get pregnant within the next 6 months, debilitated or handicapped in such a way that obtaining anthropometric measurements could be	n=216 84.3 % females age (yrs): 60.6±11.6 DM2 (%): 94 Treated with oral pills (%): 75.5 Duration of DM (yrs): 9.1±7.4 Duration of DM treatment (yrs): 8.8±7.2 Hypertension (%): 83.0 Random blood glucose (mmol/L): 14.34±3.9 BMI(kg/m²): 32.2±6.2	IG (n=108): daily SMS text-messaging SMS at an agreed time of the day, according to their needs, care plan and goal with motivational and support messages, advice on lifestyle behaviours (e.g. diets, physical activity, smoking cessation, medication and appointment reminders) vs. CG (n=108): usual diabetes care Duration: 6 months	Primary: Morning random blood sugar Secondary: co-morbid outcomes (hypertension and obesity), obtained through blood pressure measurement, anthropometric measurements (body weight, BMI) acceptability, feasibility	Over 6 months: Blood glucose levels (mmol/L): -1.58±5.29 vs. -1.95±4.69; MD 0.51(-0.8 to 1.82), MD_a 0.26 (-0.81 to 1.32)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		challenging				
Sodipo 2017 RCT	Nigeria, primary care, 03/2013-11/2013	DM2 ≥ 18 yrs. on antidiabetic medication no patients with emergencies, chronic complications such as nephropathy, neuropathy etc., those already using glucometer	n=120 gender: 50% female age (yrs): 59±10.95 HbA1c (%): 8.7±2.45 fasting glucose (mg/dl): 152±60.9 duration of diabetes (yrs): 50%> 3yrs	IG (n=60): Self-monitoring of blood glucose before and after meals 3 days a week for 12 weeks CG (n=60); non SMBG Duration: 12 wks	HbA1C, fasting glucose	after 3 months: HbA1c (%): No difference: 7.2±2.0 vs.7.7±2.0 (p= 0.174) fasting glucose (mg/dl): No difference: 123.2±35.1 vs. 137.6±50.1 (p=0.087)
Steyn 2013 Cluster-RCT	South Africa, urban, primary care, 1999-2000	public sector primary health care clinics (CHC) with ≥ 25 diabetes and ≥ hypertension patients age ≥15yrs, a documented attendee at the particular CHC with ≥ 4 visits during the previous year for hypertension or diabetes who received treatment for these conditions at each visit no patients being unable to answer a questionnaire	18 community health centres n=1096, of them n= 456 with DM age (yrs): 58.3 ± 11 gender:74 % females BMI (kg/m$^{2)}$: 30.7 ± 6.2 Type of Diabetes: • DM1: 5.8% • DM2: 91.35% uncertain DM type: 2.85%	IG (9 clinics, n=229): introduction of structured clinical record with guidelines prompts after training of doctors in their use and suggestions to incorporate them in regular patient records, contact over 1 year vs. CG (9 clinics, n= 227): usual care with passively disseminated guidelines Duration: 1 year	primary: HbA1C in the diabetes group secondary: uncontrolled glycaemia (HbA1c ≥7%) in the diabetes group.	After 3 months: HbA1c (%): IG: 8.8% vs. 8.8%; MDa -1.0 (-1.1 to -0.9) HbA1c ≥7% (%): no relevant difference: 64.1 vs. 62.6; MD 0.90 (0.53 to 1.53)
Takenga 2014 RCT	Congo, urban	DM2, 35-75 yrs	n=40 20 % females age (yrs): 53.3 ± 10.1 HbA1c (%): 8.63	IG (n=20): self-management of diabetes with Mobil DIAB (telemedical approach) vs. CG (n=20): conventional therapy without telemedical system	primary: HbA1c	after 2 months: HbA1c (%): Benefit for IG: 6.73±1.59 vs. vs. 8.6±1.35 (MD -1.87 (-2.91 to -0.83)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				Duration: 60 days		
Tawfik 2016 RCT	Egypt, urban, primary care, 05/2015-09/2015	DM2 for ≥ 1 yr, 40-79 yrs attending an outpatient clinic no patients who were already using a similar medication chart, severe or terminal health conditions, or patients with behavioural health issue that could make it difficult to understand the communication	n=255 53.7 % females age (yrs): 55.7±8.35 HbA1c (%): 8.14±1.3 duration of diabetes (yrs): 8.3±1.3	IG (n=127): comprehensive cardiovascular risk communication vs. CG (n=128): standard usual care Duration: 3 months	Primary: HbA1c Secondary: Cardiovascular risk perception, diabetes self-care, cardiovascular risk scores	After 3 months: HbA1c (%): Benefit for IG: 7.5±0.8 vs. 8.12±0.9; MD -0.62 (-0.85 to -0.39) controlled HbA1c (%): 32.7 vs. 29.9
Thuita 2020 PACTR201910518676391 RCT	Kenya Secondary care recruitment 08/2016 - 10/2016	DM2, 20-79 yrs with regular attendance of an outpatient clinic Pregnancy, complications such as renal failure, congestive heart failure, or stroke	n=153 59.5 % females age (yrs). 56±11.6 Family history of DM (%): 46.6 Poor glycaemic control (%) with HbA1c>7%: 77.8 DM for 1-5 yrs (%): 58.2 % Years with DM: 6.7±6.9 Oral medications (%): 82.4 BMP (kg/m2): 27±4.6 HbA1c (%): 8.49±1.9 fasting glucose (mmol/l): 11.0±3.3	IG2 (n=51): nutrition education programme for 2 hrs /week with peer-to-peer support vs. IG1 (n=51): Education programme vs. CG (n=51): Standard care Duration: 8 weeks	Primary: metabolic syndrome prevalence (MetS) Other: anthropometry and clinical data, blood pressure, blood glucose and lipid profile, physical activity levels, food intake	After 6 months: Metabolic syndrome prevalence: lower with IG2: Harmonized criteria:52.1 vs.69.4 vs. 91.3 (p<0.001) WHO: 58.3 vs. 77.6 vs. 89.1 (p=0.003) HbA1c (%): Mean change: no differences -2.04±2.70 vs. 1.48±2.73 vs. -0.73±2.71 High HbA1c: no differences: 47.9 vs. 29.0 vs. 34.8 % fasting glucose (mmol/l): no differences: -2.59±0.66 vs. -2.95±0.64 vs. -1.55±0.68 high fasting glucose: 79.2 vs. 83.7 vs. 91.3 %

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Webb 2015 NCT01275040 Cluster RCT	South Africa, urban, primary care, 06/2010-03/2011	primary health care clinics, patients with clinical diagnosis of DM2 or DM1 for ≥5yrs, age ≥ 18 yrs	n= 12 primary health care clinics n= 599 gender:68.5 % female age (yrs): 57.8±10.5 HbA1c (%): 8.73±2.3 HbA1c ≥ 7 %: 73 % BMI (kg/m$^{2)}$: 30.8±6.7 Typ of diabetes: • DM1: 3.7 %, • DM2: 70.3 % • unknown: 26 % duration of Diabetes: • < 5 yrs: 47.3 % • 5-10 yrs: 22.0 % • > 10 yrs: 20.2 % • unknown: 10.5 %	IG (n=328): mobile screening team visits primary care clinic and provides education and active screening for diabetic complications (foot, kidney, cardiac and renal complications) vs. CG(n=273): no mobile screening team, routine care with similar education for patients. and health care workers Duration: 1 yr	Primary: HbA1c, detected neuropathy, nephropathy and retinopathy, HbA1c categories Secondary: detected complications, referred patients for complication assessment or care, blood pressure and lipid control, costs, LDL cholesterol, creatinine	after 12 months HbA1c (%): no difference: 8.54±2.11 vs. 8,76 ±2.2, MD-0.22 (-0.64, 0.20) screening rate for complications: in IG 60% increase of screening in all complication indicator groups, in both groups testing of HbA1c and renal complications (serum-creatinine) increased , but no significant difference , screening for eye complications, only increased significantly in IG no significant difference in the proportion of actions taken beween IG and CG (p=0.83)
Strategies to enhance physical activity						
Asuako 2017 RCT	Ghana, urban, tertiary care, 08/2015-03/2016	DM, age: 20-68 yrs, ambulant patients, without diabetes complications with < 150 minutes /wk of moderate physical activity no SBP > 140 or DBP> 90 mmHg, bilateral or unilateral lower or upper limbs amputation, use of insulin pump	n=12 83% female age (yrs): 83% were 46-55 yrs. BMI (kg/m²):25.4±4.5 fasting glucose (mmol/l):9.33 ± 5.7 type of diabetes: DM1: 17 % DM2: 83 % duration of diabetes (yrs): • 1-5 yrs: 25 % • 6-10 yrs: 50 % • 10 yrs: 25 %	IG (n=7): walking aerobic exercise sessions without treadmills (3/week) vs. CG (n=5): only activity of daily living Both continued regular medical/clinical routines Duration: 8 weeks	FPG, Lipid profile, body weight, BMI	Change over 2 months: FPG (mmol/l): Benefit for IG: 6.27 ± 0.91 vs. 8.00 ± 0.96; MD 1.73 (-1.88 to -1.59; p<0.001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Fayehun 2018	Nigeria, urban 06/2014-11/2014	DM2, age 18-64 yrs, Diagnosed ≥ 12 months, non-insulin dependent, on dietary control ± hypoglycemic agents, able to walk without limitations no pregnant women, smokers, prescription of medications that might impair ability to walk	n= 46 63 % female age (yrs): 54±7.7 (33-64) BMI (kg/m²): 22.4±3.3 HbA1c (%): 6.6 (5.3-9.0) duration of diabetes (yrs):<7 yrs: 70 %, >7 yrs 30 %	IG (n=23): Goal to accumulate 10000 steps per day vs. CG (n=23): normal activity habits Duration: 10 weeks	Primary: HbA1c Secondary: step count	Change over 2.5 months: HbA1c (%): Benefit for IG: 6.26 (6.19 to 6.33) vs. 6.82 (6.69 to 6.95); MD_a: -0.74 (-1.32 to -0.02; p=0.015)
Maharaj 2016 RCT	Nigeria, rural 07/2013-06/2014	DM2, non- insulin dependent, blood glucose levels 6 - 13 mmol/l no cardiac, abdominal or spinal surgery ≤ 6 months, history of fractures of lower limbs, spine, weakness, deformities, loss of sensation in the feet, retinopathy, nephropathy	n=90 52 % females age (yrs): 39.4 ± 8.6 (30-58) BMI (kg/m²): 27.7±5.8 HbA1c (%): 8.79±2.11 duration of diabetes (yrs): 2.5±2.1	IG (n=45): rebound exercise 3 times/week for 20-30 min, moderate intensity of 40-60 % of HR maximum vs. CG (n=45): watched videos and read health magazines Duration: 9 weeks	Primary: HbA1c , FPG, BMI Other: Heart and respiratory rates, blood pressure, oxygen saturation	After 9 weeks HbA1c (%): Benefit for IG: 7.12±1.19 vs. 8.36±1.25; MD_a: 0.904 (0.832 to 0.984; p=0.017) FPG (mmol/l): Benefit for IG: 6.92±1.21 vs. 8.73±1.23; MD_a: 0.787 (0.7345- 0.841; p=0.002)
van Rooijen 2004 RCT	South Africa, urban 03/2002-11/2002	black women with DM2, age 40-65yrs, duration of DM ≥12 months no chest pain on effort, possible previous myocardial infarction and intermittent claudication, cerebro-vascular incidents, arthritis, retinopathy	n=158 gender:100 % females age (yrs): 54-55 HbA1c (%): 9.35	IG (n=80): education+ incremental daily home exercise, use of daily physical activity records+6 fortnightly supervised aerobic exercise classes vs. CG(n=77): education+ relaxation exercise Duration: 12wks	Primary: HbA1c, BMI Secondary: walking distance (6 min walk)	Change over 3 months: HbA1c (%): no difference: 8.99±2.59 vs. 8.26±1.97
Yan 2014	Mozambique,	DM2, male, age 40-70 yrs, diagnosis for ≥ 12 months	n=41 100% male	IG (n=31): low or vigorous intensity	plasma glucose, HbA1c	Change over 3 months: HbA1c (%):

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RCT	urban	no known diseases other than DM2 and hypertension, no diagnosed cardiovascular diseases	age(yrs): 54±2.5 HbA1c: 8.6±0.7 plasma glucose (mmol/l): 9.65±1.2 BMI ($kg/m^{2)}$: 27.1 ± 1.0	exercise 3-5 times/week vs. CG(n=10): walked 1 hour per day as part of their daily lifestyle Duration:12 wks		reduction in both groups with no differences between groups: 7.7±0.4 vs. 7.7±0.8 Plasma glucose (mmol/l): 9.6 ± 0.7 vs. 11.1 ± 1.3
Pharmacological strategies						
Distiller 2014 RCT	South Africa	DM2 for ≥ 1 year with total insulin requirement of >200 U/d for ≥ 3 months, BMI > 30 kg/m^2, HbA1c> 7,5 %, on long-term metformin therapy (1.7–2.5 g/d) no pregnant or with childbearing potential, endocrinopathy, chronic inflammatory or systematic autoimmune disorder, CVD, active carcinoma, chronic illness, renal dysfunction, gastroparesis, no corticosteroids, DPP-4 inhibitors, exenatide, liraglutide, no anticipated change in other concomitant medication or insulin resistence	n=28 50% female age (yrs): 51.7 (36-71) HbA1c (%): 8.95 (7.6-11.3) BMI (kg/m^2): 40.8 (31.2-47)	IG (n=14): regular Insulin (500 U/ml) + metformin + exenatide (5 µg orally twice a day for 1 month and titrated to 10 µg) vs. CG (n=14): regular Insulin (500 U/ml) +metformin Duration: 6 months	Primary: HbA1c Secondary: Body weight, insulin dose, hypoglycemia	Change to 6 months: HbA1c (%): Significant improvement in both groups 8.7→7.7(p=0.002) vs. 9.2→7.5 (p=0.0001) With no difference between groups (MD: 0.28; p=0.80) Complications: Mild hypoglycaemia: 5 vs. 2 persons with 20 vs. 5 events (p ≤ 0.001)
El-Haggar 2015 RCT	Egypt, urban 01/2013-04/2014	DM2, age: 45-55 yrs, obese (BMI≥30 kg/m^2), with duration 5-10 yrs, treated with glimepiride alone no Inflammatory disease,	n=48 79 % female age (yrs): 50.1±4.6 HbA1c (%): 7.83±0.87 fasting glucose (mg/dl): 193±50	IG1 (n=16): glimepiride (3 mg/d) + 2 (1 mg twice/d) vs. IG2 (n=16): glimepiride (3 mg/d) +	not specified: glycemic markers, metabolic markers, adiponectin, interleukin-6, leukotriene B4, mast cell tryptase, lipid panel,	Changes over 12 weeks: HbA1c (%): • Highest benefit for IG1: 7.1±0.86 vs. 8.2±0.82 vs. 8.7±0.93 (p< 0.05) fasting glucose (mg/dl): • Highest benefit for IG1: 199±38 vs.

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		severe hepatic or renal disease, epilepsy pregnant/lactating females	BMI (kg/m²): 37.6±4.6 duration of diabetes (yrs): 7.7 ±2.6	ketotifen (1 mg once/d) vs. CG (n=16): glimepiride (3 mg/d) alone Duration: 12 weeks	BMI	207.7± 47.6 (p< 0.05)
Malek 2015 RCT	Egypt, Algeria, Tunesia, South Africa 03/2010-05/2012	DM2, age ≥ 18 yrs, currently treated with suboptimal dose of oral anti-diabetic drugs; HbA1c 7-11 % (under metformin-monotherapy) and ≤ 10 % (under combination therapy), BMI≤40 kg/m^2 no allergies or contraindications to the product, pregnant or breastfeeding, impaired hepatic or renal function, cardiovascular history, uncontrolled hypertension, proliferative retinopathy, macular oedema	n=403 age (yrs): 52.8±9.6 59.8 % female HbA1c (%): 8.65 BMI (kg/m^2): 29.7±4.5 duration of diabetes (yrs): 7.5±5.1	Stepwise individual insulin intensification of IG (n=200): basal-bolus insulin analogues (insulin detemir +Insulin aspart) vs. CG (n=203): thrice daily biphasic insulin aspart depending on HbA1c-values over 50 wks	Primary: HbA1c Secondary: patients achieving HbA1c < 7.0 %, prandial plasma glucose	Change over 50 weeks: HbA1c (%): Non-inferiority: 7.4 vs. 7.3; MD 0.1 (-0.1 to 0.3 (full-analysis set), MD 0.2 (-0.1 to 0.4 (per protocol) 40.3% and 44.9% achieved HbA1c<7.0% Hypoglycaemia (events/patient year): 9.4 vs. 9.8 Serious adverse events: 6.5 vs. 3.4 % with 1 treatment-related SAE in CG Adverse events: 58.5 vs. 63.1%
Strategies on food supplementation						

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Ali 2019 RCT	Egypt Urban, tertiary care 09/2017 – 04/2018	DM2, oral antidiabetic agents with no change of type and dosage of antidiabetic agents in the past 3 months, ≥ 30 years insulin-dependence, pregnancy, lactation, use of Ca, multivitamins, Vitamin D supplements, use of drugs that affect Vitamin D status, dietary Ca intake > 1500 mg/d, hypo- or hyperthyroidism, smoking, use of antiepileptic drugs, sarcoidosis, tuberculosis, potentially terminal illness, inflammatory bowel disease, liver or kidney disease, malignancy	n=85 age (yrs): 54.6 ±2.8 68 % females BMI (kg/m²): 28.6±3.3 Diabetic duration (yrs): 4.4±2.1 fasting glucose (mg(dL): 168±54.4 fasting serum insulin (µIU/mL): 18.1±8.3 HbA1c(%):8.8±1.8	oral antidiabetic agents as usual + IG 1 (n=22): continuous oral Vitamin D3 (4000 IU/ d) vs. IG 2 (n=22): intermittent regimen of Vitamin D3 (50 000 IU/ week) vs. IG 3 (n=21): single IM injection of 300 000 IU of Vitamin D3 at the start of the study vs. CG (n=20): only oral antidiabetic agents Duration: 3 months	Not specified: serum creatinine, blood urea nitrogen, total and ionized Ca, serum phosphorus, fasting glucose, fasting serum insulin, 25(OH)D3 levels, HbA1c	After 3 months: fasting glucose (mg(dL): higher decrease in IG1 and IG2: -20.9±18.1 vs. -23.0±37.9 vs. -3.5±6.9 vs. 1.0±5.6 (p<0.001) fasting serum insulin (µIU/mL): higher decrease in IG1 and IG2: -4.44±5.2 vs.-5.88±4.6 vs. -1.55±9.4 vs. 0.10±1.0 (p< 0.001) HbA1c (%):higher decrease in IG1 and IG2: -0.81±0.77 vs. -0.82±0.87 vs. -0.34±1.47 vs. 0.05±0.08 (p<0.001)
Anderson 2001 RCT	Tunesia, urban	DM2 ≥ 5y, age< 65 yrs, fasting glucose > 8 mmol/l and HbA1C > 7.5 % no pregnant or lactating women, receiving trace element supplements in past 3 months, with gastric or diuretic treatment, acute renal, acute infection or recent surgery	n=110 age (yrs): 53.2 ±16.8 BMI (kg/m²): 29.1±1.0 HbA1c (%):8.82±3.25 fasting glucose (mmol/l): 11.45±0.83 duration of diabetes (months): 73.6±66	IG 1 (n=27): Zinc (30 mg/d) vs. IG 2 (n=27): Chromium (400 µg/d) vs. IG 3 (n=27): Zinc (30 mg /d) + Chromium (400 µg /d) vs. CG (n=29): placebo Duration: 6 months	Not specified: HbA1C, fasting glucose plasma concentrations of zinc, copper, selenium, urinary chromium and zinc, Plasma thiobarbituric acid reactive substances, copper-zinc-superoxid dismutase, selenium - glutathione peroxidase	Change over 6 months: HbA1c (%): 7.7±1.6 vs. 7.4±1.4 vs. 8.1±1.6 CG: not reported
Anyanwu 2016	Nigeria, urban	DM2, age 35-65 yrs on oral antidiabetics with vitamin D	n=42 57.6 % female	IG (n=21): Vitamin D3 supplements	Primary: HbA1c Other: fasting glucose,	Changes over 12 wks: HbA1c (%):

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT .		deficiency and poor glycemic control (HbA1c > 6.5 %) no patients on insulin, pregnancy, renal insufficiency, chronic liver disease or alanine transferase > 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state	age (yrs): 51.8±2.05 HbA1c (%): 7.88 fasting glucose (mg/dl): 152.8±56.5	(3000 IU/d) vs. CG(n=21): placebo Duration: 12 weeks	levels of serum Vitamin D, calcium, albumin, phosphate, creatinine, and alanine transaminase	• MD (IG vs. CG): -0.66 (-0.161 to 0.29) vs 0.38 (-0.08 to 0.84); • MD: -1.04 (-2.09 to 0.01) • change from poor glycemic control (HbA1c>6.5 %) to normal HbA1c (%): benefit for IF: 33.3 vs. -9.1 (p<0.05) fasting glucose (mg/dl): 137.2±33.6 vs. 154±67.5 patient adherence (tablet counts, %): 62.2 vs. 59.9
El Gayar 2019 **RCT**	Egypt, urban, outpatients 01/2017-01/2018	DM2 for < 6 months, 30-60 yrs, HbA1c level < 9%, BMI≥30 kg/m^2 no insulin therapy, any injectable or oral antidiabetic medication other than metformin, no smoking, consumption of alcohol or narcotic drugs, no acute illnesses at the baseline or during the study, no pregnancy or lactation, autoimmune disorder, cardiac or renal diseases, thyroid, chronic inflammatory diseases, peptic ulcer, regular consumption of ginger or other herbal drugs, hypersensitivity to ginger, consumption of lipid lowering drugs or oral contraceptive pills or any supplements 2 months before starting the study	n=80 49 % female age (yrs): 46.2 ± 9.1 HbA1c (%): 8.04±0.5 fasting glucose (mg/dl): 176.9±18.3 Fasting serum insulin (mIU/L): 19.3±3.3 BMI (kg/m²): 32.3±1.4	diet, physical activity, and metformin IG (n=40): ginger powder supplementation (600 mg/capsule, 3 capsules/d) vs. CG (n=40): Placebo Duration: 8 weeks	Not specified: glycemic status, lipid profile and beta-cell function	After 8 wks: HbA1c (%): decrease in both groups to 6.94±0.38 vs. 7.26±0.45 Fasting serum insulin (mIU/L): decrease in both groups to 12.86±2.59 vs. 13.21±2.08 fasting glucose (mg/dl): decrease in both groups to 120.88±9.06 vs. 151.70±13.23

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Sheikh 2019 RCT	Egypt, urban	DM2 on glimepiride alone, age ≥30 yrs no insulin sensitizers, steroids, NSAIDs, warfarin or lipid lowering medications, thyroid hormones, valproic acid or suffered from: acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism epilepsy, pregnant and breast-feeding women	n= 72 67 % female age (yrs): 50.6±8.7 HbA1c (%):9.76±1 fasting glucose (mg/dl):194.84±20.8 BMI (kg/m²): 34.4±5.45	IG (n=38): glimepiride 2 mg twice daily + L-carnitine 1 gm twice daily vs. CG (n=34): glimepiride dose 2 mg twice daily Duration: 6 months	HbA1c, fasting glucose, PPBG, fasting insulin, extracellular part of insulin regulated aminopeptidase, tumor necrosis factor-alpha, visfatin and lipid panel, BMI and homeostasis model assessment of insulin resistance	Change over 6 months: HbA1c (%): Benefit for IG: 7.41±0.5 vs. 9.5±0.78 (p<0.001) fasting glucose (mg/dl): Benefit for IG: 179.6±9.3 vs. 192.41±27.4 (p=0.018)
Matter 2020 NCT03851055 RCT	Egypt, urban, outpatients 08/2017 to 08/2018	DM, treated with insulin, 10 to 18 yrs, transfusion dependent beta-thalassemia major no other hemoglobinopathies (e.g. a-thalassemia or sickle thalassemia, disorders that may affect glucose homeostasis other than b-TM, autoimmune diseases, collagen diseases, hypo- or hyperthyroidism, infections, or tumours, or those who were taking any vitamins or food supplements < 1 month before the study and participating in a previous investigational drug study within 3 mo preceding screening	n=80 52.5% females age (yrs): 16.3±1.4 (range 12-18) fasting glucose (mg/dL): 144.5±22.4	diet schedule with optimal macronutrient distribution and pharmacologic treatment IG (n=40): zinc gluconate (2x20 mg/d) vs. CG (n=40): placebo Duration: 3 months	Primary: fasting glucose Secondary: fructosamine, fasting C-peptide, and HOMA-IR safety: any AEs (e.g. nausea, vomiting, abdominal pain, diarrhea, constipation, and reduction of appetite)	After 12 wks: fasting glucose (mg/dL): higher decrease with IG to 116.9±4.6 vs. 144.5±22.9 (p<0.001) HbA1c (%): higher in IG (no results reported) no side effects were reported
Moustafa	Egypt,	DM2, newly diagnosed	n=62	IG (n=29, 21 analysed):	Glycemic control,	After 3 months:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
2019 RCT	urban, outpatients recruitment 02/2016-03/2018	(within a time duration ≤6 months), 18–60 yrs other antidiabetic medications, pregnant and lactating women, major organ dysfunction (hepatic failure, active hepatitis, liver cirrhosis or renal complications), changed their standard medications during the 12 weeks of the study	72% females HbA1c(%): 7.51±1.4 fasting glucose (mg/dl): 154.4±51.6 BMI(kg/m^2): 33.9±6.1 family history of DM (%): 78.5 retinopathy/altered vision (%): 53 GDM (%): 9.2	nigella sativa oil capsules (3x 450 mg/d) vs. CG (n=33, 23 analysed): metformin (2000 mg/d) Duration: 3 months	oxidative stress markers, biochemical parameters, weight/BMI/waist circumference, total antioxidant capacity TAC	HbA1c (%): no difference: 7.01±0.83 vs. 6.55±0.72 fasting glucose (mg/dl): no difference: 119.8±23.7 vs. 120.7±25.4 Complications: no differences in occurrence of chills, sweating, tachycardia, lethargy/ weakness, polydipsia, polyuria, dry skin, polyphagia, blurred vision, foot problems, or tingling/numbness foot problems lower in IG: 4.8% vs. 33.3%, (p = 0.025).
Ragheb 2020 NCT03437902 RCT	Egypt, urban, outpatients care 02/2019-05/2018	DM2, receiving standard oral hypoglycemic agents, ≥ 35 yrs, no history of overt vascular disease, renal or hepatic failure or antioxidant supplementation or insulin therapy, no change of oral hypoglycemic drugs	n=70 age (yrs): 54.9±8.4 70 % females BMI (kg(m^2): 32.5±5.7 HbA1c(%): 8.50±1.86 fasting glucose (mg/dl): 142.8±52.6	IG2 (n=20): Rutin (60) + vitamin C (160 mg) 3x daily vs. IG1 (n=20): Vitamin C (500 mg) 1x daily vs. CG (n=13); only usual oral antidiabetic treatment Duration: 8 weeks	Primary: HbA1c, oxidative stress marker, antioxidant capacity, insulin resistance, lipid profile Secondary: Quality of life	After 2 months: HbA1c (%): no difference 7.494 ± 1.72 vs. 8.504 ± 2.059 vs. 8.504 ± 2.059 (p=0.1882) fasting glucose (mg/dl): lower in IG2 and CG: 111.3 (IQR 93.3-135.2) vs. 144 (114.8-201) vs. 113.3 (94-152.2) (p=0.017) Quality of life (SF 36): • Benefit of physical functioning and energy domains in IG2 vs. CG (p=0.0049, p=0.0253). • Benefit of role limitation to physical health and emotional improved in IG1 vs. CG (p=0.0267,p=0.0280) • no difference between groups in the other domains (emotional well-being, social functioning, pain and general health)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Rashad 2017 RCT	Egypt, urban	DM2, 50-62 yrs no insulin medication, allergies, recent thromboses or uncontrollable hypertension	n=34 43.3 % female age (yrs): 55.5±6.15 HbA1c (%):6.75±1.2 fasting glucose (mmol/l): 8.5±1.4 postprandial plasma glucose(mmol/l): 15.6±3.3 BMI (kg/m²):28.55±4 type of diabetes duration of diabetes (yrs): 6.1 ± 2.2	IG (n=17): Balanites aegyptiaca extract (400 mg)) vs. CG: (n=17) placebo capsules (potato maltodextrin) Duration: 8 wks	glycemic markers, lipid profile, FPG	Change over 8 wks: 2h postprandial plasma glucose: benefit for IG :26.88% decrease vs. CG 2.6% increase FPG (mmol/l): benefit for IG: 7.8 ± 0.9 vs. CG: 8.5 ± 1.1
Somanah 2012 NCT01248143 RCT	Mauritius, urban/rural 11/2010-03/2011	newly diagnosed DM, age 25–60 yrs fasting glucose range: 5.1–5.9 mmol/L no secondary complications, non-smoker or stopped for > 6 months , alcoholic consumption < 2 standard drinks/day, post-menopausal women without hormone replacement treatment, no glucose-lowering, cholesterol-lowering or anti-hypertension treatment	n=127 47% female age (yrs): range 25–60 HbA1c (%): 5.99±0.4 fasting glucose (mg/dL): 93.2±8.0 BMI (kg/m^2): 26.6 ± 3.7	IG (n=44): supplementation of a fermented papaya preparation (6g/d twice daily, over 12 wks), followed by a 2 week wash out period with the same amount of water vs. CG (n=56): consumed an equivalent amount of water Duration: 14wks	HbA1C fasting glucose, Lipid profile, diet score, blood pressure, alanine aminotransferase; aspartate aminotransferase, Ferritin, c-reactive protein, uric acid, microalbumin/urinary creatinine ratio	After 14 wks: HbA1c (%): no difference (p=0.448) fasting glucose (mg/dL): • remained relatively unchanged in boths genders: • males: 96.2±17.0 vs. 87.6±11.7 • females: 95.6±15.8 vs. 94.3±5.0
Strategies on treatment of DM related complications						

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Makaky 2020 NCT03783845 RCT	Egypt, urban/rural recruited 06/2015 to 03/2016	DM2 for >5 yrs, 40-70 yrs, HbA1c 7 to 9% at the last medical evaluation, no change in diabetes treatment over the previous 3 months, ≥ 6 permanent teeth excluding third molars, clinical attachment level and pocket depth ≥4 mm in >30 % of the sites, diagnosis of chronic periodontitis based on the presence of 4 teeth as a minimum with ≥ 1 site Pregnancy, alcoholism and smoking, Presence of any systemic disorders other than hypertension and diabetes, diabetic major complications, antimicrobial therapies or periodontal therapies in the last 6 months, allergy to metronidazole and amoxicillin	n=88 56.8 % females age (yrs): 52.6±6.8 HbA1c (%): 8.16±0.72	IG (n=44): immediate periodontal therapy: one-stage scaling and root planning, a combination of systemic antibiotics (amoxicillin 500 mg and metronidazole 400 mg 3x/day for 2 weeks), and oral hygiene instructions vs. CG(n=44): delayed periodontal therapy after 3 months Duration: 3 months	Primary: HbA1c Secondary: not named	After 3 months: HbA1c (%): benefit for IG: 7.27±0.5 vs. 8.34±0.64: MD -1.07 (-1.32 to -0.83)
El-Sharkawy 2016 NCT02794506 RCT	Egypt, urban 06/2014-03/2015.	DM2 >5 yrs, >20 teeth, chronic moderate or severe periodontitis with probing depth and clinical attachment level >5 mm, bleeding by probing, on oral hypogylcemic drug therapy > 6 months, no smoking, use of	n=50 34% female age (yrs): 50.5 ± 7.4 (38 to 63) HbA1c (%): 8.66 ±0.73 FPG (mg/dl): 183.5 ±12.547 BMI (kg/m²): 26.9± 3.1 duration of diabetes	IG (n=24): scaling and root planing (SRP)+ 400mg oral Propolis once daily vs. CG (n=26) scaling and root planing (SRP)+Placebo Duration: 6 months	Primary: HbA1c Secondary: FPG, serum N-(carboxymethyl) lysine, periodontal parameters	after 6 months HbA1c (%) Benefit for IG 7.75± 0.48 vs.8.5±0.73 (p<0.01) FPG(mg/dl) Benefit for IG

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		antibiotics, non-steroidal or anti-inflammatory drugs within the last 3 months, periodontal therapy ≤ 1 year, retinopathy grade 3/4, pregnancy, no contraceptive drugs	(yrs): 8.1 ± 3.9 hypertension: 4.5% neuropathy: 1.5% retinopathy: 0.5% nephropathy: 0%			
Ghoneim 2013 RCT	Egypt, 03/2010-03/2012	DM, duration ≥ 15 yrs, bilateral diabetic macular edema (≥ 6 months) no prior treatment with intravitreal corticosteroids, peribulbar steroid injection within ≤ 6 months, pars plana vitrectomy, history of glaucoma or steroid induced IOP elevation, ischemic maculopathy, foveal tracted, IOP≥ 23 mmHg	n=19 (38 eyes) 89.5 % female age (yrs): 52.3±11.4	IG (n=19): one eye with 8 mg triamcinolone acetonide vs. CG (n=19): other eye with4 mg of triamcinolone acetonide Duration: 6 months	Primary: Visual acuity Others: Intraocular pressure (IOP), IOP lowering drugs, complications	after 6 months: Complications: • no eyes with retinal detachment, vitreous haemorrhage, intraocular reaction or endophthalmitis. • one eye in IG developed posterior subcapsular cataract.
Nteleki 2015 RCT	South Africa, urban	DM2 with neuropathic or mixed (venous and arterial) ulcers; lower extremity ulcer; stable or worsening ulcer that has been present for ≥ 4 weeks no acute cellulitis, osteomyelitis, or gangrene, renal, hepatic, hematologic, neurologic, or immune disease not related to diabetes; presence of malignant disease not in remission for > 5 years; use of oral or parenteral	n=7 with 14 lower extremity ulcers 85 % male age (yrs): 62 duration of diabetes (yrs): 16.7	standard podiatric management and IG1 (n=2): phototherapy to the regional lymphatic nodes and ulcer(s) vs. IG2 (n=3): phototherapy on the ulcer vs. CG (n=2): placebo phototherapy Duration: 12 weeks	healing rate (area and perimeter of the ulcer)	after 3 months: Healing: • The rate of healing increased in all three groups, • 67% of ulcers received some form of phototherapeutic intervention, 40% of those ulcers resolved completely over 8 weeks no AEs

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		corticosteroids, immunosuppressive, or cytotoxic agents; known infection with human immunodeficiency virus or presence of AIDS; other leg ulcers				
Saeed 2013 RCT	Egypt, urban 11/2010-07/2012	DM, intractable diffuse diabetic macular edema without vitreomacular traction. central foveal thickness ≥300 µm no vitreomacular traction, active neovascularization of proliferative diabetic retinopathy, an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography, treatment for diabetic macular edema within ≤ 3 months, previous vitreoretinal surgery, other major ocular surgery within the previous 6 months, YAG capsulotomy within ≤2 months, macular pathology	n= 34 (34 eyes) 50% females age (yrs): 55.5 ± 8.9 duration of diabetes (yrs): 24±5.4	IG (n=15): vitrectomy with removal of the posterior hyaloid, at the end of the procedure injection of intravitreal triamcinolone acetonide (IVTA, 0.1 mL, 40 mg/mL) +bevacizumab (1.25 mg) +macular grid laser photocoagulation vs. CG (n=15); same intravitreal injection combination Duration: 12 months	primary: BCVA, central foveal thickness	Changes over 12 months Complications: • Changes in BCVA and central foveal thickness at 3, 6, and 12 *(P*< 0.01), better mean BCVA in IG at 12 months. • Better mean central foveal thickness in IG at 12 months. Major adverse events: development of cataracts (3/15 vs. 6/15) and elevation of intraocular pressure (7/15 vs. 2/15)
Tsobgny-Tsague 2018 NCT02745015 RCT	Cameroon, urban, tertiary care, 12/2014-	DM2, >11teeth, severe chronic periodontitis according to the 2012 CDC-AAP classification, no periodontal treatment,	n=34 56% female age (yrs): 51.4 ± 8.8 HbA1c (%):9.3 ± 1.3 BMI (kg/m²): 28.3± 5.4	IG (n=17): immediate ultrasonic scaling, scaling and root planning +subgingival 10% povidone iodine irrigation	Primary: change in HbA1c Secondary: Plaque index, gingival bleeding index, pocket depth, clinical attachment loss	Change over 3 months: HbA1c (%): Benefit with IG: 6.7 ± 2.0 % vs. 8.1 ± 2.6 %, MD: 2.2 (p=0.029) adverse events: 1 /15 patient reported tongue

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
	05/2015	alteration of DM treatment 6 mths prior to the study, onset of systemic diseases or an acute condition, use of immunosuppressive medications or others drugs or presence of conditions able to alter periodontitis clinical features	duration of diabetes (months): 55.5 ± 42.6 complications: neuropathy (%): 40 nephropathy (%): 7 retinopathy (%): 7 diabetic foot (%): 3	vs. CG(n=17): periodontal treatment 3 months later Duration: 3 months		irritation following chlorhexidine moth rinse in IG
Yakoot 2019 NCT01531517 RCT	Egypt, urban 07/2011-07/2013	Adult DM2 or DM1 patients, limb-threatening diabetic foot ulcerations no life-threatening extensive gangrenous lesions that needed immediate amputations; bad general condition; shock or unstable vital signs; critically ill with severe organ/system dysfunctions or advanced malignancy.	n=119 gender:44.5% female age (yrs): 54.7 ±8.4 type of diabetes: • DM1: 22.9% • DM2: 86.2%	conservative debridement of necrotic tissue and irrigation with warm normal saline and IG (n=61): local application of ointment composed of royal jelly and panthenol vs. CG (n=58): local application of Panthenol duration: 12months	primary: complete healing secondary: reduction of infection in the ulcer site, al reaction that may be due to study drug	after 12 months rate of complete healing (%): Benefit for IG: 32.4% vs. 12%; p=0.034

ADA: American Diabetes Association; BCVA: Best-corrected visual acuity; BMI: Body mass index; CG: Control group; CI: Confidence interval; CHC: Community health centre; DBP: Diastolic blood pressure; DM: diabetes mellitus; DM1: Type 1 diabetes; DM2: type 2 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG: intervention group; IQR: interquartile range; n: number of participants; NCD: Non-communicable disease; NPH: neutral protamine Hagedorn; MD: mean difference; MDa: adjusted mean difference; NCD: Non-communicable disease ;RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SAE: Serious adverse events; SBP: Systolic blood pressure; SCI: Diabetes Self-Care Inventory; SD: Standard-deviation; SMBG: self-monitoring of blood glucose; wks: weeks; yrs: years

Supplementary Table 3: Characteristics and results of studies on patients with DM2

RCTs on pregnant DM patients

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value	**Study name** registration number Design
Strategies to increase physical activity						
Embaby 2016 RCT	Egypt, urban, 07/2014-02/2015	at increased risk for GDM due to obesity (BMI ≥ 30 kg/m^2), age:> 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2 no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease, cardiac, renal impairment and malignancy	n=40 100% female age (yrs): 29.2±3.8 BMI (kg/m²):28.7±1.3 fasting glucose (mmol/l): 6.5±0.9 fasting insulin (IU/l): 15.78±1.58	IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives. Duration: appr. 4 months	Fasting plasma glucose, Insulin level	Change to 37th week of gestation: FPG (mmol/l) Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001) Fasting insulin (IU/l): Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)
Other non-pharmacological therapies						
El-Shamy 2018 RCT	Egypt, urban 12/2016-05/2017	GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus no high-risk pregnancy, bad obstetric situations or diseases, smoking, oral sedatives	n=30 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): • fasting glucose: 129.05±0.6 • 2h postprandial: 146±1.65 BMI (kg/m²): 27±1.5	IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only Duration: 12 weeks	Primary: glycemic control, requirement for insulin, insulin resistance Secondary: neonatal outcomes	Change over 3 months: 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9 Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %

Utz 2018 NCT02979756 Cluster-RCT	Marocco, urban / rural, primary care, 11/2016-02/2018	Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM no DM2, DM1	20 health centres n= 215 age (yrs):27.6±6.6 urban (%): 38.5 rural (%): 61.5	20 clinics were randomized→ 10 in each group <u>IG (n=120):</u> first screening for GDM→positive tested women received counselling on nutrition and exercise <u>vs.</u> <u>CG (n=95):</u> routine practice	Primary: birthweight Secondary: maternal weight gain, glucose control, pregnancy complications.	Follow-up visits: 7.5±4.9 vs. 3.8±3.3 (p=0.001) FBG within the norm: better with IG <1/3 of all values: 7.6 vs. 32.6 % 1/3-2/3 of all values: 17.8 vs. 32.6 % >2/3 of all values: 74.6 vs. 34.8 % Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)
Pharmacological strategies						
Ashoush 2016 RCT	Egypt, urban, tertiary care 01/2014-11/2014	GDM, mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glycemic control despite adequate diet and exercise for ≥ 1 wk no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis	n=95 100% female age (yrs): 31.8±3 HbA1c (%): 5.75 ± 0.55 75g OGTT (mg/dl) • fasting: 106.05±4.6 • 1h:310.25±11.6 • 2h:176.65±9.4 BMI (kg/m²): 31.2±1.4	<u>IG (n = 47):</u> metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed) <u>vs.</u> <u>CG (n = 48):</u> <u>regular insulin + neutral protamine Hagedorn (3:7) (starting dose 0.7 units /kg*d, adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed)</u> <u>Duration: until delivery</u>	Primary: successful maternal glycemic control Secondary: maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit	Until delivery: fasting glucose during treatment (mg/dl): better with IG: • during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008) • during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029) maternal hypoglycaemia (%): no difference: 6.25 vs. 12.5 (p=0.254) neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p=0.791) Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001) neonatal congenital anomalies (%): 2.1 vs. 2.1 p= 0.747 headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy) neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514) Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)

Beyuo 2015 ACTRN12614000942651 RCT	Ghana, urban 01/2013-12/2013	pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy no T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin	n= 104 100% female age (yrs): 33.3±4.6 fasting glucose (mmol/l): 8 2HPG (mmol/l): 10.5 BMI (kg/m²): 3.1±6.6 type of diabetes: GDM (%): 65.9 DM2 (%): 34.0	IG (n=52): Metformin (starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary) vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg, titrated to achieve the glycemic targets, if necessary, admission to the ward and therapy with soluble insulin) Duration: until delivery	Primary: 2-hour post prandial blood glucose (2HPG) Secondary: fasting glucose, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.	Change from enrolment to delivery: glycemic control (mmol/l): fasting glucose: no difference: 6.42±0.98 vs. 6.62±1.57 (p=0.928) 1HPG: no difference: 8.95±1.27 vs. 9.62±1.44 (p=0.078) 2HPG: benefit for IG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)
Ibrahim 2014 NCT01915550 RCT	Egypt, urban 08/2011-04/2012	GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance No DM1, secondary diabetes or liver or renal impairment	n=90 100% female age (yrs): 29.8 ± 5.4 BMI (kg/m²):31.83 ± 3.23 Gestational age: 28.7 ± 3.7 wks GDM: 43.3 % Pre-existing DM: 56.7 % with median duration of 4 (1-15) yrs	IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose Patients switched to CG if treatment was not successful to control blood glucose concentrations CG (n=44): insulin dose was increased according to the standard protocol	Primary: maternal gylcemic control (fasting glucose ≤ 95 mg/dl and 2-HPG ≤ 120 mg/dl) Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes	gylcemic control: • better for CG: 76.1 vs. 100 % reached glycemic control (p=0.001) • 13 vs. 18.2 % had readmission for poor glycemic control • 6.5 vs. 22.7 % had bouts of maternal hypoglycaemia Complications: • 23.3 vs. 30.8 % had fetal macrosomia • 1 new-born in each group had congenital malformations • 7 vs. 38.5 % had neonatal hypoglycaemia • 18.6 vs. 41 % had NICU admission • 0 vs. 5.1 % had stillbirths • 11.6 vs. 25.6 % with respiratory distress syndrome

BMI: Body mass index; CG: Control group; CI: Confidence interval; DM: diabetes mellitus; DM2: type 2 diabetes; FPG: fasting plasma glucose; GDM: gestational diabetes; HbA1c: haemoglobin A1c; 1 / 2HPG: 1 / 2-hour post prandial blood glucose; IG: intervention group; n: number of participants; MD: mean difference; MDa: adjusted mean difference; OGTT: Oral glucose tolerance test; RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 4: Characteristics and results of studies on pregnant women with DM

Risk of bias

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Abaza 2017	☺	☺	☹	☺	☹	☺	☺
Abdulrhman 2013	☺	😐	☹	☺	☺	☹	😐
Adibe 2013	☺	☺	☹	☹	☹	😐	☺
Adjei 2015	😐	😐	☹	☺	☺	😐	☹
Ali 2019	😐	😐	☹	😐	😐	😐	☹
Amendezo 2017	😐	😐	☹	☺	☹	☺	☹
Anderson 2001	😐	😐	☺	☺	😐	😐	☺
Anyanwu 2016	😐	😐	☹	😐	☹	😐	☺
Ashoush 2016	☺	☺	☹	😐	☺	😐	☺
Asuako 2017	😐	☺	☹	😐	☺	😐	☹
Beyuo 2015	😐	☺	☹	😐	☹	☹	☹
Chraibi 2017	😐	😐	☹	😐	☹	☺	☹
Debussche 2018	☺	☺	☹	😐	☺	☺	☺
Distiller 2014	😐	☺	☹	😐	☹	😐	☺
Elbarbary 2016	😐	😐	☹	😐	☹	😐	☹
Elbarbary 2018	☺	☺	☺	😐	☺	☺	☺
Elbarbary 2020	☺	☺	☺	☺	☺	☹	😐
El Gayar 2019	☺	☺	☺	☺	😐	😐	☹
El-Haggar 2015	😐	😐	☹	😐	😐	😐	☹
El-Makaky 2020	😐	☺	☹	☺	☺	😐	😐
El-Shamy 2018	☹	☹	😐	😐	☺	😐	☺
El-Sharkawy 2016	☺	☺	☺	☺	☺	☺	☹
El-Sheikh 2019	😐	😐	☹	😐	☹	😐	☹
Embaby 2016	😐	😐	☹	😐	☹	😐	☹
Essien 2017	☺	☺	😐	☺	☹	😐	☺
Fairall 2016	😐	☺	😐	😐	☺	☺	☺
Fayehun 2018	😐	☺	☹	☹	☺	😐	☺
Ghoneim 2013	☺	😐	☹	😐	😐	😐	☹
Hailu 2018	☺	😐	☹	☺	☹	😐	☹
Ibrahim 2014	☺	😐	☹	😐	☹	☺	☹
Krawinkel 2018	☺	😐	☹	☹	☹	☺	☺

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Labhardt 2011	☺	☺	☹	😐	☺	☺	☺
Maharaj 2016	😐	😐	☹	☺	😐	😐	☹
Malek 2015	😐	😐	☹	😐	☺	😐	😐
Malipa 2013	😐	😐	☹	☹	😐	😐	☹
Mash 2014	☺	😐	☹	☹	☹	☺	☺
Matter 2020	☺	☺	☺	☺	☺	☹	☺
Mohamad 2009	😐	😐	☹	😐	😐	😐	☹
Moustafa 2019	😐	😐	☹	😐	☹	😐	☹
Muchiri 2015	☺	☺	☹	☺	☺	😐	☹
Nteleki 2015	☹	😐	☹	😐	☺	😐	☹
Owolabi 2019	😐	☺	☹	☺	☺	☹	☹
Rashad 2017	☺	☺	☺	☺	☹	😐	☹
Ragheb 2020	☺	😐	☹	☹	☹	☺	☺
RezkAllah 2019	☺	☺	☹	☺	☺	☺	☺
Saeed 2013	😐	😐	☹	☹	☹	😐	☹
Salem 2010	😐	😐	☹	☹	😐	😐	☹
Sodipo 2017	☺	😐	☹	😐	☹	😐	☺
Somanah 2012	😐	😐	☹	😐	☹	☹	☹
Steyn 2013	☺	😐	☹	😐	☹	😐	☺
Takenga 2014	😐	😐	☹	😐	☺	😐	☹
Tawfik 2016	😐	☺	☺	☺	☹	😐	☺
Thuita 2020	😐	☺	☹	😐	☺	😐	☺
Tsobgny-Tsague 2018	☺	😐	☹	☺	☹	☺	☺
Utz 2018	☺	☺	☹	☺	☺	☹	☹
Van der Hoogt 2017	😐	😐	☹	😐	☹	😐	☹
Van Rooijen 2004	☺	☺	☹	☺	☺	😐	☹
Webb 2015	😐	😐	😐	☺	☹	☺	😐
Yakoot 2019	😐	☺	☹	☹	☺	☹	☹
Yan 2014	😐	😐	☹	😐	☺	😐	☹
☺: low, 😐: unclear, ☹: high risk of bias							

Supplementary Table 5: Judgements on risk of bias

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1 (Numbers are manuscript pages)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary data
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	not done due to the narrative approach

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	not done due to the narrative approach
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not done due to the narrative approach
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not done due to the narrative approach
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary data, list of excluded studies
Study characteristics	17	Cite each included study and present its characteristics.	9-16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Data – Table: Risk of Bias
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Data – Tables
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 3 and 4 in the results section (page 13)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9 (study designs, participants, settings) Pages 10 – 15 (interventions) narrative description of heterogenous studies
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not done due to the narrative approach

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not done due to the narrative approach
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Only for HbA1c measures: Figures 3 and 4; others not done due to narrative approach
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17
	23b	Discuss any limitations of the evidence included in the review.	21
	23c	Discuss any limitations of the review processes used.	21-22
	23d	Discuss implications of the results for practice, policy, and future research.	17-21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8 + abstract
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8 + abstract
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	23
Competing interests	26	Declare any competing interests of review authors.	23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	In the supplement: search strategy for 6 databases, list of included and excluded studies

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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PROSPERO
International prospective register of systematic reviews

Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries: a systematic review

Susanne Unverzagt, Angelika S. Sandholzer, Thomas Frese, Yeabsra Mesfinin

Citation

Susanne Unverzagt, Angelika S. Sandholzer, Thomas Frese, Yeabsra Mesfinin. Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries: a systematic review. PROSPERO 2019 CRD42019122785 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019122785

Review question

To summarize available evidence from randomized controlled trials on prevention, diagnosis and treatment of diabetes initiated from African countries.

Searches

Randomized controlled trials without time or date restriction, in English or German language. Electronic databases: MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL), registers of ongoing and completed trials (www.ClinicalTrials.gov, apps.who.int/trialsearch).

Results will be screened by 2 independent authors. Discrepancies will be resolved by discussion between the authors or with a third author.

Types of study to be included

Randomized controlled trials on prevention, diagnosis and treatment of diabetes.

Condition or domain being studied

Diabetes mellitus (type 1 and type 2), gestational diabetes.

Participants/population

African patients in primary, secondary and tertiary prevention, diagnosis and treatment of diabetes.

Intervention(s), exposure(s)

All preventive, diagnostic and curative interventions on diabetes.

Comparator(s)/control

Another intervention, or none.

Main outcome(s)

Primary outcome: all-cause mortality during the longest reported follow-up period (measured from randomisation).

Secondary outcomes: glucose control (HbA1c, insulin resistence, oral glucose tolerance test, fasting serum or plasma glucose), complications, quality of life, hospital admission, treatment adherence (at longest follow-up).

* Measures of effect

Within the longest reported follow-up period.

Additional outcome(s)

Cost.

* Measures of effect

Within the longest reported follow-up period.

Data extraction (selection and coding)

One authors will extract information on study population (diabetes type 1, type 2, gestational diabetes), intervention and outcome by using an assessment form, which will be designed especially for the topic of this review and tested for five studies. A second author will check all extractions, unclear information will be discussed. The data extraction form will include at least the following items: title, author, reference, study design, country, duration, follow-up, indication of patients (primary, secondary, tertiary prevention), sample size per group, description of intervention and control (drugs, devices, strategies), primary and secondary outcomes with results.

Risk of bias (quality) assessment

Risk of bias will be described and judged on the basis of the Cochrane risk of bias tool in seven specific domains: 1.

Sequence generation (judgement per study) 2. Allocation concealment (judgement per study) 3. Blinding of participants and personnel (judgement per study and outcome) 4. Blinding of outcome assessors (judgement per study and outcome) 5. Incomplete outcome data (judgement per study and outcome) 6. Selective outcome reporting (judgement per study and outcome 7. Other sources of bias (judgement per study and outcome). We will judge risk of bias domains as 'low', 'high' or 'unclear' and will evaluate individual bias items and present a summary figure to illustrate these findings.

Discrepancies will be resolved by discussion between the authors or with a third author.

Strategy for data synthesis

We plan a narrative synthesis to get a comprehensive overview on this area of research. We add a meta-analysis with the random-effects model on our primary and secondary outcomes on the basis of aggregated information (Hazard ratio, Relative risks or Odds Ratio) if included studies are sufficiently homogeneous in population, intervention, and outcomes and results show no substantial heterogeneity. We will use the Review Manager for data synthesis.

Analysis of subgroups or subsets

Study population (diabetes type 1, type 2, gestational diabetes), prevention, diagnosis and treatment type of prevention (primary, secondary and tertiary), type of intervention (drugs, devices, strategies) and regions (northern, eastern, central, southern Africa).

Contact details for further information

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Organisational affiliation of the review

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https://www.medizin.uni-halle.de/index.php?id=7167&L=1%27andchar%28124%29

Review team members and their organisational affiliations

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Angelika S. Sandholzer. MD student, Institute of General Practice and Family Medicine, University Halle / Wittenberg
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Yeabsra Mesfinin. School of Public Health, Addis Ababa University

Collaborators

Dr Eva Kantelhardt. Institute of Medical Epidemiology, Biostatistics and Informatics, University Halle / Wittenberg

Type and method of review

Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date
15 November 2018

Anticipated completion date
31 December 2019

Funding sources/sponsors
DAAD ("Chronic disease health service teaching and research"), project 57216764

Conflicts of interest

Language
English

Country
Ethiopia, Germany

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Africa; Diabetes Mellitus, Type 2; Humans; Randomized Controlled Trials as Topic

Date of registration in PROSPERO
25 March 2019

Date of first submission
28 January 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

25 March 2019
07 August 2019

Search strategies

Medline (Ovid)

Search on 19.11.2018, 1470 references, Update from 2018 to Current on 20.08.2020: 541 references

Nr.	Searches
1.	exp Diabetes Mellitus/
2.	Diabetes.tw
3.	**or/1-2**
4.	Africa.tw
5.	Exp Africa/
6.	Algeria$.tw or exp Algeria/
7.	Angol$.tw or exp Angola/
8.	Benin$.tw or exp Benin/
9.	Botswan$.tw or exp Botswana/
10.	Burkina Faso.tw or exp Burkina Faso/
11.	Burund$.tw or exp Burundi/
12.	Cameroon$.tw or exp Cameroon/
13.	Cape Verde.tw or exp Cape Verde/
14.	Central African Republic$.tw or exp Central African Republic/
15.	Chad$.tw or exp Chad/
16.	Comoros$.tw or exp Comoros/
17.	Cote d'Ivoire.tw or exp Cote d'Ivoire/
18.	Democratic Republic of Congo.tw or exp Democratic Republic of Congo
19.	Djibout$.tw or exp Djibouti/
20.	Egypt$.tw or exp Egypt/
21.	Equatorial Guinea$.tw or exp Equatorial Guinea/
22.	Eritrea$.tw or exp Eritrea/
23.	Ethiop$.tw or exp Ethiopia/
24.	Gabon$.tw or exp Gabon/
25.	Gambia$.tw or exp Gambia/
26.	Ghana$.tw or exp Ghana/
27.	Guinea$.tw or exp Guinea/
28.	Guinea-Bissau.tw or exp Guinea-Bissau/
29.	Kenya$.tw or exp Kenya/
30.	Lesoth$.tw or exp Lesotho/
31.	Liberia$.tw or exp Liberia/
32.	Libya$.tw or exp Libya/
33.	Madagascar$.tw or exp Madagascar/
34.	Malawi$.tw or exp Malawi/

Nr.	Searches
35.	Mali.tw or exp Mali/
36.	Mauritania$.tw or exp Mauritania/
37.	Mauritius$.tw or exp Mauritius/
38.	Morocc$.tw or exp Morocco/
39.	Mozambique$.tw or exp Mozambique/
40.	Namibia$.tw or exp Namibia/
41.	Niger.tw or exp Niger/
42.	Nigeria$.tw or exp Nigeria/
43.	Rwanda$.tw or exp Rwanda/
44.	(Sao Tome and Principe).tw
45.	Senegal$.tw or exp Senegal/
46.	Seychell$.tw
47.	Sierra Leone.tw or exp Sierra Leone/
48.	Somalia$.tw or exp Somalia/
49.	South Africa$.tw or exp South Africa.de
50.	South Sudan.tw or exp South Sudan/
51.	Sudan$.tw or exp Sudan/
52.	Swaziland$.tw or exp Swaziland/
53.	Tanzania$.tw or exp Tanzania/
54.	Togo$.tw or exp Togo/
55.	Tunisia$.tw or exp Tunisia/
56.	Uganda$.tw or exp Uganda/
57.	Zambia$.tw or exp Zambia/
58.	Zimbabwe$.tw or exp Zimbabwe/
59.	Somaliland$.tw or exp Somaliland/
60.	Sahrawi Arab Democratic Republic.tw.
61.	or/4-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	(randomized or randomised or randomly).ti,ab
65.	placebo.ti,ab.
66.	trial.ti,ab.
67.	groups.ti,ab.
68.	or/62-67
69.	3 and 61 and 68
70.	exp animals/ not humans.sh.
71.	69 not 70
72.	71 not (comment or editorial).pt.

CENTRAL

Search on 14.01.2019, 439 trials, Update from 2018 to Current on 20.08.2020: 244 trials

1	Africa, explode all trees
2	Algeria* or Angol* or Benin* or Botswan*
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)
4	Chad* or Comoros* or Cote d'Ivoire or Congo*
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor Diabetes, this term only
14	MESH descriptor Diabetes mellitus, explode all trees
15	Diabetes near 3 gestation*
16	Latent autoimmune diabetes in adults
17	Prediabetes
18	Insulin resistan*
20	HBA1C
21	Diabet* near 3 (angiopath* or foot orfeet or retinopath*)
22	Diabet* near 3 (cardiomyopathy* or coma or ketoacido* or neuropath*)
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
32	#12 and #23

CINAHL

Search on 20.08.2020: 19 results

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$

or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract
AND
diabetes in Abstract
AND
randomized or rct or randomized in Abstract
AND
In English
AND
Peer-reviewed
And
Humans

International Clinical Trials Registry Platform

Search on 9.-10.10.2019, update on 25.08.2020 (registration January 2019 to 31.08.2020)
http://apps.who.int/trialsearch/AdvSearch.aspx

1. Africa or African in the Title and diabetes or diabetic or HbA1c in the condition, Recruitment status: all**:** 90 records for 90 trials (9.10.2019)
2. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Central African Republic or Chad or Congo or Cite D'ivoire: 96 record for 63 trials
3. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia: 292 records for 159 trials
4. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Lybia: 22 records for 22 trials
5. diabetes or diabetic or HbA1c in the condition

Recruitment status: all

Countries of recruitment: Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique: 96 records for 34 trials

6. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Nigeria: 13 records for 13 trials

7. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Namibia or Niger or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Sudan or Sudan or Swaziland:

   11 records for 11 trials

8. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: South Africa: 1528 records for 429 trials:

9. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Togo or Tunesia or Ujanda or Zambia or Zimbabwe: 129 records for 50 trials

African Journals Online

https://www.ajol.info/index.php/index/search/search?query=%28diabetes+or+diabetic+or+hba1c%29+and+%28random+or+randomized+or+randomised%29&dateFromYear=2004&dateFromMonth=01&dateFromDay=1&dateToYear=2020&dateToMonth=10&dateToDay=14&authors=

Advanced search 14.10.2020
Titel: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
30 results

African Index Medicus Database

http://indexmedicus.afro.who.int/aim/opac_css/index.php?lvl=search_result&get_query=4

Advanced search 14.10.2020
Titel, Expression booléenne: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
122 results, no potentially eligible references

1 List of included and excluded studies

1.1 List of included studies

Abaza 2017

Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC public health. 2017;17(1):962.

Abaza H, Marschollek M, Schulze M. SMS Education for the Promotion of Diabetes Self-Management in Low & Middle Income Countries: A Randomized Controlled Trial in Egypt. Studies in Health Technology & Informatics. 2017;245:1209.

Abdulrhman 2013

Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. Journal of Medicinal Food. 2013;16(1):66-72.

Adibe 2013

Adibe MO, Ukwe CV, Aguwa CN. The Impact of Pharmaceutical Care Intervention on the Quality of Life of Nigerian Patients Receiving Treatment for Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):240-7.

Adibe MO, Aguwa CN, Ukwe CV. Cost-Utility Analysis of Pharmaceutical Care Intervention Versus Usual Care in Management of Nigerian Patients with Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):189-98.

Adjei 2015

Adjei DN, Agyemang C, Dasah JB, Kuranchie P, Amoah AG. The effect of electronic reminders on risk management among diabetic patients in low resourced settings. Journal of Diabetes & its Complications. 2015;29(6):818-21.

Ali 2019

Ali S, Ghanem Y, Sharaki O, Hewedy W, al. e. The impact of different regimens of vitamin d3 on glucose homeostasis in type 2 diabetic patients. Asian journal of pharmaceutical and clinical research. 2019;12(12):21- 6.

Amendezo 2017

Amendezo E, Walker Timothy D, Karamuka V, Robinson B, Kavabushi P, Ntirenganya C, et al. Effects of a lifestyle education program on glycemic control among patients with diabetes at Kigali University Hospital, Rwanda: A randomized controlled trial. Diabetes Research & Clinical Practice. 2017;126:129-37.

Anderson 2001

Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. Journal of the American College of Nutrition. 2001;20(3):212-8.

Anyanwu 2016

Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian Journal of Endocrinology and Metabolism. 2016;20(2):189-94.

Ashoush 2016

Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. Journal of obstetrics and gynaecology research. 2016;42(6):640- 7.

Asuako 2017

Asuako B, Moses MO, Eghan BA, Sarpong PA. Fasting plasma glucose and lipid profiles of diabetic patients improve with aerobic exercise training. Ghana Medical Journal. 2017;51(3):120-7.

Beyuo 2015

Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. PLoS ONE [Electronic Resource]. 2015;10(5):e0125712.

Chraibi 2017

Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshmivenkataraman B, et al. An RCT Investigating Patient-Driven Versus Physician-Driven Titration of BIAsp 30 in Patients with Type 2 Diabetes Uncontrolled Using NPH Insulin. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2017;8(4):767-80.

Debussche 2018

Debussche X, Besancon S, Balcou-Debussche M, Ferdynus C, Delisle H, Huiart L, et al. Structured peer-led diabetes self-management and support in a low-income country: The ST2EP randomised controlled trial in Mali. PLoS ONE. 2018;13(1):e0191262.

Distiller 2014

Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin. Endocrine practice. 2014;20(11):1143- 50.

El Gayar 2019

El Gayar MH, Aboromia MMM, Ibrahim NA, Abdel Hafiz MH. Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus. Obesity medicine. 2019;14.

El-Haggar 2015

El-Haggar SM, Farrag WF, Kotkata FA. Effect of ketotifen in obese patients with type 2 diabetes mellitus. Journal of Diabetes & its Complications. 2015;29(3):427-32.

El-Makaky 2020

El-Makaky Y, Shalaby HK. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: a randomized controlled trial. Oral diseases. 2020;26:822-9.

El-Shamy 2018

El-Shamy FF, El-Kholy SS, Labib M, Kabel AM. Ameliorative potential of acupressure on gestational diabetes mellitus: a randomized controlled trial. Journal of complementary and integrative medicine. 2018; 16(1).

El-Sheikh 2019

El-Sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of L-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. Diabetes and metabolic syndrome: clinical research and reviews. 2019;13(1):167-73.

El- Sharkawy 2016

El- Sharkawy HM, Anees MM, Van Dyke TE. Propolis improves periodontal status and glycemic control in patients with type 2 diabetes mellitus and chronic periodontitis: a randomized clinical trial. Journal of periodontology. 2016;87(12):1418-26.

Elbarbary 2016

Elbarbary NS. Effectiveness of the low-glucose suspend feature of insulin pump during fasting during Ramadan in type 1 diabetes mellitus. Diabetes/metabolism research and reviews. 2016;32(6):623- 33.

Elbarbary 2018

Elbarbary NS, Ismail EAR, El-Naggar AR, Hamouda MH, El-Hamamsy M. The effect of 12 weeks carnosine supplementation on renal functional integrity and oxidative stress in pediatric patients with diabetic nephropathy: a randomized placebo-controlled trial. Pediatric diabetes. 2018;19(3):470- 7.

Elbarbary 2020

Elbarbary NS, Ismail EAR, Zaki MA, Darwish YW, Ibrahim MZ, El-Hamamsy M. Vitamin B complex supplementation as a homocysteine-lowering therapy for early stage diabetic nephropathy in pediatric patients with type 1 diabetes: A randomized controlled trial. Clinical Nutrition. 2020;39(1):49-56.

Embaby 2016

Embaby H, Elsayed E, Fawzy M. Insulin Sensitivity and Plasma Glucose Response to Aerobic Exercise in Pregnant Women at Risk for Gestational Diabetes Mellitus. Ethiopian journal of health sciences. 2016;26(5):409- 14.

Essien 2017

Essien O, Otu A, Umoh V, Enang O, Hicks JP, Walley J. Intensive Patient Education Improves Glycaemic Control in Diabetes Compared to Conventional Education: A Randomised Controlled Trial in a Nigerian Tertiary Care Hospital. PLoS ONE 2017;12(1):e0168835.

Fairall 2016

Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: a Pragmatic Cluster Randomised Controlled Trial. Plos medicine. 2016;13(11):e1002178.

Fayehun 2018

Fayehun AF, Olowookere OO, Ogunbode AM, Adetunji AA, Esan A. Walking prescription of 10 000 steps per day in patients with type 2 diabetes mellitus: a randomised trial in Nigerian general practice. British Journal of General Practice. 2018;68(667):e139-e45.

Ghoneim 2013

Ghoneim EM, Abd El Ghany AA. Behavior of intraocular pressure after intravitreal injection of triamcinolone acetonide among egyptians. Ophthalmology and Therapy. 2013;2(2):121-30.

Hailu 2018

Hailu FB, Hjortdahl P, Moen A. Nurse-Led Diabetes Self-Management Education Improves Clinical Parameters in Ethiopia. Frontiers in Public Health. 2018;6:302.

Ibrahim 2014

Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Archives of Gynecology & Obstetrics. 2014;289(5):959-65.

Krawinkel 2018

Krawinkel MB, Ludwig C, Swai ME, Yang RY, Chun KP, Habicht SD. Bitter gourd reduces elevated fasting plasma glucose levels in an intervention study among prediabetics in Tanzania. Journal of Ethnopharmacology. 2018;216:1-7.

Labhardt 2011

Labhardt ND, Balo JR, Ndam M, Manga E, Stoll B. Improved retention rates with low-cost interventions in hypertension and diabetes management in a rural African environment of nurse-led care: a cluster-randomised trial. Tropical Medicine & International Health. 2011;16(10):1276-84.

Maharaj 2016

Maharaj SS, Nuhu JM. Rebound exercise: A beneficial adjuvant for sedentary non-insulin-dependent type 2 diabetic individuals in a rural environment. Australian Journal of Rural Health. 2016;24(2):123-9.

Malek 2015

Malek R, Ajili F, Assaad-Khalil SH, Shinde A, Chen JW, Van den Berg E. Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. Diabetes & Metabolism. 2015;41(3):223-30.

Marais 2018

Marais C, Hall DR, van Wyk L, Conradie M. Randomized cross-over trial comparing the diagnosis of gestational diabetes by oral glucose tolerance test and a designed breakfast glucose profile. International Journal of Gynaecology & Obstetrics. 2018;141(1):85-90.

Malipa 2013

Malipa M, Menon J. The relationship between compliance and quality of life among adolescents with diabetes mellitus type1. Medical Journal of Zambia. 2013;40(3):93-103.

Mash 2014

Mash RJ, Rhode H, Zwarenstein M, Rollnick S, Lombard C, Steyn K, et al. Effectiveness of a group diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized controlled trial. Diabetic Medicine. 2014;31(8):987-93.

Mash R, Kroukamp R, Gaziano T, Levitt N. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. Patient Education & Counseling. 2015;98(5):622-6.

Matter 2020

Matter RM, Elbarbary NS, Ismail EAR, Darwish YW, Nada AS, Banoub VP. Zinc supplementation improves glucose homeostasis in patients with Î²-thalassemia major complicated with diabetes mellitus: a randomized controlled trial. Nutrition 2020;73.

Mohamad 2009

Mohamad RH, Zekry ZK, Al-Mehdar HA, Salama O, El-Shaieb SE, El-Basmy AA, et al. Camel milk as an adjuvant therapy for the treatment of type 1 diabetes: verification of a traditional ethnomedical practice. Journal of Medicinal Food. 2009;12(2):461-5.

Moustafa 2019

Moustafa HAM, El Wakeel LM, Halawa MR, Sabri NA, El-Bahy AZ, Singab AN. Effect of Nigella Sativa oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. Endocrine. 2019;65(2):286- 94.

Muchiri 2016

Muchiri JW, Gericke GJ, Rheeder P. Effect of a nutrition education programme on clinical status and dietary behaviours of adults with type 2 diabetes in a resource-limited setting in South Africa: a randomised controlled trial. Public Health Nutrition. 2016;19(1):142-55.

Muchiri JW, Gericke GJ, Rheeder P. Impact of nutrition education on diabetes knowledge and attitudes of adults with type 2 diabetes living in a resource-limited setting in South Africa: a randomised controlled trial. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2016;21(2):26-34.

Nteleki 2015

Nteleki B, Abrahamse H, Houreld NN. Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers. Seminars in Vascular Surgery. 2015;28(3-4):172-83.

Owolabi 2019

Owolabi EO, Goon DT, Ajayi AI. Efficacy, acceptability and feasibility of daily text-messaging in promoting glycaemic control and other clinical outcomes in a low-resource setting of South Africa: A randomised controlled trial. PLoS ONE [Electronic Resource]. 2019;14(11):e0224791.

Owolabi EO, Goon DT, Ajayi AI. Impact of mobile phone text messaging intervention on adherence among patients with diabetes in a rural setting: A randomized controlled trial. Medicine. 2020;99(12):1-8.

Ragheb 2020

Ragheb SR, El Wakeel LM, Nasr MS, Sabri NA. Impact of Rutin and Vitamin C combination on oxidative stress and glycemic control in patients with type 2 diabetes. Clinical nutrition ESPEN. 2020;35:128-35.

Rashad 2017

Rashad H, Metwally FM, Ezzat SM, Salama MM, Hasheesh A, Abdel Motaal A. Randomized double-blinded pilot clinical study of the antidiabetic activity of Balanites aegyptiaca and UPLC-ESI-MS/MS identification of its metabolites. Pharmaceutical Biology. 2017;55(1):1954-61.

RezkAllah 2019

RezkAllah SS, Takla MK. Effects of different dosages of interval training on glycemic control in people with prediabetes: a randomized controlled trial. Diabetes spectrum. 2019;32(2):125- 31.

Saeed 2013

Saeed AM. Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. Clinical Ophthalmology. 2013;7:283-97.

Salem 2010

Salem MA, Aboelasrar MA, Elbarbary NS, Elhilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetology & metabolic syndrome. 2010;2(1):47.

Sodipo 2017

Sodipo OO, Adedokun A, Olusola AA. Effect of self-monitoring of blood glucose on glycaemic outcome among type 2 diabetic patients. South african family practice. 2017;59(6):208- 13.

Somanah 2012

Somanah J, Aruoma OI, Gunness TK, Kowelssur S, Dambala V, Murad F, et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. Preventive Medicine. 2012;54 Suppl:S90-7.

Steyn 2013

Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, et al. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: a randomised controlled trial. Glob Health Action. 2013;6:20796.

Takenga 2014

Takenga C, Berndt RD, Musongya O, Kitero J, Katoke R, Molo K, et al. An ICT-Based Diabetes Management System Tested for Health Care Delivery in the African Context. International Journal of Telemedicine & Applications. 2014;2014:437307.

Tawfik 2016

Tawfik MY, Mohamed RA. The impact of communicating cardiovascular risk in type 2 diabetics on patient risk perception, diabetes self-care, glycosylated hemoglobin, and cardiovascular risk. Journal of public health. 2016;24(2):153- 64.

Thuita 2020

Thuita AW, Kiage BN, Onyango AN, Makokha AO. Effect of a nutrition education programme on the metabolic syndrome in type 2 diabetes mellitus patients at a level 5 Hospital in Kenya: "a randomized controlled trial". BMC Nutr. 2020;6:30.

Tsobgny-Tsague 2018

Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, Tankeu AT, Katte JC, Dehayem MY, et al. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health. 2018;18(1):28.

Utz 2018

Utz B, Assarag B, Smekens T, Ennassiri H, Lekhal T, El Ansari N, et al. Detection and initial management of gestational diabetes through primary health care services in Morocco: An effectiveness-implementation trial. PloS one. 2018;13(12):e0209322.

van der Hoogt 2017

van der Hoogt M, van Dyk JC, Dolman RC, Pieters M. Protein and fat meal content increase insulin requirement in children with type 1 diabetes - Role of duration of diabetes. Journal of clinical and translational endocrinology. 2017;10:15- 21.

van Rooijen 2004

van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A1C in Black females with type 2 diabetes mellitus. Qjm. 2004;97(6):343-51.

Webb 2015

Webb EM, Rheeder P, Van Zyl DG. Diabetes care and complications in primary care in the Tshwane district of South Africa. Primary care diabetes. 2015;9(2):147-54.

Webb EM, Rheeder P, Roux P. Screening in Primary Care for Diabetic Retinopathy, Maculopathy and Visual Loss in South Africa. Ophthalmologica. 2016;235(3):141-9.

Webb EM, Rheeder P. A cluster-randomized trial to estimate the effect of mobile screening and treatment feedback on HbA1c and diabetes-related complications in Tshwane primary health care clinics, South Africa. Primary care diabetes. 2017;11(6):546-54.

Yakoot 2019

Yakoot M, Abdelatif M, Helmy S. Efficacy of a new local limb salvage treatment for limb-threatening diabetic foot wounds-a randomized controlled study. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2019;12:1659.

Yan 2014

Yan H, Prista A, Ranadive SM, Damasceno A, Caupers P, Kanaley JA, et al. Effect of Aerobic Training on Glucose Control and Blood Pressure in T2DDM East African Males. Isrn Endocrinology Print. 2014;2014:864897.

1.2 List of excluded studies

1.2.1 Other design (28 references)

1. Abd El Hameed AA, Shreif HE, Mowafy HE. The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. Middle east fertility society journal. 2011;16(3):204- 8.

2. Abdelaziz TS, Sadek KM. Effect of reducing medication regimen complexity on glycaemic control in patients with diabetes. Romanian Journal of Internal Medicine. 2019;57(1):23-9.

3. Agboola-Abu CF, Ohwovoriole AE, Akinlade KS. The effect of oral hypoglycaemic agents on dyslipidaemia in Nigerian patients with newly diagnosed non-insulin dependent diabetes mellitus--a prospective study. West African Journal of Medicine. 2000;19(2):126-31.

4. Assah FK, Atanga EN, Enoru S, Sobngwi E, Mbanya JC. Community-based peer support significantly improves metabolic control in people with Type 2 diabetes in Yaounde, Cameroon. Diabetic Medicine. 2015;32(7):886-9.

5. Bahramikia S, Yazdanparast R. Phytochemistry and medicinal properties of Teucrium polium L. (Lamiaceae). Phytotherapy Research. 2012;26(11):1581-93.

6. Bailey CJ, Iqbal N, T'Joen C, List JF. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes, Obesity & Metabolism. 2012;14(10):951-9.

7. Bekkouche L, Bouchenak M, Malaisse WJ, Yahia DA. The Mediterranean diet adoption improves metabolic, oxidative, and inflammatory abnormalities in Algerian metabolic syndrome patients. Hormon- und Stoffwechselforschung / Hormones et metabolisme [Hormone and metabolic research]. 2014;46(4):274- 82.

8. Bello SI, Ganiyu KA, Dakop YO, Erah PO. Pharmacist's intervention in the control of blood sugar levels in randomised diabetes patients at a primary health care setting in Benin City. Nigerian Quarterly Journal of Hospital Medicine. 2012;22(4):245-8.

9. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database of Systematic Reviews. 2017;1:CD011967.

10. Chou HS, Truitt KE, Moberly JB, Merante D, Choi Y, Mun Y, et al. A 26-week, placebo- and pioglitazone-controlled monotherapy study of rivoglitazone in subjects with type 2 diabetes mellitus. Diabetes, Obesity & Metabolism. 2012;14(11):1000-9.

11. De Caterina R, Andersson U, Alexander JH, Al-Khatib SM, Bahit MC, Goto S, et al. History of bleeding and outcomes with apixaban versus warfarin in patients with atrial fibrillation in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial. American Heart Journal. 2016;175:175-83.

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Randomized controlled trials on prevention, diagnosis, and treatment of diabetes in African countries - a systematic review

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ABSTRACT

Objectives The epidemiological transition from infectious to chronic diseases leads to novel challenges in African health systems. The prevalence of diabetes mellitus (DM) is increasing dramatically. Undiagnosed and undertreated DM leads to numerous complications including end-organ damage and death. Our objectives were to collect the best locally generated evidence on DM interventions, identify knowledge gaps, and determine underexplored research areas.

Design A systematic review and meta-analysis of randomized controlled trials.

Participants and setting African patients in primary, secondary and tertiary prevention, diagnosis and treatment DM type 1 (DM1), type 2 (DM2) and gestational DM (GDM).

Outcome All-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs.

Data sources Articles published in MEDLINE Ovid, CENTRAL, CINAHL, African Journals Online and African Index Medicus and the International Clinical Trials Registry Platform in English language without time restrictions. The systematic search was last updated in October 2020.

Results Out of 3736 identified publications, we included 60 eligible studies conducted in 15 countries, 75 % were conducted in urban health care settings, including 10,112 participants. We included eight studies on DM1, six on GDM, two on pre-DM, 37 on mainly DM2 including seven on DM related complications. The design of the studied intervention was heterogeneous with a focus on educational strategies. The other studies investigated the efficacy of nutritional strategies including food supplementations, pharmacological strategies and strategies to enhance physical activity. Seven studies included interventions on DM-related complications.

Conclusions: Research activities increased in recent years, but available evidence is still not representative for all African countries. There is a big lack of evidence in primary health care and rural settings, implementation research, pharmacological interventions, especially in poorer countries. Nevertheless, the identified studies offer a variety of effective interventions that can inform medical care and future research.

PROSPERO registration number: CRD42019122785.

Keywords: Diabetes mellitus, Africa, systematic review, randomized-controlled trial

Strengths and limitations of this systematic review

- This systematic review includes studies at the highest level of evidence to provide an overview of the best available interventions to prevent, diagnose and treat DM in the African context.
- Inclusion criteria are restricted to randomized controlled trials conducted in African countries published in English language with no restrictions on time of publication.
- We performed a systematic search in four international databases and updated the search in October 2020.
- The main aim of our systematic review is to provide an overview of interventions for DM. Meta-analyses are restricted to regularly reported results on HbA1c as strong clinical outcome indicator of an efficient DM management.
- Limited external validity due to the origin from few countries and urban areas, results concentrate on glycemic control due to short follow-up periods.

INTRODUCTION

Diabetes mellitus (DM) and other non-communicable diseases (NCDs) are responsible for a double burden in African countries due to the epidemiological transition from communicable to non-communicable diseases and resulting disabilities and deaths (1-3). In Africa, around 19.4 million adults are living with DM. Prevalence rates range from 4.7 % in Sub Saharan Africa (SSA) to 12.2 % in the Middle East and North Africa region (4). Due to the increasing prevalence of risk factors such as obesity and westernized lifestyle, the prevalence of DM is expected to increase by 96 % in SSA until 2045 (4). Currently, about 50 to 60 % of adults living with DM in African countries are undiagnosed (4, 5). Low awareness as well as genetic differences and lifestyle habits result in very heterogeneous prevalence rates of DM between different countries in Africa as well as rural and urban regions (6, 7). Undiagnosed and undertreated DM can result in organ damage, and lead to complications like cardiovascular diseases, peripheral neuropathy, retinopathy and diabetic foot (7, 8). Moreover, these factors attribute to substantial financial costs for households and governments (9). Recently, almost one fifth of COVID-19 deaths in African countries occurred among DM patients (10).

The United Nations 2030 Agenda aims to reduce the burden of premature mortality from NCD including DM through improvement in prevention and treatment (11). Proven and effective actions to prevent or delay the onset of DM base on the empowerment of the population, patients and health care providers (12). Measures on DM include early detection in primary health-care settings, lifestyle modifications including diet, physical activity and, if necessary, medication. Primary prevention programs include lifestyle measures to reduce consumption of sugar-sweetened beverages, mandatory detailed labels on food packaging as well as education and awareness campaigns to increase physical activity are crucial since onset of DM can be detained (13). Moreover, health systems must ensure technical and financial resources as well as training of healthcare staff to recognize the symptoms of DM, to perform and interpret diagnostic tests and provide adequate treatment and care (4). Since DM patients need regular specialist assessment, a functioning referral system is necessary (14). Concerning pharmacotherapy, prioritization of metformin, gliclazide and human insulin is recommended (15). Glucometers, needles and test strips should be provided for people with DM (4).

Only a fraction of patients in African countries have access to the same treatment as recommended in high-income countries (16, 17). At the moment, most guideline recommendations in LMIC are based on studies conducted in high-income Western countries (18). These general management strategies have to be adjusted to local

contexts in African countries including environmental, cultural and social aspects like the relatively young age of patients, co-infections, long distances to health-care facilities, traditional beliefs, decision making in the families and socioeconomic status. Furthermore, there is a huge genetic diversity on the African continent (19, 20) .

The purpose of this review was to collect the best locally generated evidence, regarding preventive, diagnostic and therapeutic intervention on DM, as the lack of evidence is one of the major challenges to prevent and control DM in African countries. Therefore, we aimed to address existing knowledge gaps and identify unexplored research areas in the African context. This may support the formulation of local evidence-based strategies to systematically strengthen clinical and preventive capacities of healthcare systems in African countries.

METHODS

We prospectively registered a protocol of this systematic review in the PROSPERO International Prospective Register of systematic reviews (CRD42019122785). This systematic review follows the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (21) and the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (22).

Inclusion criteria and exclusion criteria

This systematic review includes studies conducted in African countries on the efficacy of interventions for prevention, diagnosis and treatment of patients with DM including prediabetes, type 1 (DM1), type 2 (DM2) and gestational DM (GDM). Primary outcome was defined to be all-cause mortality. Secondary outcomes included glycemic control (HbA1c, fasting serum or plasma glucose, insulin resistance, oral glucose tolerance test), quality of life, treatment adherence, hospital admissions, complications of DM and resulting costs (see Table 1 for detailed inclusion criteria).

We included full-text publications on randomized controlled trials (RCTs) (e.g. individual RCTs, cluster-RCTs and randomized cross-over trials) according to the Consolidated Standards of Reporting Trials (CONSORT) (23) published in English language. We excluded international multicenter studies with less than 50 % of sites in African countries to ensure that the study location was in Africa.

Design and setting	RCTs, mainly conducted in African countries (at least 50 % African countries in international studies)
Population	African patients in primary, secondary or tertiary prevention with a clinical diagnosis of • Prediabetes • Diabetes mellitus type 1 (DM1, due to autoimmune β-cell destruction) • Diabetes mellitus type 2 (DM2, due to a progressive loss of adequate β-cell insulin secretion)

	• Gestational diabetes (diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation) As described by the authors
Interventions	All interventions to of prevent, diagnose and treat diabetes
Comparison	Placebo or standard care Another intervention or the same intervention with a different dose or timing
Outcome	Primary: all-cause mortality Secondary: • glucose control (HbA1c, oral glucose tolerance test, insulin resistance, fasting serum or blood glucose) • complications • quality of life • hospital admission • treatment adherence Additional: costs at longest follow-up
Publications	Full-text publications according to CONSORT
CONSORT: Consolidated Standards of Reporting Trials; DM: Diabetes mellitus; DM1: Type 1 diabetes; DM2: Type 2 diabetes; GDM: Gestational diabetes; HbA1c: hemoglobin A1c; RCT: randomized controlled trial	

Table 1: Inclusion and exclusion criteria

Systematic search

We performed a systematic search in electronic bibliographic databases (MEDLINE Ovid, CENTRAL, International Clinical Trials Registry Platform of the WHO) as planned in the protocol and added a search in CINAHL and regional electronic databases (African Journals Online and African Index Medicus) (see Online Supplemental File 1 material). All searches were performed without time constrictions. The last search was conducted in October 2020. Search strings were based on Medical Subject Headings (MeSH) and terms on DM, Africa, a list of all 54 African countries and terms related to RCTs. All references retrieved from the literature search were exported into a reference manager software (EndNote) (24). Duplicate references were identified in case of congruence of authors, title, year and journal and thusly deleted. The search strategy is available in the supplementary file.

Study selection and data extraction.

Two authors independently checked titles and abstracts based on the inclusion criteria (Table 1). The full texts of all potentially eligible papers were assessed for final inclusion. All disagreements were resolved by discussion until consensus was obtained (21). All reported information on the following were extracted and checked by another author:

- publications, registration, and design,
- time and place (country, urban/ rural setting and health care setting)

- study population (inclusion and exclusion criteria, sample size and baseline characteristics on age, gender, type and length of DM, body mass index (BMI) and gylcemic control at baseline)
- intervention and control groups with the number of randomized participants per group and duration of the interventions
- outcomes (classified into primary, secondary, non-specified) and
- results on pre-planned outcomes within the longest follow up period with intervention effects with their 95 % confidence intervals (CI) and level of significance.

The study names were defined by the surname of the first author and the year of the first full-text publication of the results. We compared study and patient characteristics across studies to ensure that each included study represents a unique publication of study data. In cross-over RCTs, only data from the first period were used (25).

Quality assessment and risk of bias

Risk of bias was judged based on seven specific categories (sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) of the Cochrane risk of bias tool as 'low', 'high' or 'unclear' (22). Judgments were done by two of the authors and all discrepancies were resolved by discussion.

Judgments on blinding and incomplete outcome data were based on the primary outcome of included studies. Selective outcome reporting was defined as low when the study protocol with pre-defined primary and secondary outcomes was available and high when any result of pre-planned outcomes was missing. Incomplete outcome data was judged as high when more than 10% of randomized participants dropped out from analyses. Other sources of bias were judged as high risk of bias including missing reporting of sample size calculation, no description of a primary endpoint, and relevant differences of main baseline characteristics between intervention and control groups (22).

Data synthesis

The results of all pre-defined outcomes were described. Effect sizes on HbA1c for the longest follow-up period were visualized in forest plots using RevMan (26). Negative mean differences (MDs) describe lower HbA1c in the intervention compared to the control group. Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant (27). Heterogeneity was interpreted based

on the I^2 statistics as not important (I^2 < 30 %), moderate (30-60 %) and substantial (I^2> 60 %) (22).

Protocol registration

We registered a protocol of this systematic review on the PROSPERO website: https://www.crd.york.ac.uk/prospero/ under the registration number: CRD42019122785.

Patient and Public Involvement

There is no patient involved

RESULTS

A total of 2865 references were identified from electronic databases and 871 additional trials from the Clinical Trials Registry Platform were checked. We evaluated 185 potentially eligible full-text publications and included 60 eligible studies in 68 publications in this review (Figure 1 and Supplementary file).

Figure 1: PRISMA flow chart describing the process of study selection

Setting

In total 60 studies, which were conducted in 64 study centers of 15 African countries; North Africa (33 studies from four countries), West Africa (10 studies from three countries), East Africa (seven studies from 7 countries), Central Africa (three studies from two countries) and Southern Africa (11 studies only from South Africa) were included. Two studies (Malek 2015 and Chraibi 2017) were conducted in more than one African country and partially conducted in non-African countries. Chraibi (2017) was conducted in Egypt, Morocco, South Arabia and Vietnam. Malek (2015) included four study centers in Algeria, Tunisia, Egypt and South Africa. Those additional study centers are presented in brackets behind the country names in Figure 2. Egypt, South Africa and Nigeria are the three study centers included most often in this review (Figure 2 and supplemenary Table 1 available in the supplement).

Figure 2: Geographical regions, countries, and type of DM of the included studies

Seventy-five percent of the studies (45/60) were set in urban areas, 5 % (3/60) were in rural areas only. The setting of the remaining 20 % (12/60 studies) was mixed or remained unclear. The majority, 83 % (50/60) of the studies, were conducted in secondary and tertiary health care centers, while 17 % (10/60) took place in primary care settings.

Though the search had no time restrictions, the oldest eligible study (Anderson 2001) was published in 2001. More than 60 % of the studies were published since 2015, and 22 % of them had been published in 2019 or 2020 (see supplementary Table 1 available in the supplement).

Design

Fifty parallel-group studies randomized individual participants with DM. Six cluster-randomized studies (Fairall 2016, Labhardt 2011, Mash 2014, Steyn 2013, Utz 2018,

Webb 2015) randomly assigned health care facilities to intervention and control groups. In three randomized cross-over studies (Abdulrhman 2013, Krawinkel 2018, van der Hoogt 2017) each participant received different interventions in a random sequence, and in one study (Ghoneim 2013) each patient received two different treatment doses for each eye based on a random allocation of eyes and doses.

Interventions for patients with pre-DM

Two studies randomized a total of 112 overweight or obese patients (BMI 25–35 kg/m^2) with pre-DM (HbA1c 5.7-7.5 %) and a mean age of 32.9 and 47.5 years (see supplementary Table 1: Characteristics and results of studies on patients with pre-DM available in the supplement). These studies stated the efficacy regarding glycemic control of low and high volume, high-intensity interval training strategies (RezkAllah 2019), and the consumption of bitter gourd to improve glucose control (Krawinkel 2018).

Interventions for patients with DM1

A total of 8 studies were conducted including 595 patients diagnosed with DM1 (Abdulrhman 2013, Elbarbary 2016, Elbarbary 2018, Elbarbary 2020, Malipa 2013, Mohamad 2009, Salem 2010, van der Hoogt 2017) (see supplementary Table 2 Characteristics and results of studies on patients with DM1 available in the supplement). They mainly included children, adolescents, and young adults with a mean age between 10.4-19.9 years. The mean duration of DM ranged from 3.5 to 8.6 years and the mean baseline HbA1c from 7.21 to 9.52 %. The studies investigated heterogeneous strategies. Malipa 2013 showed the efficacy of weekly meetings to improve treatment compliance, reduce impact and worries about DM and improve general life satisfaction in adolescents. Salem 2010 evaluated the efficacy of two exercise programs to reduce cardiovascular risk with no relevant effect on glucose control. Three studies investigated different nutritional strategies and stated the beneficial effects of honey (Abdulrhman 2013) and camel milk (Mohamad 2009) on glucose control. Meals with low fat and protein (van der Hoogt 2017) caused less frequent hypoglycemic events. Elbarbary 2016 showed the efficacy of a low-glucose suspension algorithm during Ramadan to reduce the number of hypo- and hyperglycemic excursions. Two studies on food supplementation stated improved glycemic control with carnosine (Elbarbary 2018), but no benefit from a vitamin B complex (Elbarbary 2020).

Interventions for patients with DM2

A total of 44 studies were conducted including 8881 patients suffering from DM2 or different diabetic illnesses (see supplementary Table 3: Characteristics and results of studies on patients with DM2 availble in the supplement). Most studies included patients with a mean age between 50 and 60 years, only four studies included younger patients (Adjei 2015, El Gayar 2019, Matter 2020, Maharaj 2016). Most studies included more females than males. These studies presented a wide variety of patients in different stages of DM2 and general conditions. They ranged from newly diagnosed DM (El Gayar 2019, Labhardt 2011, Mostafa 2019, Owolabi 2019, Somanah 2012), non-insulin dependency or oral insulin therapy (Adibe 2013, Ali 2019, Fayehun 2018, Maharaj 2016, Malek 2015, Ragheb 2020) to durations of over 10 years with severe DM related complications (Abaza 2017, Nteleki 2015, Tsobigny-Tsague 2018, El-Shakawy 2016, Ghoneim 2013, Saeed 2013, Yakoot 2019). Thus, mean baseline HbA1c ranged from 6.75% to 11.1%. Most studies included high proportions of overweight and obese participants with mean BMIs ranging from 22.4 to 40.8 kg/m².

Educational strategies

A total of 19 studies with 6942 patients and follow-up periods between 2-14 months investigated the impact of educational strategies on diabetes treatment. These included providing information about lifestyle modification measures, dietary recommendations, drug-based therapy, DM-related complications, and self-management. Training sessions were provided based on group-based educational sessions or individual treatment plans by nursing staff or pharmacists and complemented by lectures, discussion services, brochures, newsletters, computer programs, electronic communication devices and tele-monitoring systems. Three of these studies were led by nurses (Adibe 2013, Hailu 2018, Labhardt 2011) and two cluster-randomized studies trained nurses to expand their role in the treatment of patients with NCDs (Fairall 2016) or aimed to improve guideline implementation in the treatment of patients with DM (Steyn 2013).

Three studies (Abaza 2017, Adjei 2015, Labhardt 2011) reported results on treatment adherence. All strategies lead to improved adherence, measured by improved perception of patients to treatment recommendations (Abaza 2017) or higher regularity of appointment schedules (Adjei 2015, Labhardt 2011). Two studies (Adibe 2013, Mash 2014) reported results on costs with lower costs for patients receiving educational strategies. Two studies reported fewer admissions to different health-care facilities (hospital or emergency room and clinic visits) (Abaza 2017, Chraibi 2017).

Results on quality of life were reported in two studies with follow-up periods over 12 months and conflicting results. A structured self-care education program by pharmacists and nurses (Adibe 2013) improved quality of life, but no benefit was shown after group education by trained professionals (Mash 2014).

The majority of the educational strategies resulted in lower mean HbA1c levels in the intervention groups with a clinically relevant mean decrease of -0.66 % (95 %-CI -0.94 to -0.39) and substantial heterogeneity between results of different studies (I^2=64 %) (Figure 3).

Figure 3: Results of educational strategies on HbA1c levels or changes of HbA1c levels of patients with DM2

Strategies to enhance physical activity

Five studies with 359 participants evaluated the efficacy of different strategies to enhance physical activity on glucose control. Strategies included counselling, setting goals and training sessions with different intensities or both over periods between 8-12 weeks.

Two studies were successful in lowering HbA1c where patients were given goals to accumulate 10,000 steps per day (Fayehun 2018) or patients were allocated to rebound exercise (Maharaj 2016). A third study investigated the effects of aerobic exercise training and was able to decrease fasting plasma glucose (28).

Two other exercise interventions failed to reduce HbA1c by incremental exercises compared to relaxation (Van Rooijen 2004) or higher intensity of exercises (Yan 2014) (Figure 4). Results were not pooled due to considerable heterogeneity with different directions of treatment effects.

Figure 4: Results of strategies to enhance physical activity on HbA1c levels of patients with DM2

Pharmacological strategies

Three studies with 479 participants tested the efficacy of pharmacological treatment strategies on glucose control of patients with DM2. El-Haggar 2015 found ketotifen and glimepiride an effective dual therapy. Malek 2015 described the non-inferiority of once-

daily basal-bolus insulin analogues and thrice daily insulin therapy. Distiller 2014 did not find an additional improvement with exenatide in addition to insulin and metformin therapy on glycemic control.

Strategies on food supplementations

Several different food supplementations were tested in 10 studies including 762 participants. Vitamin D3 supplementation had a positive effect on glycemic control in two studies (Ali 2019, Anyanwu 2016). Four studies tested the effect of plant-based substances. Ginger powder and balantines aegyptiaca (desert date) extract regimes supported glucose control (El Gayar 2019, Rashad 2017). Nigella sativa (black cumin) oil capsules slightly improved glucose control but were inferior to metformin (Moustafa 2019). A regime based on fermented papaya did show beneficial results (Somanah 2012). Anderson 2001 and Matter 2020 showed positive effects of zinc/ chromium in chronic DM and zinc supplementation in diabetic beta-thalassemia major patients. The addition of rutin and vitamin C did not improve the results of oral antidiabetics (Ragheb 2020). The addition of l-carnitine improved diabetic control achieved by glimepiride treatment (El-Sheikh 2019).

Strategies on the treatment of DM related complications

Seven studies with 351 participants and follow-up periods between 3-12 months evaluated different strategies to treat possibly DM-related complications including periodontitis (3 studies), foot ulcerations (2 studies) and macular edema (2 studies).
El-Makaky 2020 and Tsobgny-Tsague 2018 described the benefit of immediate vs. delayed non-surgical periodontal interventions on glucose control and El-Sharkawy 2016 stated the effectiveness of propolis as an additive in periodontitis treatment. Two studies stated a benefit of combined phototherapy and podiatric management (Nteleki 2015) and an additional local ointment application of royal jelly and panthenol (Yakoot 2019) on the healing of lower extremity ulcers. Ghoneim 2013 and Saeed 2013 tested different diabetic macular edema treatment strategies. Both studies described generally positive treatment effects but also considerable adverse events including rise of intra ocular pressure and glaucoma.

Interventions for patients with DM in a pregnant woman

Six studies included a total of 574 pregnant women at increased risk for gestational DM (GDM) (Embaby 2016), with newly diagnosed GDM (Utz 2018, El-Shamy 2018, Ashoush 2016) or with newly diagnosed GDM or pre-existing DM (Beyuo 2015, Ibrahim 2014) between the 20th and 34th week of pregnancy. The mean age ranged from 24.2-

33.3 years (see supplementary Table 4: Characteristics and results of studies on pregnant women with DM available in the supplements).

Three studies (Ashoush 2016, Beyuo 2015, Ibrahim 2014) with 289 participants examined metformin as an additional medication to insulin in comparison to insulin therapy only. Effects on glycemic control of metformin supported therapy ranged from a relevant decrease (Ashoush 2016) to no effect on fasting plasma glucose, but beneficial effect on two hour plasma glucose in a 75 g OGTT (Beyuo 2015) in women without insulin resistance.Adding metformin to insulin therapy of pregnant women with insulin resistant diabetes was associated with several benefits concerning the time of hospital stay, reduced occurrence of maternal or neonatal hyperglycemia, less neonatal intensive care unit (NICU) admissions and reduced cases of respiratory distress syndrome (Ibrahim 2014).

The other studies (285 participants) investigated non-pharmacological interventions. The tested interventions were aerobic exercise program (treadmill walking) (Embaby 2016), acupressure (El-Shamy 2018) and screening for GDM, followed by nutritional and exercise counseling for positive tested women (Utz 2018). The aerobic exercise program resulted in a relevant reduction of fasting plasma glucose until delivery (Embaby 2016). The acupressure intervention did not manage to show a benefit regarding glycemic control (El-Shamy 2018). Screening, counselling and intensive follow-up were able to improve glycemic control and reduce the number of newborns with macrosomia (Utz 2018).

Potential biases

None of the included studies was categorized as low risk of bias in all seven domains only (see supplementary Table 5: Judgement on risk of bias available in the supplements).

The most common restriction on study quality was found in the domain performance bias due to a lack of blinding of participants and personnel in 48 studies. Detection bias due to blinding of the outcome assessors was judged as high or unclear in 38 studies. 14 studies with high risk of bias due to no blinding of participants and personnel, reported adequate methods to ensure blinding of the outcome assessors.

Another frequent problem was an incomplete analyses of outcome data in 26 studies defined as a loss to follow-up over 10 % of randomized participants or per-protocol analyses.

In 23 studies a protocol was available. Risk of bias due to selective outcome reporting was judged as low in 15 studies. High risk of bias, meaning lack of reporting of results

of some pre-planned outcomes was judged in eight studies (Abdulrhman 2013, Beyuo 2015, Elbarbary 2020, Matter 2020, Owolabi 2019, Somanah 2012, Utz 2018 Yakoot 2019).

In the domain sequence generation, two studies were assessed as high risk. El- Nteleki 2015 randomized only seven patients into three different treatment groups. Shamy 2018 used a non-probability sampling method on the basis of the hospital admission code and was subsequently judged as high risk in domains sequence generation and allocation concealment.

In 31 studies, we identified further methodological limitations including missing reporting of information on sample-size calculation, definition of primary and secondary target criteria, relevant differences regarding baseline characteristics or reporting of intermediate results only.

DISCUSSION

This systematic review describes interventions from 60 studies to summarize the available randomized trials on to prevention, diagnosis and treatment of DM with a total of 12,113 participants from 15 African countries. Several promising interventions were identified that can be used in settings with limited resources or involved locally available materials. Despite a trend of increasing research activity in recent years, many areas of diabetes research in African countries are still underexplored leaving knowledge gaps that should be tackled in the future.

Scarcity of randomized DM trials in African countries

While 60 included randomized trials are not nothing it also means an average only slightly higher than one randomized DM study per country for all types of diabetes that has ever been conducted and published. Only two studies on pre-diabetic interventions have been conducted, despite a clear need and aim to tackle early to avoid the future DM burden that is expected to arise (17). Implementation research, considered important in addressing know-do gaps in real-world settings, especially in primary care settings are still very rare (29). Implementing evidence-based care while observing, evaluating und publishing it's result deems crucial in the massive challenge of creating diabetes care infrastructure for millions of diabetes patients. Nevertheless, forty-three of the 60 studies have been conducted since 2015 demonstrating at positive trend of research activity.

Rural vs. urban, primary vs. secondary care and geographic disparities

Three out of four studies were set in urban areas and only 5 % (3/60) were set in rural areas only. Despite decreasing population shares over the last decades, still almost 60 % of people in Sub-Saharan Africa are living in rural areas with rising absolute numbers (currently about 667 million) (30). Despite diabetes being considered to be associated with westernized lifestyle more prevalent in urban areas, prevalence rates in rural areas are still high, in some parts even higher (31, 32).

Moreover, the majority (83 %) of the studies were conducted in secondary and tertiary health care centers, leaving less than one fifth in primary care settings were most routine and day-to-day diabetes care should be carried out to support people in their everyday life with this chronic long-term illness to prevent long-term consequences.

Another considerable aspect is the geographical distribution of the conducted studies. Almost half (46%) of the included trial were conducted in Egypt, the country ranking 2nd on the African Infrastructure Development Index 2018 with the highest prevalence in

Northern Africa (33). South Africa, ranking fourth on the index, contributed another share of 18% (11 studies) (7). Almost three quarters of the studies were set in the top ten ranking countries on that list, all Northern and Southern Africa leaving huge blank spaces in Central, Western and Eastern Africa including countries with high prevalences including Kenya and Zimbabwe and pointing to both the infrastructural necessities of research as well as the structural development that is still ahead before to increase research activity (34). The broad majority of included studies was conducted in urban settings, this is likely due to the better health care infrastructure and thusly the increased practicability of research. Health care workers, including doctors and nurses, seem to prefer providing services in urban areas leading to an even higher deficit of health care access in rural areas. The consequence is limited generalizability of the results on the needs of the rural population.

Screening strategies to diagnose DM and its complications

The rate of undiagnosed patients with DM is estimated to be between 3.9 % in SSA (35) and 12 % in North Africa (36). This might be related to genetic disparities in the development level of the health care system and awareness in the general population (19). The high rates of undiagnosed DM highlight a high need for research on and implementation of DM screening strategies in the African context. We identified two studies (37-39) investigating primary care strategies to detect and manage women with GDM (37) and screen diabetic patients for complications (40). The observed GDM prevalence of 23.7% among pregnant Moroccan women underlines the importance of regular screening and management to enable early interventions at a primary care level (37). A diabetic population receiving primary care found a high rate of complications including retinopathy, maculopathy, neuropathy, nephropathy, possible infarction and severe erectile dysfunction (38-40).

Intervention for patients with pre-DM for primary prevention of DM

We identified two studies patients (41, 42) with elevated blood glucose levels below diagnosis criteria of DM improving glucose levels via interval training bitter gourd, a plant with antidiabetic properties that is consumed in many Asian as well as some African countries. Both studies offer effective strategies, but further research is necessary, exemplarily on early educational strategies, as a measure of patient empowerment and early tackling of DM (43).

Educational strategies for patients and health-care providers

Education is essential for effective diabetes control. It must be accomplished at, personal (patient empowement), community (raise the awereness of the disease and its risk factors) and health care provider level (training of medical staff to diagnose, monitor and treat it correctely) to manage the rising burden of diabetes (44).

Due to complex challenges for DM patients and health care providers, educational campaigns are necessary to support health care providers and empower patients to manage their disease-associated decisions, lifestyle habits and medication use. Best benefits are proposed to be achieved by continuous individualized education, guided by patients' concerns, preferences and needs (12, 45).

Several studies on DM2 (46-58), DM1 (59) and GDM (37) investigated long-term interventions to support patient empowerment based on improved knowledge, motivation, and capacity to take control of their disease (12). Three studies trialed nurse-led (47, 53, 54, 60) and 2 studies investigated strategies to train healthcare providers in the management of patients with DM (61, 62). Improvement of patient empowerment improved adherence and glucose control, fewer admissions to healthcare facilities and lower costs. Only two studies reported on the quality of life with heterogeneous results (47, 60, 63).

Currently, the COVID-19 pandemic has forced all nations to implement alternative, oftentimes digital strategies including tele-monitoring and teleconsultation to continue care of NCDs (64). The application of telemedicine in DM management showed beneficial results (56, 65). Lifestyle focused messages might be an effective low-cost option to keep patients motivated to adhere to healthy lifestyles and further research seems advisable (66).

All included studies were adapted to local contexts and the trialed strategies hold the promise of adaptability to health care systems in other African and LMIC. Moreover, the tasks of nurses in NCD care could be reshaped and expanded in countries with comparably few physicians in order to improve DM diagnostics, treatment and education.

Strategies to increase physical activity

As in the literature (GDM (67), DM1 (68, 69) and DM2 (70, 71)), exercise therapy generally showed positive effects (DM2 (28, 72-75), DM1 (76), GDM (77)) on glycemic control. Exemplarily, four weeks by setting the goal to accumulate 10,000 steps per day significantly reduced HbA1C levels (72). Due to limited follow up periods, it is advisable to target long-term adherence to these strategies in future research.

Pharmacological strategies

Currently, the available research on pharmacological interventions for DM is sparse in Africa. We identified only six studies (3 on DM2 (78-80), 3 on GDM (81-83)) testing pharmacological interventions as a central part of DM care (84) despite known differences between African and European Americans (19). This might be attributable to our criteria excluding international studies with less than 50% of the sites in African countries (e.g. (85-90)). Many major multi centric pharmacological studies only have few study centers in Africa. Nevertheless, in-depth research into differing effectiveness of diabetic medications is still lacking.

reported the usability and safety of a basal-bolus insulin regime with stepwise intensification in an African setting The efficacy of basal-bolus insulin regimes, as an easy to handle, practical DM treatment option was successfully tested by Malek 2015 (80) and has been previously described in other settings (91, 92). Further research should consider regional contexts like availability of medication, practicability of the medication (e.g. insulin needs proper storage (93, 94)) lifestyle habits and genetic aspects (95, 96). Consideration of findings on African American cohorts seems advisable (97, 98).

Strategies on nutrition and food supplementations

Nutritional and food supplementation interventions can successfully be used supporting pharmacological care or in early and pre-DM stages improving glycemic control, lipid profiles and management of DM-related complications (99-111). In this review, nutritional interventions (41, 112-114), including long-term consumption of honey (112), camel milk (113) and a low fat and protein content of meals (114) with positive effects on metabolic control. Camel milk, traditionally used for treatment of DM in arid areas of Africa and Asia, improves glycemic control, reduces insulin requirement and limits diabetic complications (115). Rashad 2017 (116) stated the beneficial effects of balanites aegyptiaca (desert date) extract on glycemic control. This evergreen tree is common in arid regions in Africa and was traditionally used in Egyptian traditional medicine (117).

Several food supplementations (zinc-gluconate (118) and zinc-chromium (119) supplementations, ginger powder (120), Nigella sativa oil capsules (121), L-carnitine (122), L-carnosine (123) as well as vitamin B, C or D supplementation (63, 124-126)) had positive effects on glycemic control.

Strategies on the treatment of DM related complications

Three studies tested the role of periodontitis treatment in diabetic patients (127-129). Tsobgny-Tsague et al. (129) and El-Makaky et al. (127) described the importance of early treatment start, resulting in favorable patient outcomes in periodontal health and glucose control. El-Sharkawy et al. (128) found propolis to be a favorable addition to planing and scaling. In an Ethiopian cohort, only 21% of DM patients received oral health screening (130). The WHO regards oral health as a crucial component of health care with 12-14 % of 35 to 44-year-old Africans suffering from periodontitis (131).

Treatment options for diabetic wounds were tested in two studies (132, 133). Phototherapy in addition to usual care was first trialed in an African cohort of patients suffering from diabetic foot ulcers, showing beneficial wound healing outcomes. Similar results were described in other settings (134). The addition of propolis to usual care regimes showed improved wound healing. These findings are supported by studies from other settings (135, 136).

Strength and limitations

The external validity of this systematic review is limited by the focus on a limited number of countries and urban health care setting. The included studies were set in 15 of the 54 African countries with a focus on the North African region, especially Egypt. Egypt is the country with the highest known prevalence of DM in the African continent (4, 7). This might be related to economic expansion and urbanization, but also due to specific dietary issues (e.g. white bread, polished rice, trans fats), reduced physical activity due to prohibition of exercise in public places, shortage of exercise facilities, poor physical education in schools. Poor diet and physical inactivity are causing a high rate of overweight and obesity among the Egyptian population (137).

Our pre-planned primary outcome was mortality which was not reported in any of the included studies. Since DM is a chronic disease with a slow progression and long-term development of organ damage, the survival time is higher than the follow-up time of most of the studies. The included studies looked at long-term treatment strategies rather than treatment for acute hypo- or hyperglycemic events that can lead to acutely fatal events. Nevertheless, long-term glucose control, being represented by the HbA1c value is one of the strongest clinical-outcome indicators of efficient DM management and health outcomes (138). It is easy to measure and serves as a representation of the individual's average blood glucose levels in the previous 3 months (138). Furthermore, it is up to discussion if improvement of glycemic control based on blood glucose measures like HbA1C are necessary the best strategic in LMIC or if diabetes

complications are more effectively prevented by targeting blood pressure or blood lipids (139).

Next, this review does not include non-randomized study types including prospective cohort trials or qualitative research, probable not taking into account the evidence that has been accumulated. Nevertheless, our aim was to search for randomized trials, since these study types, if conducted well, have a high evidence quality, allowing to minimize biases. Moreover, many of the studies included had a high risk of bias.

This systematic review includes studies as the highest level of evidence to investigate the benefits and harms of interventions (140). We included studies published in the English language without time restrictions. Language bias was shown to be unlikely. Despite the high linguistic diversity on the African continent, the languages mostly spoken are English, Arabic, and French (141). Eventually, we did not exclude any study due to the publication language, but we might have missed studies from journals that are not listened in searched databases.

CONCLUSION

This systematic review shows an increasing number of studies due to the rising prevalence and awareness of DM in African countries. However, the number of high-quality studies is still low and emphasizes knowledge gaps and underexplored research areas. Available studies are not representative of all African regions and were mainly conducted in urban areas of higher developed countries. Especially primary care settings and implementation research are underrepresented.

An improvement of the prognosis of DM patients in Africa requires adequate technical and financial resources, training of healthcare staff and the implementation of comprehensive strategies to improve early diagnostics, adherence to medical treatment and subsequent regular checks. The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances.

Ethics approval

No ethical approval is necessary

Authors contribution

Sandholzer-Yilmaz AS developed the concept of the review, performed the initial systematic search in the International Trials Registry, screened the references, extracted study data in 2019, wrote a draft of the manuscript and worked in the

coauthors comments on the final version of the manuscript and finally submitted the manuscript.

Kroeber ES updated the systematic search, added a search in 2 regional databases, screened the updated search results and extracted the updated data and wrote the final version of the manuscript.

Unverzagt S has expertise in systematic reviews and is the guarantor of the methodological quality of the systematic review, developed the review concept has registered the protocol, performed the systematic search in 2 databases, screened all references, checked the initial as well as the updated data extraction and wrote the final version of this manuscript.

Ayele W provided expertise on the needs of evidence in the African context, developed the review concept, discussed the protocol and critically read and commented on the manuscript.

Frese T and provided expertise on primary care, developed the review concept, critically read and commented on the manuscript.

Kantelhardt EJ provided expertise on the needs of evidence in the African context, developed the review concept, critically read and commented on the manuscript.

Sandholzer-Yilmaz AS and Kroeber ES are joint first authors of this manuscript.

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Competing interests statement

The authors declare no competing interests.

Data sharing statement

No additional data available

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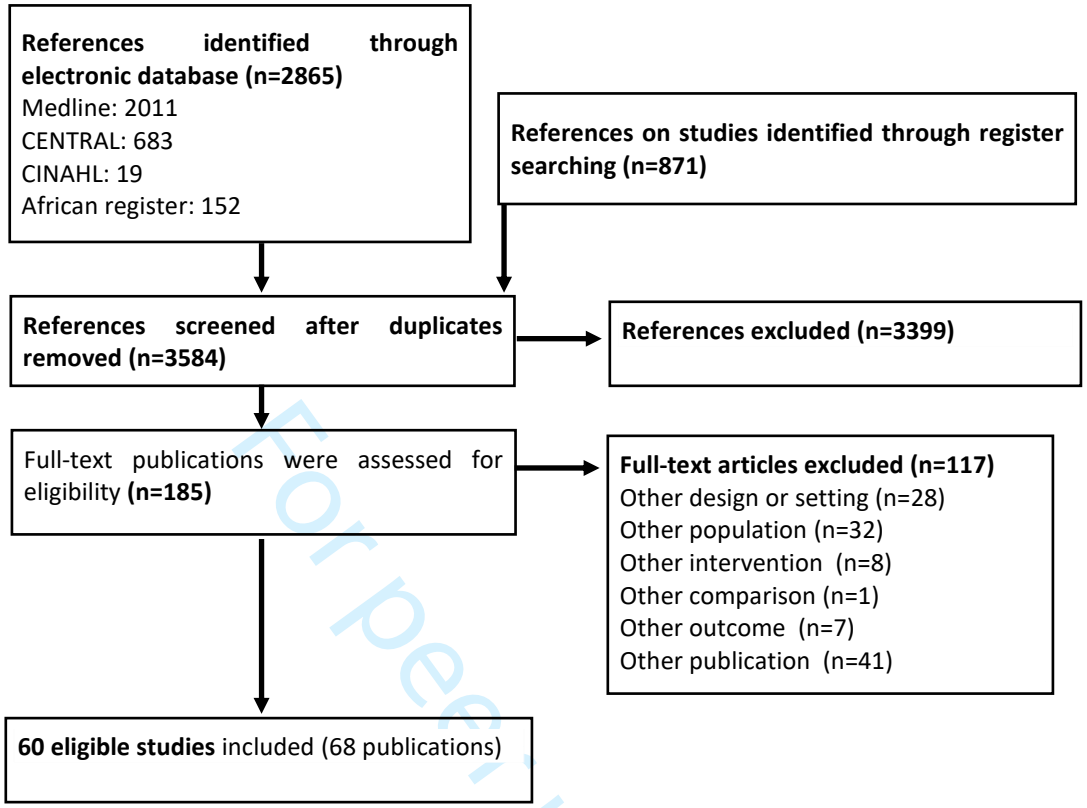
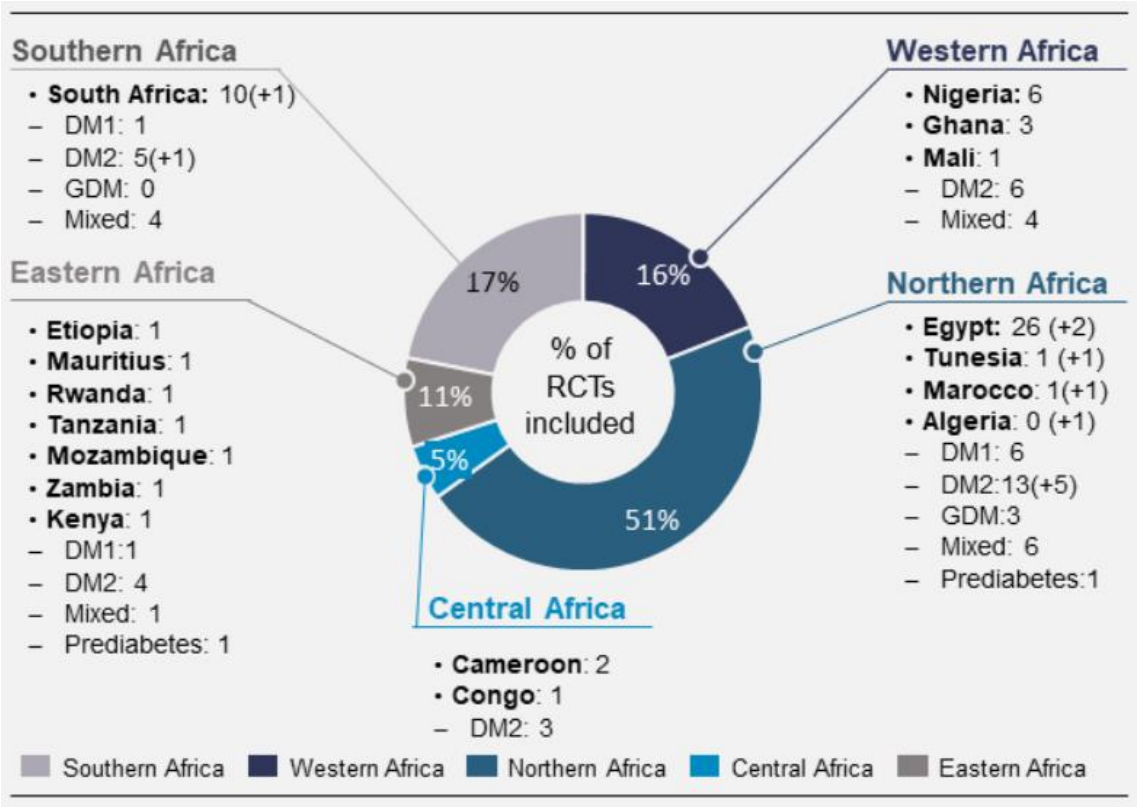
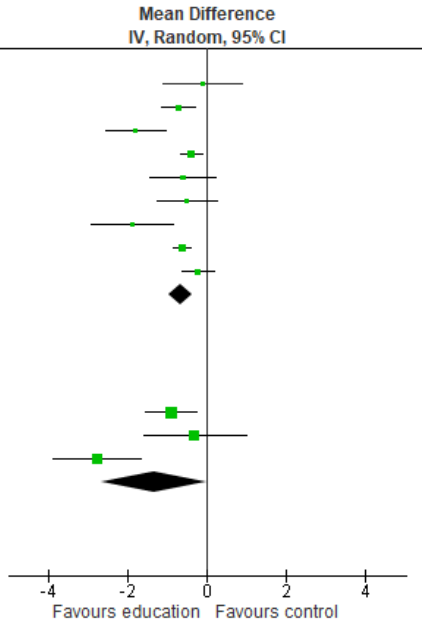
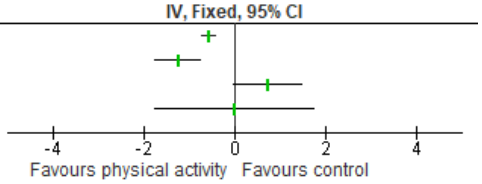




Study or Subgroup	Education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 End of follow-up								
Abaza 2017 (Egypt)	8.73	1.98	34	8.84	2.4	39	5.7%	-0.11 [-1.12, 0.90]
Amendezo 2017 (Rwanda)	7.49	1.48	115	8.21	1.72	108	14.3%	-0.72 [-1.14, -0.30]
Essien 2017 (Nigeria)	8.4	1.67	53	10.2	2.19	51	8.4%	-1.80 [-2.55, -1.05]
Mash 2014 (South Africa)	8.4	2	391	8.8	2.2	475	17.5%	-0.40 [-0.68, -0.12]
Muchiri 2016 (South Africa)	9.8	1.92	41	10.4	1.92	41	7.4%	-0.60 [-1.43, 0.23]
Sodipo 2017 (Nigeria)	7.2	2	55	7.7	2	52	8.3%	-0.50 [-1.26, 0.26]
Takenga 2014 (Congo)	6.73	1.59	17	8.6	1.35	14	5.4%	-1.87 [-2.91, -0.83]
Tawfik 2016 (Egypt)	7.5	0.8	107	8.12	0.9	107	18.6%	-0.62 [-0.85, -0.39]
Webb 2015 (South Africa)	8.54	2.11	225	8.76	2.22	191	14.4%	-0.22 [-0.64, 0.20]
Subtotal (95% CI)			**1038**			**1078**	**100.0%**	**-0.66 [-0.94, -0.39]**
Heterogeneity: Tau² = 0.10; Chi² = 21.97, df = 8 (P = 0.005); I² = 64%								
Test for overall effect: Z = 4.66 (P < 0.00001)								
1.1.2 Change until end of follow-up								
Debussche 2018 (Mali)	-1.05	2.09	70	-0.15	1.75	70	38.0%	-0.90 [-1.54, -0.26]
Hailu 2018 (Ethiopia)	-2.88	4.28	78	-2.57	3.59	64	29.7%	-0.31 [-1.60, 0.98]
Thuita 2020 (Kenya)	-2.04	2.7	48	0.73	2.71	46	32.4%	-2.77 [-3.86, -1.68]
Subtotal (95% CI)			**196**			**180**	**100.0%**	**-1.33 [-2.65, -0.01]**
Heterogeneity: Tau² = 1.08; Chi² = 10.57, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 1.98 (P = 0.05)								



Study or Subgroup	Physical education Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fayehun 2018 (Nigeria)	6.26	0.17	23	6.82	0.32	23	-0.56 [-0.71, -0.41]
Maharaj 2016 (Nigeria)	7.12	1.19	45	8.36	1.25	45	-1.24 [-1.74, -0.74]
van Rooijen 2004 (South Africa)	8.99	2.59	75	8.26	1.97	74	0.73 [-0.01, 1.47]
Yan 2014 (Mozambique)	7.7	2.23	31	7.7	2.53	10	0.00 [-1.75, 1.75]



Studies on patients with pre-DM

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Strategies to enhance physical activity						
RezkAllah 2019 ACTRN126170 00631303 RCT	Egypt, urban 07/2017-01/2018	Pre-DM, 25-45 yrs, BMI of 25–30 kg/m2, HbA1C 5.7–6.4%, fasting glucose 100–125 mg/dL, sedentary lifestyle No history of diabetes, cancer, prediabetic neuropathy, stroke, pulmonary embolism, or severe musculoskeletal problems restricting physical activity	n=60 45 % females age (yrs): 32.9±5.5 BMI (kg/m²): 28.3±1.4	IG2 (n=20): High-volume high intensity interval training, 40 min/session vs. IG1 (n=20): Low-volume high intensity interval training, 25 min/session Both with 90 % HR maximum, 3 times/week CG (n=20): No exercise intervention Duration: 12 weeks	Primary: HbA1c Other: fasting glucose	After 3 months HbA1c (%): Benefit for IG2 and IG1: Benefit for IG: 4.87±0.34 (-26 %) vs. 5.13±0.57 (-14.5 %) vs. 6.25±0.48 (+3.38 %) (p=0.0001) fasting glucose (mg/dL): Benefit for IG2 and IG1: 90.8±4.13 (-17.8 %) vs. 93.8±4.16 (-13.2 %) vs. 103.8±7.21 (+2.9 %) (p=0.0001)
Strategies on nutrition						
Krawinkel 2018 DRKS 00005131 Cross-over-RCT	Tanzania, urban 10/2013-03/2014	Individuals with pre-DM age (yrs): 30 -65, FPG 5.6-6.9 mmol/l (100–125 mg/dL) on 2 days or on one day + HbA1c 5.7-7.5 %, BMI 27–35 kg/m^2, BP 90/60-160/110 mmHg, waist circumference > 80/90 cm for women / men No chronic disease, taking regular intake of medication, identified glucose-6-phosphatase-dehydrogenase deficiency, heavy alcohol consumption, pregnancy,	n=52 55% female age (yrs): 47.5±8.7 HbA1c (%):5.85±0.43 FPG: (mmol/l): 5.34±0.49 BMI (kg/m²):29.6±2.2	IG/CG (n=30): started with bitter gourd supplementation (2,5 g) over 8 wks, followed by placebo over 8 wks vs. CG/IG (n=31): first placebo over 8 wks, followed by bitter gourd over 8 wks washout period: 4 wks Duration 8 weeks	Primary: FPG Secondary: HbA1c, Insulin, SBP, DBP, lipids	after 8 wks FPG (mmol/l): Benefit for IG/CG: MD 0.31 (0.08-0.54) HbA1c: (%): No differences (MD 0.05)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		lactation				

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DBP: Diastolic blood pressure; DM: diabetes mellitus; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants; MD: mean difference; RCT: randomized controlled trial; SBP: Systolic blood pressure; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 1: Characteristics and results of studies on patients with pre-DM

Studies on patients with DM1

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Malipa 2013 RCT	Zambia	DM1, 16-19 yrs	n=40 55% females 16-17 yrs: 35 % 18-19 yrs: 65 % Compliance: worse in IG 26.4 vs. 14.6 (p=0.001) Impact of diabetes: 20.5 Worries about diabetes: 20.5 Satisfaction with life: 20.5	IG (n=20): 1 meeting /wk over 8 wks CG (n=20); waiting list Duration: 8 wks	Compliance to treatment (Rating scale for compliance) Quality of life (impact and worries about diabetes, satisfaction with life)	After 2 months: Compliance: better in IG (11.0 vs. 30; p<0.001) Impact of diabetes: better in IG (16.8 vs. 24.2; p=0.045) Worries about diabetes: better in IG (14.32 vs. 26.68; p=0.001) Satisfaction with life: better in IG (28.5 vs. 12.5; p<0.001)
Strategies to enhance physical activity						
Salem 2010 RCT	Egypt, urban 02/2009-11/2009	DM1 for ≥3 years, 12-18 yrs, HbA1c ≥7.5 % for ≥6 months no significant diabetic complications limiting exercise like, uncontrolled hypertension, diabetic keto-acidosis, severe hypoglycemia within the past 3 months, patients on lipid lowering therapy	n=196 61.7 % female age (yrs): 14.78 ± 2.31 HbA1c (%): 8.7±1.7 duration of diabetes (yrs): 4.6 ± 1.9	IG2 (n=73): attended exercise sessions three times/week vs. IG 1 (n=75): attended exercise sessions once times/week vs. CG (n=48): no exercise Duration: 6 months	glycemic control, plasma lipids values, blood pressure, severity and frequency of hypoglycemia, anthropometric measurements and insulin dose	Change over 6 months: HbA1c (%): Benefit for IG2 and IG1: 7.8 ± 1.0 vs. 8.1 ± 1.1 vs. 8.9 ± 1.3% (p=0.2)
Strategies on nutrition						
Abdulrhman 2013 NCT01554566 Cross-over	Egypt, urban, tertiary care 01/2010 -	DM1, age > 2 yrs, HbA1c< 10 % no renal or hepatic impairment, coexisting	n=20 50 % females age (yrs): 11.3 ± 4.3 duration of diabetes (yrs): 4.7±4.5	IG/ CG (n=10): Honey consumption (0.5 ml/kg body weight per day) vs.	Primary: serum lipids, c-peptide Secondary: anthropometric measures (e.g. BMI), fasting and 2h-	After 12 weeks: (IG/CG vs. CG/IG): HbA1c (%): • Benefit with CG/IG: 6.7±0.9 vs. 5.9±0.8 (p<0.01) • no differences in change in period 1: -

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT	10 / 2011	diseases or therapies that may affect body weight or serum lipids	HbA1c (%):7.21± 0.76 fasting glucose (mg/dl): 154.5±22.5	CG/IG (n=10): changed after 12 wks and received than honey Duration: 12 wks.	postprandial glucose, HBA1c, serum lipid profile	5.83 ± 13.66 vs. 2.94±8.82 (p=0.105) Fasting glucose (mg/dl): benefit with CG/IG: 142.7 ±26.6 vs. 116.7±19.4 (p<0.01) benefit with IG/CG in period 1:-21.51 ± 10.84 vs. -0.08±5.14 (p=0.001)
Mohamad 2009 RCT	Egypt, urban	DM1, age 17 to 20 yrs no acute metabolic complications like diabetic ketoacidosis, hypoglycaemia, cardiovascular events, renal or acute infections	n=64 30 % female age (yrs): 19.9±6.8 HbA1c (%): 9.52±2.08 fasting glucose (mg/dl): 228.7±13.5 BMI (kg/m²): 18.82±3.01	IG (n=27): camel milk (500 ml) +usual care vs. CG (n=27): usual care for diabetes (i.e. diet, exercise, insulin mixtard) Duration: 16 weeks	Not specified: HbA1c, human C-peptide, lipid profile, serum insulin, anti-insulin antibodies, creatinine clearance, albumin extraction in 24 h urine, BMI, Diabetes QoL score, fasting glucose	After 16 wks HbA1c (%): Benefit for IG: 7.16±1.84 vs. 9.59±2.05 fasting glucose (mg/dl): benefit for IG: 227.2±17.7 vs. 98.9±16.2
van der Hoogt 2017 cross-over RCT	South Africa	DM1, age 4-17 yrs on insulin pump therapy, HbA1c>9,6% for ≥3months, BMI/age z.score -1 to < 3, total daily insulin use of >0,5 u/kg no remission of diabetes, smoking, coeliac disease, cystic fibrosis, diseases or medication that are associated with delayed gastric emptying or altered digestation, glucocorticoids, oral diabetic drugs, no acute illnesses	n=32 41% female age (yrs): 10.4±4.0 HbA1c (%): 8.2±0.8 duration of Diabetes (yrs): 3.5 (1.5-8.0)	IG1 (n=22): 1 home-based low fat and protein meal vs. IG2 (n=22): 1 high fat and protein meal with identical carbohydrate content two meals were consumed at dinner time (18:00) under parental supervision at least 1 day apart within one month Duration: 3months	primary: peak sensor glucose value post-meal, time to peak sensor glucose, time of first and largest correction bolus, total correction insulin, total meal insulin, additional insulin required ,area under the sensor glucose response curve (AUC) (≥ 8 mmol/L), duration of elevated post-prandial glucose	Change over 12 weeks Occurance of hypoglycaemic events: 7 (32 %) vs. 1 patients after IG1 vs. IG2
Medical device						
Elbarbary 2016 RCT	Egypt, urban 06/2014-07/2014	DM1, adolescents and adults who wished to fast the month of Ramadan with insulin pump for ≥6 months and attending the whole	n=73 68.3% female age (yrs): 15.6±2.7 HbA1c (%): 7.65±0.9 BMI (kg/m²):	Insulin pump therapy during Ramadan fasting IG (n=25): sensor with low glucose	Primary: hypoglycaemia Other: glucose value, number of 'full fasted days', emergency hospital visit for diabetes-related	After 1 months: Glucose value (mg/dl): 152.5±17.3 vs. 141±33.8 (p=0.9) Complications: Number of hypoglycaemic excursions:

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		education session 2 months before fasting and committed to follow-up the given instructions no diabetic ketoacidosis, episodes of severe hypoglycaemia or symptoms of uncontrolled diabetes in the last 6 months, diabetic microvascular complications or macrovascular disease, pregnant women	24.56±3.5 duration of diabetes (yrs): 5.8±2.9 on pump therapy (yrs): 1.73±0.99	suspension activation vs. CG (n=35): sensor without low glucose suspension activation Duration:1 month	problem	3.68±1.62 vs. 6.7±2.1 (p=0.001) Number of hyperglycaemic excursions: 17.0±4.0 vs. 23.0±7.6 (p=0.001) No severe hypoglycaemic events, no episodes of diabetic ketoacidosis, no hyperglycaemic events associated with ketosis no deaths or device-related SAE
Pharmacological Strategies						
Elbarbary 2018 NCT0292825 RCT	Egypt, urban	DM1, age: 9 - 18 yrs, ≥ 5 yrs disease duration, active diabetic nephropathy in the form of microalbuminuria, HbA1c ≤ 8.5 % no infection, renal impairment due to other causes other than diabetes, other diabetic complications, hypersensitivity to carnosine	n=90 52.3 % female age (yrs): 12.85±3.1 HbA1c (%):7.85±1.95	IG (n=45): 1 g/d carnosine vs. CG (n=45): control/placebo group Patients in both groups received oral ACE-Is captopril 25 mg Duration: 12 wks	Primary: change in tubular damage marker Secondary: urinary albumin excretion (UAE), oxidative stress markers Safety: any AE	After 12 wks: HbA1c (%): • Benefit for IG: 7.4 ±1.3 vs. 8.3±2.4 • change -9.88±7.12 vs. 3.89±2.28 (p=0.005) No adverse reactions were reported
Elbarbary 2020 NCT03594240 RCT	Egypt, urban 03/2017-03/2018	DM1 on insulin therapy with > 5 yrs of disease duration, 12-18 yrs, active nephropathy, HbA1c< 8.5 %, no infections, renal impairment due to other causes than diabetes, other diabetic complications ,	n=80 55% female age (yrs): 15.4 ± 1.6 HbA1c (%):7.95±0.5 fasting glucose (mg/dl): 114.5±21.8 duration of diabetes (years): 8.65 ± 2.65	both groups received oral angiotensis-converting-enzyme inhibitors (captopril) IG (n=40) oral vitamin B complex (B1,B6,B12) once daily vs.	Primary: Cystatin C diet, physical activity, and metformin dosage	after 12 weeks HbA1c (%): Benefit for IG: 7.5±0.6 vs. 8.0±0.6 Fasting glucose (mg/dl): 107.7±14.1 vs. 116.4±17 (p=131)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	 Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		elevated liver enzymes, hyper-or hypothyroidism, hypertension, neoplasm, taking any vitamins or food supplements within 1 months before study start		CG (n=40): placebo Duration: 12 weeks		

BMI: Body mass index; CG: Control group; CG/IG: Crossover from CG to IG; CI: Confidence interval; DM1: Type 1 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG/CG: cross over from IG to CG; IG: intervention group; n: number of participants ;RCT: randomized controlled trial; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 2: Characteristics and results of studies on patients with DM1

RCTs mainly including patients with DM2

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Educational strategies						
Abaza 2017 NCT02868320 RCT	Egypt, urban, tertiary care, 03-07/2015	DM2, mobile phone, capable to read SMS or live with someone who could read	n=73 56 % females age (yrs): 51.5±9.2 majority had had diabetes for > 1 yr hypertension: 41.1 % on insulin: 19.2 % DM complication: 80.8 % HbA1c (%): 9.7±2.7	Diabetes awareness program: paper-based educations material plus IG (n=34): daily messages and weekly reminders addressing various diabetes care categories vs. CG (n=39): paper-based educations material Duration: 12 wks.	Primary: change in Hba1C Secondary: Random blood glucose levels, body weight, adherence of treatment and medication, diabetes self-efficacy and knowledge, rate of hospital/ER visits, frequency of measurements, regular exercise, patients confidence in healthcare provider and satisfaction, healthcare provider's reputation	After 3 months: HbA1c (%): • No differences: 8.73 ±1.98 vs. 8.84±2.40, MD_a: 0.290 (-0.402 to 0.983; p = 0.406) • Benefit with IG: 47 vs. 15 % achieved the targeted 1% drop (p = 0.003) Random blood glucose (mg/dl): • No difference: 181±65 vs. 201±87 (p=0.288) Treatment adherence (scores): • Benefit with IG in SCI 3.42±0.48 vs. 2.52±0.49 (p<0.001) and Morisky: 3.76±0.55 vs. 2.74±1.07 (p<0.001) Hospital /ER admission (%): No differences: 0 vs. 10.3 (p=0.118)
Adibe 2013 RCT	Nigeria, urban, tertiary care	DM2, age≥ 18 yrs with oral hypoglycemic and / or insulin therapy no pregnancy	n=220 58 % females age (yrs): 52.6±7.9 duration of diabetes (yrs): 4.7±2.5, 60.5% with diabetes > 5 yrs on insulin: 13.6 % hypertension: 60.5 %	IG (n=110): structured self-care education and training program by pharmacists and nurses vs. CG (n=110): usual / conventional care Duration: 12 months	Primary: incremental cost-utility ratio, net monetary benefit Other: quality of life	After 12 months: Quality of life: • Benefit with IG: 0.86 ± 0.12 vs. 0.64 ± 0.10 (p=0.0001) improved single attributes except "hearing" functioning of the patients Costs: • benefit of \$0.76±0.15 vs. \$0.64± 0.15 QALY/patient and year; MD: \$ 0.12 (0.07 to 0.16) • incremental cost-utility ratio of \$571 per QALY
Adjei 2015	Ghana, urban	DM	n=200 64.5% female	IG: (n=100): electronical reminder for	Primary: Compliance with appointment dates	After 6 months: Adherence to appointment schedules

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
RCT			age (yrs): < 50 yrs: 63 % > 50 yrs: 37 % fasting glucose (mmol/l): 10.4±3.8	clinical appointments of patients + alert system for abnormal laboratory results vs. CG: (n=100): usual diabetes care, paper based method Duration: 6 months	Other: metabolic risk factors, BMI	(%) Benefit for IG: 97.8 vs. 89.4 (p=0.010) Fasting glucose (mmol/l): Benefit for IG: 8.04±2.14 vs. 8.85±2.63; MD 0.4 (-0.59 to -0.36, p=0.022)
Amendezo 2017 NCT02032108 RCT	Rwanda, urban, tertiary care	DM2>3mths, age>21yrs no pregnancy or severe co-morbid illnesses.	n=251 69.3% females age (yrs): 50.9 ±10.9 BMI (kg/m²): 27.9 (27.0-28.5) duration of diabetes : <10 yrs: 73.7%, >10 yrs: 16.3% HbA1c (%): 8.98±8.6-9.3	IG (n=115): standard care plus monthly lifestyle education sessions of 45 min duration vs. CG (n=108): standard care Duration: 12 months	Primary: difference in HbA1c Secondary: fasting glucose, systolic and diastolic blood pressure, BMI	after 12 months: HbA1c (%): Benefit for IG with median reductions of -1.70 (-2.09 to-1.31) vs. -0.52 (-0.95 to -0.10); MD: -0.72 (-1.14 to -0.30; p< 0.001) Fasting glucose (mmol/L): 6.9 (6.45 to 7.36) vs. 9.02 (8.18 to 9.87) (p<0.001)
Chraibi 2017 NCT01589653 RCT	Egypt, Indonesia, Morocco, Saudi Arabia, Vietnam 05/2012-07/2015	DM2 with diagnosis ≥ 12 months, age≥18 , currently being treated with NPH Insulin for ≥ 3 months + metformin (1000-1500 mg) for ≥ 2 months, HbA1c ≥ 7.0% ≤10%, BMI ≤ 40.0 kg/m^2 no treatment with thiazolidinedione, glucagon-like peptide-1 receptor agonists, pramlintide within the last 3 months , >1 IU/kg NPH insulin daily; previous use of premixed or bolus insulin, > 1 severe hypoglycemic episode during	n=155 74.9 % female age (yrs): 54.5 ±10.0 BMI (kg/m²): 29.05±4.9 HbA1c (%): 8.6 ±0.83 fasting glucose (mmol/L): 8.97 duration of diabetes (yrs): 9.5±5.8 African patients: • Egypt: 25.75 % • Morocco: 27.7 % Diabetic nephropathy / neuropathy / retinopathy (%): 3.2 / 16.1 / 3.2	IG (n=76): patient driven titration of Biphasic insulin aspart 30 twice daily, 3 clinic visits vs. CG (n=79): physician driven titration twice daily, 6 clinic visits Titration in both arms according to the titration protocol bases on self-measured plasma glucose values, measured twice daily on 3 preceding days, telephone contact whenever deemed	Primary: change in HbA1c Secondary: proportion of patients achieving the ADA target of HbA1c <7.0 % and the HbA1c target of <6.5 % after 20 weeks, FPG changes, hypoglycemic episodes,	Change over 5 months: HbA1c (%): • Decreased in both arms with non-inferiority between groups: MD -0.23 (-0.54 to 0.08) • More patients reached HbA1c <7.0%: 40.8 vs. 29.1 %, RR: 1.79 (0.87 to 3.65) and <6.5%: 25 vs. 19 %; RR: 1.52 (0.67 to 3.46) • More patients reached target HbA1c levels without severe or minor hypoglycemic episodes: <7.0%: 38 vs. 27.8 %, RR: 1.52 (0.61 to 3.79), <6.5%: 18 vs. 14.8 %; RR 1.13 (0.36 to 3.52) FPG (mmol/l): • Decreased in both arms with no difference between groups: 0.95±0.28

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		the previous 12 month, impaired kidney or hepatic function, proliferative retinopathy or maculopathy requiring treatment	Macroangiopathy (%): 5.2	necessary Duration: 20 weeks		vs. 0.67±0.28; MD: -0.28 (-1.07 to 0.52) Costs • Less frequent clinic visits to healthcare professionals in IG: 4.8±0.65 vs. 7.5±1.42 visits/patient Complications: • hypoglycemic episodes: no difference: 608.4 vs. 789.2 / 100 patient-years of exposure; RR: 0.74 (0.44; 1.23) treatment-emergent AEs: no difference: 324.2 vs. 302.2 events / 100 patient-years of exposure
Debussche 2018 NCT01485913 RCT	Mali, urban, secondary care, 07/2011-02/2013	DM2, age 30-80 yrs, HbA1c ≥ 8 %, no DM1, severe diabetes complications or concomitant illnesses that threatened their functional or vital prognosis	n=151 76.2% female age (yrs): 52.5±9.8 BMI (kg/m²):28.6±5.4	IG (n=76): peer-led structured patient education received culturally tailored structured patient education (3 courses of 4 sessions) delivered in the community by five trained peer educators vs. CG (n=75): conventional care alone Duration:1 yr	Primary: HbA1c Secondary: anthropometric indicators (weight and BMI, waist circumference), SBP, DBP, anti-diabetic and anti-hypertensive treatment, knowledge score, dietary practices	Change to 12 months HbA1c (%): • Benefit in IG: MD 1.05 % (-1.54;-0.56) vs. -0.15 % (-0.56; 0.26) (p = 0.006)
Essien 2017 PACTR201302 00047835 RCT	Nigeria, urban, tertiary care, 09/2013-05/2014	DM1 or DM2, age: ≥ 18 yrs, HbA1c> 8.5 %, able to engage in moderate exercise, no eye disease that would limit the ability to read	n=118 60.2 % female age (yrs): 52.7±10.5 BMI (kg/m²): 28.9±7.5 HbA1c (%):10.7±1.6 type of diabetes • DM1: 14.4 % • DM2: 85.6 %	IG: (n=59): intensive and systematic disease self-management education programme (invitation and encouragement by clinical staff to attend 12 structured teaching sessions) vs.	Primary: HbA1c	After 6 months: HbA1c (%): 8.4 (8 to 8.9) vs. 10.2 (9.8 to 10.7); MD_a: -1.8 (-2.4 to -1.2); (p < 0.0001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				CG (n=59): conventional disease-self-management education Duration: 6 months		
Fairall 2016 ISRCTN20283604 Cluster-RCT	South Africa, urban/rural, primary care, 03/2011 – 11 / 2011	age ≥ 18 yrs , clinics providing service for NCD Patients with DM, hypertension, chronic respiratory disease or depression, with self-reported hypoglycaemic (in case of DM)	n= 38 public sector primary care clinics, 4393 patients, n=1842 with DM 73 % female age (yrs):median, IQR): 52 (42-61) vs. 52 (44-62) BMI (kg/m²): 30±8 HbA1c (%):9 (4-17), in HbA1c in DM≥ 7 %: 77 %	IG (n=2166, 851 with DM): Nurses were trained to use a primary care programme to support and expand nurses`role in NCD care and contains a clinical management tool with enhances prescribing provisions vs. CG (n=2227, 991 with DM): Nurses continued to use the Lung Health and HIV/AIDS approach with usual training Duration: 14 months	Primary (for DM): treatment intensification (addition or increase in dose of metformin and/or sulphonylurea, insulin, ACE-inhibitor, aspirin, statin	over 14 months HbA1c (%): • <7 %: 41 vs. 38 %; RR 1.08 (0.77 to 1.52; p=0.638) • 7-10 %: 69 vs. 55 %; RR 1.30 (1.16 to 1.47; p<0.001) • >10 %: 71 vs. 73 %; RR 0.97 (0.81 to 1.16; p=0.703) Treatment intensification rates* (%): • 57% vs. 50%, RRa: 1.11 (0.99 to 1.26) (p=0.083) for patients with DM
Hailu 2018 NCT03185689 RCT	Ethiopia, urban, 02/2016-10/2017	DM2, age > 18 yrs no DM1 or GDM, pregnant women, severe cognitive or physical impairment, and terminally ill people	n=220 33 % female age (yrs): 54.5±10 BMI (kg/m²):25±4 HbA1c (%):10.5±4	IG (n= 116): Nurse-led disease-management education: 6 sessions, supported with illustrative pictures handbooks and fliers, customized to local conditions by trained nurses vs. CG (n=104): usual follow-up care Duration: 9 months	Primary: patients with target HbA1c (≤ 7 %) Secondary: systolic and diastolic blood pressure, fasting glycose, BMI, waist circumference	Change over 9 months: HbA1c (%): • No difference: 45 % vs. 50 % with target values (p=0.21), MD: 2.88% (-3.85 to -1.92) vs. 2.57% (-3.47 to -1.67) fasting glucose (mg/dl): • Benefit with IG: 36 % vs.25 % with target values, MD: -27 (-45 to -9; p=0.003)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Labhardt 2011 NCT00744458 Cluster-RCT	Cameroon rural, primary care, 08/2008-02/2010	newly detected adult patients with DM2 and /or hypertension in the catchment area of nurse-led health centres, staffed, equipped and trained to care for DM2 and hypertension	n=33 facilities, 221 patients 64% females age (yrs): 59.8±12.7 diabetes: 15.4 % Overweight (BMI 25-29.9 kg/m^2): 28.5 % Obesity (BMI> 30 kg/m^2): 20.4 %	IG 1 (11 centres, n=55): incentive group free treatment for 1 months for patients who regularly attended follow up visits vs. IG 2 (11 centres, n=77): letter group: reminder letters in case of a missed follow-up visit vs. CG (11 centres, n=89): no additional intervention Duration: 12 months	Primary: Patient retention at 1 yr (≥ 12 follow-up visits within 12 months) Secondary: Adherence with timely attendance of follow-up visit schemes and changes in blood pressure and blood glucose levels.	After 12 months: Retention rates (%): • Benefit for IG1 and IG2 vs.CG: 60 vs. 65 vs. 29 %; MD 34 (21 to 46) with no differences between IG1 and IG2; MD -5 (-22 to 12) Loss to follow-up: • Benefit for IG1 and IG2: IG1 vs. CG: HR 0.44 (0.27 to 0.72; p< 0.001) • IG2 vs. CG: HR 0.38 (0.24 to 0.61; p<0.001) Adherence (%): • Benefit for IG1 and IG2: 38 vs. 35 vs. 10; MD 26 (14 to 42), IG1 vs CG: MD 28(13 to 37); IG2 vs. CG: MD 25 (13 to 37) • no difference between IG1 and IG2: MD 3 (-14 to 20) FPG: No differences between groups
Mash 2014 Cluster RCT	South Africa, urban, primary care, 12/2010 -12/2012	DM2 with any therapy attending community health centres in the working class areas of Cape Town Metropole no DM1, dementia, mental illness or acute illness	n=34 public sector community health centres, 1570 patients 73.8% females age (yrs): 56.1±11.6 HbA1c (%): 9.1±2.3	IG (17 health centres, n=710): 4 monthly sessions lasting 60 min with group education about diabetes topics (understanding diabetes and medication, living a healthy lifestyle and preventing complications), delivered by a health promotion officer vs. CG (17 health centres, n=860): usual care: ad hoc advice during consultations and	Primary: improvement of diabetes self-care activities (5 % weight loss, and a 1 % reduction in HbA1c level) Secondary: improved diabetes specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol levels, quality of life	After 12 months: HbA1c (%): No differences: 8.4±2.0 vs. 8.8±2.2; MD_a: 0.01 (-0.27 to 0.28; p=0.967) Adherence (self-care activities): No differences in scores of physical activity, use of diet plan or medication, foot care or frequency of smoking Quality of life: No differences in physical functioning, role or social functioning, mental or general health and pain Costs: Incremental cost effectiveness ratio: 1862 Dollar/ QALY gained

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				occasional educational talks in waiting room Duration: 12 months		
Muchiri 2015 RCT	South Africa, rural, primary care, 04/2010-11/2011	DM2, age 40-70 yrs attending community health centres, HbA1c≥ 8 %, blood sugar levels ≥ 10 mmol/l, duration of diabetes ≥ 1 yr no insulin therapy, pregnant women, full time employed	n=82 86.6 % female age (yrs): 59±7.4 BMI(kg/m²): 30.9±6.9 HbA1c (%): 11.1±2.0 duration of diabetes (yrs): 6	IG (n=41): education materials+ 8 weekly group educational sessions about diabetes and nutrition, follow-up sessions+vegetable gardening CG (n=41): education materials Duration: 12 months	Primary: HbA1c Secondary: Other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c, dietary behaviours	over 12 months HbA1c (%): • no difference: 9.8±1.92 vs. 10.4±1.92; MD −0.63 (-0.26 to 1.50; p=0.16)
Owolabi 2019 PACTR201810599931422 RCT	South Africa urban/rural, primary care 07/2018-04/2019	DM, age ≥18 yrs, DM diagnosed at least in the last 6 months, currently receiving treatment at the selected clinics, on stable medication for ≥ 3 months prior to recruitment, uncontrolled glycaemic control, in possession of a mobile phone, able to retrieve and read SMSs and willing to receive SMSs health or mental conditions that could interfere with the study, pregnant or planning to get pregnant within the next 6 months, debilitated or handicapped in such a way that obtaining anthropometric measurements could be	n=216 84.3 % females age (yrs): 60.6±11.6 DM2 (%): 94 Treated with oral pills (%): 75.5 Duration of DM (yrs): 9.1±7.4 Duration of DM treatment (yrs): 8.8±7.2 Hypertension (%): 83.0 Random blood glucose (mmol/L): 14.34±3.9 BMI(kg/m²): 32.2±6.2	IG (n=108): daily SMS text-messaging SMS at an agreed time of the day, according to their needs, care plan and goal with motivational and support messages, advice on lifestyle behaviours (e.g. diets, physical activity, smoking cessation, medication and appointment reminders) vs. CG (n=108): usual diabetes care Duration: 6 months	Primary: Morning random blood sugar Secondary: co-morbid outcomes (hypertension and obesity), obtained through blood pressure measurement, anthropometric measurements (body weight, BMI) acceptability, feasibility	Over 6 months: Blood glucose levels (mmol/L): -1.58±5.29 vs. -1.95±4.69; MD 0.51(-0.8 to 1.82), MD_a 0.26 (-0.81 to 1.32)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		challenging				
Sodipo 2017 RCT	Nigeria, primary care, 03/2013-11/2013	DM2 ≥ 18 yrs. on antidiabetic medication no patients with emergencies, chronic complications such as nephropathy, neuropathy etc., those already using glucometer	n=120 gender: 50% female age (yrs): 59±10.95 HbA1c (%): 8.7±2.45 fasting glucose (mg/dl): 152±60.9 duration of diabetes (yrs): 50%> 3yrs	IG (n=60): Self-monitoring of blood glucose before and after meals 3 days a week for 12 weeks CG (n=60); non SMBG Duration: 12 wks	HbA1C, fasting glucose	after 3 months: HbA1c (%): No difference: 7.2±2.0 vs.7.7±2.0 (p= 0.174) fasting glucose (mg/dl): No difference: 123.2±35.1 vs. 137.6±50.1 (p=0.087)
Steyn 2013 Cluster-RCT	South Africa, urban, primary care, 1999-2000	public sector primary health care clinics (CHC) with ≥ 25 diabetes and ≥ hypertension patients age ≥15yrs, a documented attendee at the particular CHC with ≥ 4 visits during the previous year for hypertension or diabetes who received treatment for these conditions at each visit no patients being unable to answer a questionnaire	18 community health centres n=1096, of them n= 456 with DM age (yrs): 58.3 ± 11 gender:74 % females BMI (kg/m$^{2)}$: 30.7 ± 6.2 Type of Diabetes: • DM1: 5.8% • DM2: 91.35% uncertain DM type: 2.85%	IG (9 clinics, n=229): introduction of structured clinical record with guidelines prompts after training of doctors in their use and suggestions to incorporate them in regular patient records, contact over 1 year vs. CG (9 clinics, n= 227): usual care with passively disseminated guidelines Duration: 1 year	primary: HbA1C in the diabetes group secondary: uncontrolled glycaemia (HbA1c ≥7%) in the diabetes group.	After 3 months: HbA1c (%): IG: 8.8% vs. 8.8%; MDa -1.0 (-1.1 to -0.9) HbA1c ≥7% (%): no relevant difference: 64.1 vs. 62.6; MD 0.90 (0.53 to 1.53)
Takenga 2014 RCT	Congo, urban	DM2, 35-75 yrs	n=40 20 % females age (yrs): 53.3 ± 10.1 HbA1c (%): 8.63	IG (n=20): self-management of diabetes with Mobil DIAB (telemedical approach) vs. CG (n=20): conventional therapy without telemedical system	primary: HbA1c	after 2 months: HbA1c (%): Benefit for IG: 6.73±1.59 vs. vs. 8.6±1.35 (MD -1.87 (-2.91 to -0.83)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
				Duration: 60 days		
Tawfik 2016 RCT	Egypt, urban, primary care, 05/2015-09/2015	DM2 for ≥ 1 yr, 40-79 yrs attending an outpatient clinic no patients who were already using a similar medication chart, severe or terminal health conditions, or patients with behavioural health issue that could make it difficult to understand the communication	n=255 53.7 % females age (yrs): 55.7±8.35 HbA1c (%): 8.14±1.3 duration of diabetes (yrs): 8.3±1.3	IG (n=127): comprehensive cardiovascular risk communication vs. CG (n=128): standard usual care Duration: 3 months	Primary: HbA1c Secondary: Cardiovascular risk perception, diabetes self-care, cardiovascular risk scores	After 3 months: HbA1c (%): Benefit for IG: 7.5±0.8 vs. 8.12±0.9; MD -0.62 (-0.85 to -0.39) controlled HbA1c (%): 32.7 vs. 29.9
Thuita 2020 PACTR201910518676391 RCT	Kenya Secondary care recruitment 08/2016 - 10/2016	DM2, 20-79 yrs with regular attendance of an outpatient clinic Pregnancy, complications such as renal failure, congestive heart failure, or stroke	n=153 59.5 % females age (yrs). 56±11.6 Family history of DM (%): 46.6 Poor glycaemic control (%) with HbA1c>7%: 77.8 DM for 1-5 yrs (%): 58.2 % Years with DM: 6.7±6.9 Oral medications (%): 82.4 BMP (kg/m2): 27±4.6 HbA1c (%): 8.49±1.9 fasting glucose (mmol/l): 11.0±3.3	IG2 (n=51): nutrition education programme for 2 hrs /week with peer-to-peer support vs. IG1 (n=51): Education programme vs. CG (n=51): Standard care Duration: 8 weeks	Primary: metabolic syndrome prevalence (MetS) Other: anthropometry and clinical data, blood pressure, blood glucose and lipid profile, physical activity levels, food intake	After 6 months: Metabolic syndrome prevalence: lower with IG2: Harmonized criteria:52.1 vs.69.4 vs. 91.3 (p<0.001) WHO: 58.3 vs. 77.6 vs. 89.1 (p=0.003) HbA1c (%): Mean change: no differences -2.04±2.70 vs. 1.48±2.73 vs. -0.73±2.71 High HbA1c: no differences: 47.9 vs. 29.0 vs. 34.8 % fasting glucose (mmol/l): no differences: -2.59±0.66 vs. -2.95±0.64 vs. -1.55±0.68 high fasting glucose: 79.2 vs. 83.7 vs. 91.3 %

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Webb 2015 NCT01275040 Cluster RCT	South Africa, urban, primary care, 06/2010-03/2011	primary health care clinics, patients with clinical diagnosis of DM2 or DM1 for ≥5yrs, age ≥ 18 yrs	n= 12 primary health care clinics n= 599 gender:68.5 % female age (yrs): 57.8±10.5 HbA1c (%): 8.73±2.3 HbA1c ≥ 7 %: 73 % BMI (kg/m$^{2)}$: 30.8±6.7 Typ of diabetes: • DM1: 3.7 %, • DM2: 70.3 % • unknown: 26 % duration of Diabetes: • < 5 yrs: 47.3 % • 5-10 yrs: 22.0 % • > 10 yrs: 20.2 % • unknown: 10.5 %	IG (n=328): mobile screening team visits primary care clinic and provides education and active screening for diabetic complications (foot, kidney, cardiac and renal complications) vs. CG(n=273): no mobile screening team, routine care with similar education for patients. and health care workers Duration: 1 yr	Primary: HbA1c, detected neuropathy, nephropathy and retinopathy, HbA1c categories Secondary: detected complications, referred patients for complication assessment or care, blood pressure and lipid control, costs, LDL cholesterol, creatinine	after 12 months HbA1c (%): no difference: 8.54±2.11 vs. 8,76 ±2.2, MD-0.22 (-0.64, 0.20) screening rate for complications: in IG 60% increase of screening in all complication indicator groups, in both groups testing of HbA1c and renal complications (serum-creatinine) increased , but no significant difference , screening for eye complications, only increased significantly in IG no significant difference in the proportion of actions taken beween IG and CG (p=0.83)
Strategies to enhance physical activity						
Asuako 2017 RCT	Ghana, urban, tertiary care, 08/2015-03/2016	DM, age: 20-68 yrs, ambulant patients, without diabetes complications with < 150 minutes /wk of moderate physical activity no SBP > 140 or DBP> 90 mmHg, bilateral or unilateral lower or upper limbs amputation, use of insulin pump	n=12 83% female age (yrs): 83% were 46-55 yrs. BMI (kg/m²):25.4±4.5 fasting glucose (mmol/l):9.33 ± 5.7 type of diabetes: DM1: 17 % DM2: 83 % duration of diabetes (yrs): • 1-5 yrs: 25 % • 6-10 yrs: 50 % • 10 yrs: 25 %	IG (n=7): walking aerobic exercise sessions without treadmills (3/week) vs. CG (n=5): only activity of daily living Both continued regular medical/clinical routines Duration: 8 weeks	FPG, Lipid profile, body weight, BMI	Change over 2 months: FPG (mmol/l): Benefit for IG: 6.27 ± 0.91 vs. 8.00 ± 0.96; MD 1.73 (-1.88 to -1.59; p<0.001)

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Fayehun 2018	Nigeria, urban 06/2014-11/2014	DM2, age 18-64 yrs, Diagnosed ≥ 12 months, non-insulin dependent, on dietary control ± hypoglycemic agents, able to walk without limitations no pregnant women, smokers, prescription of medications that might impair ability to walk	n= 46 63 % female age (yrs): 54±7.7 (33-64) BMI (kg/m²): 22.4±3.3 HbA1c (%): 6.6 (5.3-9.0) duration of diabetes (yrs):<7 yrs: 70 %, >7 yrs 30 %	IG (n=23): Goal to accumulate 10000 steps per day vs. CG (n=23): normal activity habits Duration: 10 weeks	Primary: HbA1c Secondary: step count	Change over 2.5 months: HbA1c (%): Benefit for IG: 6.26 (6.19 to 6.33) vs. 6.82 (6.69 to 6.95); MD_a: -0.74 (-1.32 to -0.02; p=0.015)
Maharaj 2016 RCT	Nigeria, rural 07/2013-06/2014	DM2, non- insulin dependent, blood glucose levels 6 - 13 mmol/l no cardiac, abdominal or spinal surgery ≤ 6 months, history of fractures of lower limbs, spine, weakness, deformities, loss of sensation in the feet, retinopathy, nephropathy	n=90 52 % females age (yrs): 39.4 ± 8.6 (30-58) BMI (kg/m²): 27.7±5.8 HbA1c (%): 8.79±2.11 duration of diabetes (yrs): 2.5±2.1	IG (n=45): rebound exercise 3 times/week for 20-30 min, moderate intensity of 40-60 % of HR maximum vs. CG (n=45): watched videos and read health magazines Duration: 9 weeks	Primary: HbA1c , FPG, BMI Other: Heart and respiratory rates, blood pressure, oxygen saturation	After 9 weeks HbA1c (%): Benefit for IG: 7.12±1.19 vs. 8.36±1.25; MD_a: 0.904 (0.832 to 0.984; p=0.017) FPG (mmol/l): Benefit for IG: 6.92±1.21 vs. 8.73±1.23; MD_a: 0.787 (0.7345- 0.841; p=0.002)
van Rooijen 2004 RCT	South Africa, urban 03/2002-11/2002	black women with DM2, age 40-65yrs, duration of DM ≥12 months no chest pain on effort, possible previous myocardial infarction and intermittent claudication, cerebro-vascular incidents, arthritis, retinopathy	n=158 gender:100 % females age (yrs): 54-55 HbA1c (%): 9.35	IG (n=80): education+ incremental daily home exercise, use of daily physical activity records+6 fortnightly supervised aerobic exercise classes vs. CG(n=77): education+ relaxation exercise Duration: 12wks	Primary: HbA1c, BMI Secondary: walking distance (6 min walk)	Change over 3 months: HbA1c (%): no difference: 8.99±2.59 vs. 8.26±1.97
Yan 2014	Mozambique,	DM2, male, age 40-70 yrs, diagnosis for ≥ 12 months	n=41 100% male	IG (n=31): low or vigorous intensity	plasma glucose, HbA1c	Change over 3 months: HbA1c (%):

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RCT	urban	no known diseases other than DM2 and hypertension, no diagnosed cardiovascular diseases	age(yrs): 54±2.5 HbA1c: 8.6±0.7 plasma glucose (mmol/l): 9.65±1.2 BMI ($kg/m^{2)}$: 27.1 ± 1.0	exercise 3-5 times/week vs. CG(n=10): walked 1 hour per day as part of their daily lifestyle Duration:12 wks		reduction in both groups with no differences between groups: 7.7±0.4 vs. 7.7±0.8 Plasma glucose (mmol/l): 9.6 ± 0.7 vs. 11.1 ± 1.3
Pharmacological strategies						
Distiller 2014 RCT	South Africa	DM2 for ≥ 1 year with total insulin requirement of >200 U/d for ≥ 3 months, BMI > 30 kg/m^2, HbA1c> 7,5 %, on long-term metformin therapy (1.7–2.5 g/d) no pregnant or with childbearing potential, endocrinopathy, chronic inflammatory or systematic autoimmune disorder, CVD, active carcinoma, chronic illness, renal dysfunction, gastroparesis, no corticosteroids, DPP-4 inhibitors, exenatide, liraglutide, no anticipated change in other concomitant medication or insulin resistence	n=28 50% female age (yrs): 51.7 (36-71) HbA1c (%): 8.95 (7.6-11.3) BMI (kg/m^2): 40.8 (31.2-47)	IG (n=14): regular Insulin (500 U/ml) + metformin + exenatide (5 µg orally twice a day for 1 month and titrated to 10 µg) vs. CG (n=14): regular Insulin (500 U/ml) +metformin Duration: 6 months	Primary: HbA1c Secondary: Body weight, insulin dose, hypoglycemia	Change to 6 months: HbA1c (%): Significant improvement in both groups 8.7→7.7(p=0.002) vs. 9.2→7.5 (p=0.0001) With no difference between groups (MD: 0.28; p=0.80) Complications: Mild hypoglycaemia: 5 vs. 2 persons with 20 vs. 5 events (p ≤ 0.001)
El-Haggar 2015 RCT	Egypt, urban 01/2013-04/2014	DM2, age: 45-55 yrs, obese (BMI≥30 kg/m^2), with duration 5-10 yrs, treated with glimepiride alone no Inflammatory disease,	n=48 79 % female age (yrs): 50.1±4.6 HbA1c (%): 7.83±0.87 fasting glucose (mg/dl): 193±50	IG1 (n=16): glimepiride (3 mg/d) + 2 (1 mg twice/d) vs. IG2 (n=16): glimepiride (3 mg/d) +	not specified: glycemic markers, metabolic markers, adiponectin, interleukin-6, leukotriene B4, mast cell tryptase, lipid panel,	Changes over 12 weeks: HbA1c (%): • Highest benefit for IG1: 7.1±0.86 vs. 8.2±0.82 vs. 8.7±0.93 (p< 0.05) fasting glucose (mg/dl): • Highest benefit for IG1: 199±38 vs.

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		severe hepatic or renal disease, epilepsy pregnant/lactating females	BMI (kg/m²): 37.6±4.6 duration of diabetes (yrs): 7.7 ±2.6	ketotifen (1 mg once/d) vs. CG (n=16): glimepiride (3 mg/d) alone Duration: 12 weeks	BMI	207.7± 47.6 (p< 0.05)
Malek 2015 RCT	Egypt, Algeria, Tunesia, South Africa 03/2010-05/2012	DM2, age ≥ 18 yrs, currently treated with suboptimal dose of oral anti-diabetic drugs; HbA1c 7-11 % (under metformin-monotherapy) and ≤ 10 % (under combination therapy), BMI≤40 kg/m^2 no allergies or contraindications to the product, pregnant or breastfeeding, impaired hepatic or renal function, cardiovascular history, uncontrolled hypertension, proliferative retinopathy, macular oedema	n=403 age (yrs): 52.8±9.6 59.8 % female HbA1c (%): 8.65 BMI (kg/m^2): 29.7±4.5 duration of diabetes (yrs): 7.5±5.1	Stepwise individual insulin intensification of IG (n=200): basal-bolus insulin analogues (insulin detemir +Insulin aspart) vs. CG (n=203): thrice daily biphasic insulin aspart depending on HbA1c-values over 50 wks	Primary: HbA1c Secondary: patients achieving HbA1c < 7.0 %, prandial plasma glucose	Change over 50 weeks: HbA1c (%): Non-inferiority: 7.4 vs. 7.3; MD 0.1 (-0.1 to 0.3 (full-analysis set), MD 0.2 (-0.1 to 0.4 (per protocol) 40.3% and 44.9% achieved HbA1c<7.0% Hypoglycaemia (events/patient year): 9.4 vs. 9.8 Serious adverse events: 6.5 vs. 3.4 % with 1 treatment-related SAE in CG Adverse events: 58.5 vs. 63.1%
Strategies on food supplementation						

Study name registration number Design	Setting Place, setting and time	Population Inclusion / Exclusion criteria	Characteristics	Intervention vs. Control Description with duration	Outcomes Primary and secondary	Results Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
Ali 2019 RCT	Egypt Urban, tertiary care 09/2017 – 04/2018	DM2, oral antidiabetic agents with no change of type and dosage of antidiabetic agents in the past 3 months, ≥ 30 years insulin-dependence, pregnancy, lactation, use of Ca, multivitamins, Vitamin D supplements, use of drugs that affect Vitamin D status, dietary Ca intake > 1500 mg/d, hypo- or hyperthyroidism, smoking, use of antiepileptic drugs, sarcoidosis, tuberculosis, potentially terminal illness, inflammatory bowel disease, liver or kidney disease, malignancy	n=85 age (yrs): 54.6 ±2.8 68 % females BMI (kg/m²): 28.6±3.3 Diabetic duration (yrs): 4.4±2.1 fasting glucose (mg(dL): 168±54.4 fasting serum insulin (µIU/mL): 18.1±8.3 HbA1c(%):8.8±1.8	oral antidiabetic agents as usual + IG 1 (n=22): continuous oral Vitamin D3 (4000 IU/ d) vs. IG 2 (n=22): intermittent regimen of Vitamin D3 (50 000 IU/ week) vs. IG 3 (n=21): single IM injection of 300 000 IU of Vitamin D3 at the start of the study vs. CG (n=20): only oral antidiabetic agents Duration: 3 months	Not specified: serum creatinine, blood urea nitrogen, total and ionized Ca, serum phosphorus, fasting glucose, fasting serum insulin, 25(OH)D3 levels, HbA1c	After 3 months: fasting glucose (mg(dL): higher decrease in IG1 and IG2: -20.9±18.1 vs. -23.0±37.9 vs. -3.5±6.9 vs. 1.0±5.6 (p<0.001) fasting serum insulin (µIU/mL): higher decrease in IG1 and IG2: -4.44±5.2 vs.-5.88±4.6 vs. -1.55±9.4 vs. 0.10±1.0 (p< 0.001) HbA1c (%):higher decrease in IG1 and IG2: -0.81±0.77 vs. -0.82±0.87 vs. -0.34±1.47 vs. 0.05±0.08 (p<0.001)
Anderson 2001 RCT	Tunesia, urban	DM2 ≥ 5y, age< 65 yrs, fasting glucose > 8 mmol/l and HbA1C > 7.5 % no pregnant or lactating women, receiving trace element supplements in past 3 months, with gastric or diuretic treatment, acute renal, acute infection or recent surgery	n=110 age (yrs): 53.2 ±16.8 BMI (kg/m²): 29.1±1.0 HbA1c (%):8.82±3.25 fasting glucose (mmol/l): 11.45±0.83 duration of diabetes (months): 73.6±66	IG 1 (n=27): Zinc (30 mg/d) vs. IG 2 (n=27): Chromium (400 µg/d) vs. IG 3 (n=27): Zinc (30 mg /d) + Chromium (400 µg /d) vs. CG (n=29): placebo Duration: 6 months	Not specified: HbA1C, fasting glucose plasma concentrations of zinc, copper, selenium, urinary chromium and zinc, Plasma thiobarbituric acid reactive substances, copper-zinc-superoxid dismutase, selenium - glutathione peroxidase	Change over 6 months: HbA1c (%): 7.7±1.6 vs. 7.4±1.4 vs. 8.1±1.6 CG: not reported
Anyanwu 2016	Nigeria, urban	DM2, age 35-65 yrs on oral antidiabetics with vitamin D	n=42 57.6 % female	IG (n=21): Vitamin D3 supplements	Primary: HbA1c Other: fasting glucose,	Changes over 12 wks: HbA1c (%):

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RCT .		deficiency and poor glycemic control (HbA1c > 6.5 %) no patients on insulin, pregnancy, renal insufficiency, chronic liver disease or alanine transferase > 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state	age (yrs): 51.8±2.05 HbA1c (%): 7.88 fasting glucose (mg/dl): 152.8±56.5	(3000 IU/d) vs. CG(n=21): placebo Duration: 12 weeks	levels of serum Vitamin D, calcium, albumin, phosphate, creatinine, and alanine transaminase	• MD (IG vs. CG): -0.66 (-0.161 to 0.29) vs 0.38 (-0.08 to 0.84); • MD: -1.04 (-2.09 to 0.01) • change from poor glycemic control (HbA1c>6.5 %) to normal HbA1c (%): benefit for IF: 33.3 vs. -9.1 (p<0.05) fasting glucose (mg/dl): 137.2±33.6 vs. 154±67.5 patient adherence (tablet counts, %): 62.2 vs. 59.9
El Gayar 2019 **RCT**	Egypt, urban, outpatients 01/2017-01/2018	DM2 for < 6 months, 30-60 yrs, HbA1c level < 9%, BMI≥30 kg/m^2 no insulin therapy, any injectable or oral antidiabetic medication other than metformin, no smoking, consumption of alcohol or narcotic drugs, no acute illnesses at the baseline or during the study, no pregnancy or lactation, autoimmune disorder, cardiac or renal diseases, thyroid, chronic inflammatory diseases, peptic ulcer, regular consumption of ginger or other herbal drugs, hypersensitivity to ginger, consumption of lipid lowering drugs or oral contraceptive pills or any supplements 2 months before starting the study	n=80 49 % female age (yrs): 46.2 ± 9.1 HbA1c (%): 8.04±0.5 fasting glucose (mg/dl): 176.9±18.3 Fasting serum insulin (mIU/L): 19.3±3.3 BMI (kg/m²): 32.3±1.4	diet, physical activity, and metformin IG (n=40): ginger powder supplementation (600 mg/capsule, 3 capsules/d) vs. CG (n=40): Placebo Duration: 8 weeks	Not specified: glycemic status, lipid profile and beta-cell function	After 8 wks: HbA1c (%): decrease in both groups to 6.94±0.38 vs. 7.26±0.45 Fasting serum insulin (mIU/L): decrease in both groups to 12.86±2.59 vs. 13.21±2.08 fasting glucose (mg/dl): decrease in both groups to 120.88±9.06 vs. 151.70±13.23

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Sheikh 2019 RCT	Egypt, urban	DM2 on glimepiride alone, age ≥30 yrs no insulin sensitizers, steroids, NSAIDs, warfarin or lipid lowering medications, thyroid hormones, valproic acid or suffered from: acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism epilepsy, pregnant and breast-feeding women	n= 72 67 % female age (yrs): 50.6±8.7 HbA1c (%):9.76±1 fasting glucose (mg/dl):194.84±20.8 BMI (kg/m²): 34.4±5.45	IG (n=38): glimepiride 2 mg twice daily + L-carnitine 1 gm twice daily vs. CG (n=34): glimepiride dose 2 mg twice daily Duration: 6 months	HbA1c, fasting glucose, PPBG, fasting insulin, extracellular part of insulin regulated aminopeptidase, tumor necrosis factor-alpha, visfatin and lipid panel, BMI and homeostasis model assessment of insulin resistance	Change over 6 months: HbA1c (%): Benefit for IG: 7.41±0.5 vs. 9.5±0.78 (p<0.001) fasting glucose (mg/dl): Benefit for IG: 179.6±9.3 vs. 192.41±27.4 (p=0.018)
Matter 2020 NCT03851055 RCT	Egypt, urban, outpatients 08/2017 to 08/2018	DM, treated with insulin, 10 to 18 yrs, transfusion dependent beta-thalassemia major no other hemoglobinopathies (e.g. a-thalassemia or sickle thalassemia, disorders that may affect glucose homeostasis other than b-TM, autoimmune diseases, collagen diseases, hypo- or hyperthyroidism, infections, or tumours, or those who were taking any vitamins or food supplements < 1 month before the study and participating in a previous investigational drug study within 3 mo preceding screening	n=80 52.5% females age (yrs): 16.3±1.4 (range 12-18) fasting glucose (mg/dL): 144.5±22.4	diet schedule with optimal macronutrient distribution and pharmacologic treatment IG (n=40): zinc gluconate (2x20 mg/d) vs. CG (n=40): placebo Duration: 3 months	Primary: fasting glucose Secondary: fructosamine, fasting C-peptide, and HOMA-IR safety: any AEs (e.g. nausea, vomiting, abdominal pain, diarrhea, constipation, and reduction of appetite)	After 12 wks: fasting glucose (mg/dL): higher decrease with IG to 116.9±4.6 vs. 144.5±22.9 (p<0.001) HbA1c (%): higher in IG (no results reported) no side effects were reported
Moustafa	Egypt,	DM2, newly diagnosed	n=62	IG (n=29, 21 analysed):	Glycemic control,	After 3 months:

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2019 RCT	urban, outpatients recruitment 02/2016-03/2018	(within a time duration ≤6 months), 18–60 yrs other antidiabetic medications, pregnant and lactating women, major organ dysfunction (hepatic failure, active hepatitis, liver cirrhosis or renal complications), changed their standard medications during the 12 weeks of the study	72% females HbA1c(%): 7.51±1.4 fasting glucose (mg/dl): 154.4±51.6 BMI(kg/m^2): 33.9±6.1 family history of DM (%): 78.5 retinopathy/altered vision (%): 53 GDM (%): 9.2	nigella sativa oil capsules (3x 450 mg/d) vs. CG (n=33, 23 analysed): metformin (2000 mg/d) Duration: 3 months	oxidative stress markers, biochemical parameters, weight/BMI/waist circumference, total antioxidant capacity TAC	HbA1c (%): no difference: 7.01±0.83 vs. 6.55±0.72 fasting glucose (mg/dl): no difference: 119.8±23.7 vs. 120.7±25.4 Complications: no differences in occurrence of chills, sweating, tachycardia, lethargy/ weakness, polydipsia, polyuria, dry skin, polyphagia, blurred vision, foot problems, or tingling/numbness foot problems lower in IG: 4.8% vs. 33.3%, (p = 0.025).
Ragheb 2020 NCT03437902 RCT	Egypt, urban, outpatients care 02/2019-05/2018	DM2, receiving standard oral hypoglycemic agents, ≥ 35 yrs, no history of overt vascular disease, renal or hepatic failure or antioxidant supplementation or insulin therapy, no change of oral hypoglycemic drugs	n=70 age (yrs): 54.9±8.4 70 % females BMI (kg(m^2): 32.5±5.7 HbA1c(%): 8.50±1.86 fasting glucose (mg/dl): 142.8±52.6	IG2 (n=20): Rutin (60) + vitamin C (160 mg) 3x daily vs. IG1 (n=20): Vitamin C (500 mg) 1x daily vs. CG (n=13); only usual oral antidiabetic treatment Duration: 8 weeks	Primary: HbA1c, oxidative stress marker, antioxidant capacity, insulin resistance, lipid profile Secondary: Quality of life	After 2 months: HbA1c (%): no difference 7.494 ± 1.72 vs. 8.504 ± 2.059 vs. 8.504 ± 2.059 (p=0.1882) fasting glucose (mg/dl): lower in IG2 and CG: 111.3 (IQR 93.3-135.2) vs. 144 (114.8-201) vs. 113.3 (94-152.2) (p=0.017) Quality of life (SF 36): • Benefit of physical functioning and energy domains in IG2 vs. CG (p=0.0049, p=0.0253). • Benefit of role limitation to physical health and emotional improved in IG1 vs. CG (p=0.0267,p=0.0280) • no difference between groups in the other domains (emotional well-being, social functioning, pain and general health)

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Rashad 2017 RCT	Egypt, urban	DM2, 50-62 yrs no insulin medication, allergies, recent thromboses or uncontrollable hypertension	n=34 43.3 % female age (yrs): 55.5±6.15 HbA1c (%):6.75±1.2 fasting glucose (mmol/l): 8.5±1.4 postprandial plasma glucose(mmol/l): 15.6±3.3 BMI (kg/m²):28.55±4 type of diabetes duration of diabetes (yrs): 6.1 ± 2.2	IG (n=17): Balanites aegyptiaca extract (400 mg)) vs. CG: (n=17) placebo capsules (potato maltodextrin) Duration: 8 wks	glycemic markers, lipid profile, FPG	Change over 8 wks: 2h postprandial plasma glucose: benefit for IG :26.88% decrease vs. CG 2.6% increase FPG (mmol/l): benefit for IG: 7.8 ± 0.9 vs. CG: 8.5 ± 1.1
Somanah 2012 NCT01248143 RCT	Mauritius, urban/rural 11/2010-03/2011	newly diagnosed DM, age 25–60 yrs fasting glucose range: 5.1–5.9 mmol/L no secondary complications, non-smoker or stopped for > 6 months , alcoholic consumption < 2 standard drinks/day, post-menopausal women without hormone replacement treatment, no glucose-lowering, cholesterol-lowering or anti-hypertension treatment	n=127 47% female age (yrs): range 25–60 HbA1c (%): 5.99±0.4 fasting glucose (mg/dL): 93.2±8.0 BMI (kg/m^2): 26.6 ± 3.7	IG (n=44): supplementation of a fermented papaya preparation (6g/d twice daily, over 12 wks), followed by a 2 week wash out period with the same amount of water vs. CG (n=56): consumed an equivalent amount of water Duration: 14wks	HbA1C fasting glucose, Lipid profile, diet score, blood pressure, alanine aminotransferase; aspartate aminotransferase, Ferritin, c-reactive protein, uric acid, microalbumin/urinary creatinine ratio	After 14 wks: HbA1c (%): no difference (p=0.448) fasting glucose (mg/dL): • remained relatively unchanged in boths genders: • males: 96.2±17.0 vs. 87.6±11.7 • females: 95.6±15.8 vs. 94.3±5.0
Strategies on treatment of DM related complications						

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
El-Makaky 2020 NCT03783845 RCT	Egypt, urban/rural recruited 06/2015 to 03/2016	DM2 for >5 yrs, 40-70 yrs, HbA1c 7 to 9% at the last medical evaluation, no change in diabetes treatment over the previous 3 months, ≥ 6 permanent teeth excluding third molars, clinical attachment level and pocket depth ≥4 mm in >30 % of the sites, diagnosis of chronic periodontitis based on the presence of 4 teeth as a minimum with ≥ 1 site Pregnancy, alcoholism and smoking, Presence of any systemic disorders other than hypertension and diabetes, diabetic major complications, antimicrobial therapies or periodontal therapies in the last 6 months, allergy to metronidazole and amoxicillin	n=88 56.8 % females age (yrs): 52.6±6.8 HbA1c (%): 8.16±0.72	IG (n=44): immediate periodontal therapy: one-stage scaling and root planning, a combination of systemic antibiotics (amoxicillin 500 mg and metronidazole 400 mg 3x/day for 2 weeks), and oral hygiene instructions vs. CG(n=44): delayed periodontal therapy after 3 months Duration: 3 months	Primary: HbA1c Secondary: not named	After 3 months: HbA1c (%): benefit for IG: 7.27±0.5 vs. 8.34±0.64: MD -1.07 (-1.32 to -0.83)
El-Sharkawy 2016 NCT02794506 RCT	Egypt, urban 06/2014-03/2015.	DM2 >5 yrs, >20 teeth, chronic moderate or severe periodontitis with probing depth and clinical attachment level >5 mm, bleeding by probing, on oral hypogylcemic drug therapy > 6 months, no smoking, use of	n=50 34% female age (yrs): 50.5 ± 7.4 (38 to 63) HbA1c (%): 8.66 ±0.73 FPG (mg/dl): 183.5 ±12.547 BMI (kg/m²): 26.9± 3.1 duration of diabetes	IG (n=24): scaling and root planing (SRP)+ 400mg oral Propolis once daily vs. CG (n=26) scaling and root planing (SRP)+Placebo Duration: 6 months	Primary: HbA1c Secondary: FPG, serum N-(carboxymethyl) lysine, periodontal parameters	after 6 months HbA1c (%) Benefit for IG 7.75± 0.48 vs.8.5±0.73 (p<0.01) FPG(mg/dl) Benefit for IG

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		antibiotics, non-steroidal or anti-inflammatory drugs within the last 3 months, periodontal therapy ≤ 1 year, retinopathy grade 3/4, pregnancy, no contraceptive drugs	(yrs): 8.1 ± 3.9 hypertension: 4.5% neuropathy: 1.5% retinopathy: 0.5% nephropathy: 0%			
Ghoneim 2013 RCT	Egypt, 03/2010-03/2012	DM, duration ≥ 15 yrs, bilateral diabetic macular edema (≥ 6 months) no prior treatment with intravitreal corticosteroids, peribulbar steroid injection within ≤ 6 months, pars plana vitrectomy, history of glaucoma or steroid induced IOP elevation, ischemic maculopathy, foveal tracted, IOP≥ 23 mmHg	n=19 (38 eyes) 89.5 % female age (yrs): 52.3±11.4	IG (n=19): one eye with 8 mg triamcinolone acetonide vs. CG (n=19): other eye with4 mg of triamcinolone acetonide Duration: 6 months	Primary: Visual acuity Others: Intraocular pressure (IOP), IOP lowering drugs, complications	after 6 months: Complications: • no eyes with retinal detachment, vitreous haemorrhage, intraocular reaction or endophthalmitis. • one eye in IG developed posterior subcapsular cataract.
Nteleki 2015 RCT	South Africa, urban	DM2 with neuropathic or mixed (venous and arterial) ulcers; lower extremity ulcer; stable or worsening ulcer that has been present for ≥ 4 weeks no acute cellulitis, osteomyelitis, or gangrene, renal, hepatic, hematologic, neurologic, or immune disease not related to diabetes; presence of malignant disease not in remission for > 5 years; use of oral or parenteral	n=7 with 14 lower extremity ulcers 85 % male age (yrs): 62 duration of diabetes (yrs): 16.7	standard podiatric management and IG1 (n=2): phototherapy to the regional lymphatic nodes and ulcer(s) vs. IG2 (n=3): phototherapy on the ulcer vs. CG (n=2): placebo phototherapy Duration: 12 weeks	healing rate (area and perimeter of the ulcer)	after 3 months: Healing: • The rate of healing increased in all three groups, • 67% of ulcers received some form of phototherapeutic intervention, 40% of those ulcers resolved completely over 8 weeks no AEs

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
		corticosteroids, immunosuppressive, or cytotoxic agents; known infection with human immunodeficiency virus or presence of AIDS; other leg ulcers				
Saeed 2013 RCT	Egypt, urban 11/2010-07/2012	DM, intractable diffuse diabetic macular edema without vitreomacular traction. central foveal thickness ≥300 µm no vitreomacular traction, active neovascularization of proliferative diabetic retinopathy, an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography, treatment for diabetic macular edema within ≤ 3 months, previous vitreoretinal surgery, other major ocular surgery within the previous 6 months, YAG capsulotomy within ≤2 months, macular pathology	n= 34 (34 eyes) 50% females age (yrs): 55.5 ± 8.9 duration of diabetes (yrs): 24±5.4	IG (n=15): vitrectomy with removal of the posterior hyaloid, at the end of the procedure injection of intravitreal triamcinolone acetonide (IVTA, 0.1 mL, 40 mg/mL) +bevacizumab (1.25 mg) +macular grid laser photocoagulation vs. CG (n=15); same intravitreal injection combination Duration: 12 months	primary: BCVA, central foveal thickness	Changes over 12 months Complications: • Changes in BCVA and central foveal thickness at 3, 6, and 12 *(P*< 0.01), better mean BCVA in IG at 12 months. • Better mean central foveal thickness in IG at 12 months. Major adverse events: development of cataracts (3/15 vs. 6/15) and elevation of intraocular pressure (7/15 vs. 2/15)
Tsobgny-Tsague 2018 NCT02745015 RCT	Cameroon, urban, tertiary care, 12/2014-	DM2, >11teeth, severe chronic periodontitis according to the 2012 CDC-AAP classification, no periodontal treatment,	n=34 56% female age (yrs): 51.4 ± 8.8 HbA1c (%):9.3 ± 1.3 BMI (kg/m²): 28.3± 5.4	IG (n=17): immediate ultrasonic scaling, scaling and root planning +subgingival 10% povidone iodine irrigation	Primary: change in HbA1c Secondary: Plaque index, gingival bleeding index, pocket depth, clinical attachment loss	Change over 3 months: HbA1c (%): Benefit with IG: 6.7 ± 2.0 % vs. 8.1 ± 2.6 %, MD: 2.2 (p=0.029) adverse events: 1 /15 patient reported tongue

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria	Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value
	05/2015	alteration of DM treatment 6 mths prior to the study, onset of systemic diseases or an acute condition, use of immunosuppressive medications or others drugs or presence of conditions able to alter periodontitis clinical features	duration of diabetes (months): 55.5 ± 42.6 complications: neuropathy (%): 40 nephropathy (%): 7 retinopathy (%): 7 diabetic foot (%): 3	vs. CG(n=17): periodontal treatment 3 months later Duration: 3 months		irritation following chlorhexidine moth rinse in IG
Yakoot 2019 NCT01531517 RCT	Egypt, urban 07/2011-07/2013	Adult DM2 or DM1 patients, limb-threatening diabetic foot ulcerations no life-threatening extensive gangrenous lesions that needed immediate amputations; bad general condition; shock or unstable vital signs; critically ill with severe organ/system dysfunctions or advanced malignancy.	n=119 gender:44.5% female age (yrs): 54.7 ±8.4 type of diabetes: • DM1: 22.9% • DM2: 86.2%	conservative debridement of necrotic tissue and irrigation with warm normal saline and IG (n=61): local application of ointment composed of royal jelly and panthenol vs. CG (n=58): local application of Panthenol duration: 12months	primary: complete healing secondary: reduction of infection in the ulcer site, al reaction that may be due to study drug	after 12 months rate of complete healing (%): Benefit for IG: 32.4% vs. 12%; p=0.034

ADA: American Diabetes Association; BCVA: Best-corrected visual acuity; BMI: Body mass index; CG: Control group; CI: Confidence interval; CHC: Community health centre; DBP: Diastolic blood pressure; DM: diabetes mellitus; DM1: Type 1 diabetes; DM2: type 2 diabetes; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; IG: intervention group; IQR: interquartile range; n: number of participants; NCD: Non-communicable disease; NPH: neutral protamine Hagedorn; MD: mean difference; MDa: adjusted mean difference; NCD: Non-communicable disease ;RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SAE: Serious adverse events; SBP: Systolic blood pressure; SCI: Diabetes Self-Care Inventory; SD: Standard-deviation; SMBG: self-monitoring of blood glucose; wks: weeks; yrs: years

Supplementary Table 3: Characteristics and results of studies on patients with DM2

RCTs on pregnant DM patients

Study name registration number Design	**Setting** Place, setting and time	**Population** Inclusion / Exclusion criteria Characteristics	**Intervention vs. Control** Description with duration	**Outcomes** Primary and secondary	**Results** Longest follow-up period with intervention effects (IG vs. CG) with SD, 95%-CI or p value	**Study name** registration number Design
Strategies to increase physical activity						
Embaby 2016 RCT	Egypt, urban, 07/2014-02/2015	at increased risk for GDM due to obesity (BMI ≥ 30 kg/m^2), age:> 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2 no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease, cardiac, renal impairment and malignancy	n=40 100% female age (yrs): 29.2±3.8 BMI (kg/m²):28.7±1.3 fasting glucose (mmol/l): 6.5±0.9 fasting insulin (IU/l): 15.78±1.58	IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives. Duration: appr. 4 months	Fasting plasma glucose, Insulin level	Change to 37th week of gestation: FPG (mmol/l) Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001) Fasting insulin (IU/l): Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)
Other non-pharmacological therapies						
El-Shamy 2018 RCT	Egypt, urban 12/2016-05/2017	GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus no high-risk pregnancy, bad obstetric situations or diseases, smoking, oral sedatives	n=30 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): • fasting glucose: 129.05±0.6 • 2h postprandial: 146±1.65 BMI (kg/m²): 27±1.5	IG (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only Duration: 12 weeks	Primary: glycemic control, requirement for insulin, insulin resistance Secondary: neonatal outcomes	Change over 3 months: 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9 Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %

Utz 2018 NCT02979756 Cluster-RCT	Marocco, urban / rural, primary care, 11/2016-02/2018	Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM no DM2, DM1	20 health centres n= 215 age (yrs):27.6±6.6 urban (%): 38.5 rural (%): 61.5	20 clinics were randomized→ 10 in each group <u>IG (n=120):</u> first screening for GDM→positive tested women received counselling on nutrition and exercise <u>vs.</u> <u>CG (n=95):</u> routine practice	Primary: birthweight Secondary: maternal weight gain, glucose control, pregnancy complications.	Follow-up visits: 7.5±4.9 vs. 3.8±3.3 (p=0.001) FBG within the norm: better with IG <1/3 of all values: 7.6 vs. 32.6 % 1/3-2/3 of all values: 17.8 vs. 32.6 % >2/3 of all values: 74.6 vs. 34.8 % Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)
Pharmacological strategies						
Ashoush 2016 RCT	Egypt, urban, tertiary care 01/2014-11/2014	GDM, mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glycemic control despite adequate diet and exercise for ≥ 1 wk no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis	n=95 100% female age (yrs): 31.8±3 HbA1c (%): 5.75 ± 0.55 75g OGTT (mg/dl) • fasting: 106.05±4.6 • 1h:310.25±11.6 • 2h:176.65±9.4 BMI (kg/m²): 31.2±1.4	<u>IG (n = 47):</u> metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed) <u>vs.</u> <u>CG (n = 48):</u> <u>regular insulin + neutral protamine Hagedorn (3:7) (starting dose 0.7 units /kg*d, adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed)</u> <u>Duration: until delivery</u>	Primary: successful maternal glycemic control Secondary: maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit	Until delivery: fasting glucose during treatment (mg/dl): better with IG: • during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008) • during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029) maternal hypoglycaemia (%): no difference: 6.25 vs. 12.5 (p=0.254) neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p=0.791) Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001) neonatal congenital anomalies (%): 2.1 vs. 2.1 p= 0.747 headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy) neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514) Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)

Beyuo 2015 ACTRN12614000942651 RCT	Ghana, urban 01/2013-12/2013	pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy no T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin	n= 104 100% female age (yrs): 33.3±4.6 fasting glucose (mmol/l): 8 2HPG (mmol/l): 10.5 BMI (kg/m²): 3.1±6.6 type of diabetes: GDM (%): 65.9 DM2 (%): 34.0	IG (n=52): Metformin (starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary) vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg, titrated to achieve the glycemic targets, if necessary, admission to the ward and therapy with soluble insulin) Duration: until delivery	Primary: 2-hour post prandial blood glucose (2HPG) Secondary: fasting glucose, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.	Change from enrolment to delivery: glycemic control (mmol/l): fasting glucose: no difference: 6.42±0.98 vs. 6.62±1.57 (p=0.928) 1HPG: no difference: 8.95±1.27 vs. 9.62±1.44 (p=0.078) 2HPG: benefit for IG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)
Ibrahim 2014 NCT01915550 RCT	Egypt, urban 08/2011-04/2012	GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance No DM1, secondary diabetes or liver or renal impairment	n=90 100% female age (yrs): 29.8 ± 5.4 BMI (kg/m²):31.83 ± 3.23 Gestational age: 28.7 ± 3.7 wks GDM: 43.3 % Pre-existing DM: 56.7 % with median duration of 4 (1-15) yrs	IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose Patients switched to CG if treatment was not successful to control blood glucose concentrations CG (n=44): insulin dose was increased according to the standard protocol	Primary: maternal gylcemic control (fasting glucose ≤ 95 mg/dl and 2-HPG ≤ 120 mg/dl) Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes	gylcemic control: • better for CG: 76.1 vs. 100 % reached glycemic control (p=0.001) • 13 vs. 18.2 % had readmission for poor glycemic control • 6.5 vs. 22.7 % had bouts of maternal hypoglycaemia Complications: • 23.3 vs. 30.8 % had fetal macrosomia • 1 new-born in each group had congenital malformations • 7 vs. 38.5 % had neonatal hypoglycaemia • 18.6 vs. 41 % had NICU admission • 0 vs. 5.1 % had stillbirths • 11.6 vs. 25.6 % with respiratory distress syndrome

BMI: Body mass index; CG: Control group; CI: Confidence interval; DM: diabetes mellitus; DM2: type 2 diabetes; FPG: fasting plasma glucose; GDM: gestational diabetes; HbA1c: haemoglobin A1c; 1 / 2HPG: 1 / 2-hour post prandial blood glucose; IG: intervention group; n: number of participants; MD: mean difference; MDa: adjusted mean difference; OGTT: Oral glucose tolerance test; RCT: randomized controlled trial; RR: Relative risk; RRa: adjusted relative risk; SD: Standard-deviation; wks: weeks; yrs: years

Supplementary Table 4: Characteristics and results of studies on pregnant women with DM

Risk of bias

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Abaza 2017	☺	☺	☹	☺	☹	☺	☺
Abdulrhman 2013	☺	😐	☹	☺	☺	☹	😐
Adibe 2013	☺	☺	☹	☹	☹	😐	☺
Adjei 2015	😐	😐	☹	☺	☺	😐	☹
Ali 2019	😐	😐	☹	😐	😐	😐	☹
Amendezo 2017	😐	😐	☹	☺	☹	☺	☹
Anderson 2001	😐	😐	☺	☺	😐	😐	☺
Anyanwu 2016	😐	😐	☹	😐	☹	😐	☺
Ashoush 2016	☺	☺	☹	😐	☺	😐	☺
Asuako 2017	😐	☺	☹	😐	☺	😐	☹
Beyuo 2015	😐	☺	☹	😐	☹	☹	☹
Chraibi 2017	😐	😐	☹	😐	☹	☺	☹
Debussche 2018	☺	☺	☹	😐	☺	☺	☺
Distiller 2014	😐	☺	☹	😐	☹	😐	☺
Elbarbary 2016	😐	😐	☹	😐	☹	😐	☹
Elbarbary 2018	☺	☺	☺	😐	☺	☺	☺
Elbarbary 2020	☺	☺	☺	☺	☺	☹	😐
El Gayar 2019	☺	☺	☺	☺	😐	😐	☹
El-Haggar 2015	😐	😐	☹	😐	😐	😐	☹
El-Makaky 2020	😐	☺	☹	☺	☺	😐	😐
El-Shamy 2018	☹	☹	😐	😐	☺	😐	☺
El-Sharkawy 2016	☺	☺	☺	☺	☺	☺	☹
El-Sheikh 2019	😐	😐	☹	😐	☹	😐	☹
Embaby 2016	😐	😐	☹	😐	☹	😐	☹
Essien 2017	☺	☺	😐	☺	☹	😐	☺
Fairall 2016	😐	☺	😐	😐	☺	☺	☺
Fayehun 2018	😐	☺	☹	☹	☺	😐	☺
Ghoneim 2013	☺	😐	☹	😐	😐	😐	☹
Hailu 2018	☺	😐	☹	☺	☹	😐	☹
Ibrahim 2014	☺	😐	☹	😐	☹	☺	☹
Krawinkel 2018	☺	😐	☹	☹	☹	☺	☺

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Labhardt 2011	☺	☺	☹	😐	☺	☺	☺
Maharaj 2016	😐	😐	☹	☺	😐	😐	☹
Malek 2015	😐	😐	☹	😐	☺	😐	😐
Malipa 2013	😐	😐	☹	☹	😐	😐	☹
Mash 2014	☺	😐	☹	☹	☹	☺	☺
Matter 2020	☺	☺	☺	☺	☺	☹	☺
Mohamad 2009	😐	😐	☹	😐	😐	😐	☹
Moustafa 2019	😐	😐	☹	😐	☹	😐	☹
Muchiri 2015	☺	☺	☹	☺	☺	😐	☹
Nteleki 2015	☹	😐	☹	😐	☺	😐	☹
Owolabi 2019	😐	☺	☹	☺	☺	☹	☹
Rashad 2017	☺	☺	☺	☺	☹	😐	☹
Ragheb 2020	☺	😐	☹	☹	☹	☺	☺
RezkAllah 2019	☺	☺	☹	☺	☺	☺	☺
Saeed 2013	😐	😐	☹	☹	☹	😐	☹
Salem 2010	😐	😐	☹	☹	😐	😐	☹
Sodipo 2017	☺	😐	☹	😐	☹	😐	☺
Somanah 2012	😐	😐	☹	😐	☹	☹	☹
Steyn 2013	☺	😐	☹	😐	☹	😐	☺
Takenga 2014	😐	😐	☹	😐	☺	😐	☹
Tawfik 2016	😐	☺	☺	☺	☹	😐	☺
Thuita 2020	😐	☺	☹	😐	☺	😐	☺
Tsobgny-Tsague 2018	☺	😐	☹	☺	☹	☺	☺
Utz 2018	☺	☺	☹	☺	☺	☹	☹
Van der Hoogt 2017	😐	😐	☹	😐	☹	😐	☹
Van Rooijen 2004	☺	☺	☹	☺	☺	😐	☹
Webb 2015	😐	😐	😐	☺	☹	☺	😐
Yakoot 2019	😐	☺	☹	☹	☺	☹	☹
Yan 2014	😐	😐	☹	😐	☺	😐	☹
☺: low, 😐: unclear, ☹: high risk of bias							

Supplementary Table 5: Judgements on risk of bias

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries: a systematic review

Susanne Unverzagt, Angelika S. Sandholzer, Thomas Frese, Yeabsra Mesfinin

Citation

Susanne Unverzagt, Angelika S. Sandholzer, Thomas Frese, Yeabsra Mesfinin. Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries: a systematic review. PROSPERO 2019 CRD42019122785 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019122785

Review question

To summarize available evidence from randomized controlled trials on prevention, diagnosis and treatment of diabetes initiated from African countries.

Searches

Randomized controlled trials without time or date restriction, in English or German language. Electronic databases: MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL), registers of ongoing and completed trials (www.ClinicalTrials.gov, apps.who.int/trialsearch).

Results will be screened by 2 independent authors. Discrepancies will be resolved by discussion between the authors or with a third author.

Types of study to be included

Randomized controlled trials on prevention, diagnosis and treatment of diabetes.

Condition or domain being studied

Diabetes mellitus (type 1 and type 2), gestational diabetes.

Participants/population

African patients in primary, secondary and tertiary prevention, diagnosis and treatment of diabetes.

Intervention(s), exposure(s)

All preventive, diagnostic and curative interventions on diabetes.

Comparator(s)/control

Another intervention, or none.

Main outcome(s)

Primary outcome: all-cause mortality during the longest reported follow-up period (measured from randomisation).

Secondary outcomes: glucose control (HbA1c, insulin resistence, oral glucose tolerance test, fasting serum or plasma glucose), complications, quality of life, hospital admission, treatment adherence (at longest follow-up).

* Measures of effect

Within the longest reported follow-up period.

Additional outcome(s)

Cost.

* Measures of effect

Within the longest reported follow-up period.

Data extraction (selection and coding)

One authors will extract information on study population (diabetes type 1, type 2, gestational diabetes), intervention and outcome by using an assessment form, which will be designed especially for the topic of this review and tested for five studies. A second author will check all extractions, unclear information will be discussed. The data extraction form will include at least the following items: title, author, reference, study design, country, duration, follow-up, indication of patients (primary, secondary, tertiary prevention), sample size per group, description of intervention and control (drugs, devices, strategies), primary and secondary outcomes with results.

Risk of bias (quality) assessment

Risk of bias will be described and judged on the basis of the Cochrane risk of bias tool in seven specific domains: 1.

Sequence generation (judgement per study) 2. Allocation concealment (judgement per study) 3. Blinding of participants and personnel (judgement per study and outcome) 4. Blinding of outcome assessors (judgement per study and outcome) 5. Incomplete outcome data (judgement per study and outcome) 6. Selective outcome reporting (judgement per study and outcome 7. Other sources of bias (judgement per study and outcome). We will judge risk of bias domains as 'low', 'high' or 'unclear' and will evaluate individual bias items and present a summary figure to illustrate these findings.

Discrepancies will be resolved by discussion between the authors or with a third author.

Strategy for data synthesis

We plan a narrative synthesis to get a comprehensive overview on this area of research. We add a meta-analysis with the random-effects model on our primary and secondary outcomes on the basis of aggregated information (Hazard ratio, Relative risks or Odds Ratio) if included studies are sufficiently homogeneous in population, intervention, and outcomes and results show no substantial heterogeneity. We will use the Review Manager for data synthesis.

Analysis of subgroups or subsets

Study population (diabetes type 1, type 2, gestational diabetes), prevention, diagnosis and treatment type of prevention (primary, secondary and tertiary), type of intervention (drugs, devices, strategies) and regions (northern, eastern, central, southern Africa).

Contact details for further information

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https://www.medizin.uni-halle.de/index.php?id=7167&L=1%27andchar%28124%29

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Collaborators

Dr Eva Kantelhardt. Institute of Medical Epidemiology, Biostatistics and Informatics, University Halle / Wittenberg

Type and method of review

Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date
15 November 2018

Anticipated completion date
31 December 2019

Funding sources/sponsors
DAAD ("Chronic disease health service teaching and research"), project 57216764

Conflicts of interest

Language
English

Country
Ethiopia, Germany

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Africa; Diabetes Mellitus, Type 2; Humans; Randomized Controlled Trials as Topic

Date of registration in PROSPERO
25 March 2019

Date of first submission
28 January 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

25 March 2019
07 August 2019

Search strategies

Medline (Ovid)

Search on 19.11.2018, 1470 references, Update from 2018 to Current on 20.08.2020: 541 references

Nr.	Searches
1.	exp Diabetes Mellitus/
2.	Diabetes.tw
3.	**or/1-2**
4.	Africa.tw
5.	Exp Africa/
6.	Algeria$.tw or exp Algeria/
7.	Angol$.tw or exp Angola/
8.	Benin$.tw or exp Benin/
9.	Botswan$.tw or exp Botswana/
10.	Burkina Faso.tw or exp Burkina Faso/
11.	Burund$.tw or exp Burundi/
12.	Cameroon$.tw or exp Cameroon/
13.	Cape Verde.tw or exp Cape Verde/
14.	Central African Republic$.tw or exp Central African Republic/
15.	Chad$.tw or exp Chad/
16.	Comoros$.tw or exp Comoros/
17.	Cote d'Ivoire.tw or exp Cote d'Ivoire/
18.	Democratic Republic of Congo.tw or exp Democratic Republic of Congo
19.	Djibout$.tw or exp Djibouti/
20.	Egypt$.tw or exp Egypt/
21.	Equatorial Guinea$.tw or exp Equatorial Guinea/
22.	Eritrea$.tw or exp Eritrea/
23.	Ethiop$.tw or exp Ethiopia/
24.	Gabon$.tw or exp Gabon/
25.	Gambia$.tw or exp Gambia/
26.	Ghana$.tw or exp Ghana/
27.	Guinea$.tw or exp Guinea/
28.	Guinea-Bissau.tw or exp Guinea-Bissau/
29.	Kenya$.tw or exp Kenya/
30.	Lesoth$.tw or exp Lesotho/
31.	Liberia$.tw or exp Liberia/
32.	Libya$.tw or exp Libya/
33.	Madagascar$.tw or exp Madagascar/
34.	Malawi$.tw or exp Malawi/

Nr.	Searches
35.	Mali.tw or exp Mali/
36.	Mauritania$.tw or exp Mauritania/
37.	Mauritius$.tw or exp Mauritius/
38.	Morocc$.tw or exp Morocco/
39.	Mozambique$.tw or exp Mozambique/
40.	Namibia$.tw or exp Namibia/
41.	Niger.tw or exp Niger/
42.	Nigeria$.tw or exp Nigeria/
43.	Rwanda$.tw or exp Rwanda/
44.	(Sao Tome and Principe).tw
45.	Senegal$.tw or exp Senegal/
46.	Seychell$.tw
47.	Sierra Leone.tw or exp Sierra Leone/
48.	Somalia$.tw or exp Somalia/
49.	South Africa$.tw or exp South Africa.de
50.	South Sudan.tw or exp South Sudan/
51.	Sudan$.tw or exp Sudan/
52.	Swaziland$.tw or exp Swaziland/
53.	Tanzania$.tw or exp Tanzania/
54.	Togo$.tw or exp Togo/
55.	Tunisia$.tw or exp Tunisia/
56.	Uganda$.tw or exp Uganda/
57.	Zambia$.tw or exp Zambia/
58.	Zimbabwe$.tw or exp Zimbabwe/
59.	Somaliland$.tw or exp Somaliland/
60.	Sahrawi Arab Democratic Republic.tw.
61.	or/4-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	(randomized or randomised or randomly).ti,ab
65.	placebo.ti,ab.
66.	trial.ti,ab.
67.	groups.ti,ab.
68.	or/62-67
69.	3 and 61 and 68
70.	exp animals/ not humans.sh.
71.	69 not 70
72.	71 not (comment or editorial).pt.

CENTRAL

Search on 14.01.2019, 439 trials, Update from 2018 to Current on 20.08.2020: 244 trials

1	Africa, explode all trees
2	Algeria* or Angol* or Benin* or Botswan*
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)
4	Chad* or Comoros* or Cote d'Ivoire or Congo*
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor Diabetes, this term only
14	MESH descriptor Diabetes mellitus, explode all trees
15	Diabetes near 3 gestation*
16	Latent autoimmune diabetes in adults
17	Prediabetes
18	Insulin resistan*
20	HBA1C
21	Diabet* near 3 (angiopath* or foot orfeet or retinopath*)
22	Diabet* near 3 (cardiomyopathy* or coma or ketoacido* or neuropath*)
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
32	#12 and #23

CINAHL

Search on 20.08.2020: 19 results

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$

or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract

AND

diabetes in Abstract

AND

randomized or rct or randomized in Abstract

AND

In English

AND

Peer-reviewed

And

Humans

International Clinical Trials Registry Platform

Search on 9.-10.10.2019, update on 25.08.2020 (registration January 2019 to 31.08.2020)

http://apps.who.int/trialsearch/AdvSearch.aspx

1. Africa or African in the Title and diabetes or diabetic or HbA1c in the condition, Recruitment status: all**:** 90 records for 90 trials (9.10.2019)
2. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Central African Republic or Chad or Congo or Cite D'ivoire: 96 record for 63 trials
3. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia: 292 records for 159 trials
4. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Lybia: 22 records for 22 trials
5. diabetes or diabetic or HbA1c in the condition

Recruitment status: all

Countries of recruitment: Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique: 96 records for 34 trials

6. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Nigeria: 13 records for 13 trials

7. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Namibia or Niger or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Sudan or Sudan or Swaziland:

   11 records for 11 trials

8. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: South Africa: 1528 records for 429 trials:

9. diabetes or diabetic or HbA1c in the condition

   Recruitment status: all

   Countries of recruitment: Togo or Tunesia or Ujanda or Zambia or Zimbabwe: 129 records for 50 trials

African Journals Online

https://www.ajol.info/index.php/index/search/search?query=%28diabetes+or+diabetic+or+hba1c%29+and+%28random+or+randomized+or+randomised%29&dateFromYear=2004&dateFromMonth=01&dateFromDay=1&dateToYear=2020&dateToMonth=10&dateToDay=14&authors=

Advanced search 14.10.2020
Titel: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
30 results

African Index Medicus Database

http://indexmedicus.afro.who.int/aim/opac_css/index.php?lvl=search_result&get_query=4

Advanced search 14.10.2020
Titel, Expression booléenne: (diabetes or diabetic or hba1c) and (random or randomized or randomised)
122 results, no potentially eligible references

1 List of included and excluded studies

1.1 List of included studies

Abaza 2017

Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC public health. 2017;17(1):962.

Abaza H, Marschollek M, Schulze M. SMS Education for the Promotion of Diabetes Self-Management in Low & Middle Income Countries: A Randomized Controlled Trial in Egypt. Studies in Health Technology & Informatics. 2017;245:1209.

Abdulrhman 2013

Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. Journal of Medicinal Food. 2013;16(1):66-72.

Adibe 2013

Adibe MO, Ukwe CV, Aguwa CN. The Impact of Pharmaceutical Care Intervention on the Quality of Life of Nigerian Patients Receiving Treatment for Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):240-7.

Adibe MO, Aguwa CN, Ukwe CV. Cost-Utility Analysis of Pharmaceutical Care Intervention Versus Usual Care in Management of Nigerian Patients with Type 2 Diabetes. Value in Health Regional Issues. 2013;2(2):189-98.

Adjei 2015

Adjei DN, Agyemang C, Dasah JB, Kuranchie P, Amoah AG. The effect of electronic reminders on risk management among diabetic patients in low resourced settings. Journal of Diabetes & its Complications. 2015;29(6):818-21.

Ali 2019

Ali S, Ghanem Y, Sharaki O, Hewedy W, al. e. The impact of different regimens of vitamin d3 on glucose homeostasis in type 2 diabetic patients. Asian journal of pharmaceutical and clinical research. 2019;12(12):21- 6.

Amendezo 2017

Amendezo E, Walker Timothy D, Karamuka V, Robinson B, Kavabushi P, Ntirenganya C, et al. Effects of a lifestyle education program on glycemic control among patients with diabetes at Kigali University Hospital, Rwanda: A randomized controlled trial. Diabetes Research & Clinical Practice. 2017;126:129-37.

Anderson 2001

Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. Journal of the American College of Nutrition. 2001;20(3):212-8.

Anyanwu 2016

Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian Journal of Endocrinology and Metabolism. 2016;20(2):189-94.

Ashoush 2016

Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. Journal of obstetrics and gynaecology research. 2016;42(6):640- 7.

Asuako 2017

Asuako B, Moses MO, Eghan BA, Sarpong PA. Fasting plasma glucose and lipid profiles of diabetic patients improve with aerobic exercise training. Ghana Medical Journal. 2017;51(3):120-7.

Beyuo 2015

Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. PLoS ONE [Electronic Resource]. 2015;10(5):e0125712.

Chraibi 2017

Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshmivenkataraman B, et al. An RCT Investigating Patient-Driven Versus Physician-Driven Titration of BIAsp 30 in Patients with Type 2 Diabetes Uncontrolled Using NPH Insulin. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2017;8(4):767-80.

Debussche 2018

Debussche X, Besancon S, Balcou-Debussche M, Ferdynus C, Delisle H, Huiart L, et al. Structured peer-led diabetes self-management and support in a low-income country: The ST2EP randomised controlled trial in Mali. PLoS ONE. 2018;13(1):e0191262.

Distiller 2014

Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin. Endocrine practice. 2014;20(11):1143- 50.

El Gayar 2019

El Gayar MH, Aboromia MMM, Ibrahim NA, Abdel Hafiz MH. Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus. Obesity medicine. 2019;14.

El-Haggar 2015

El-Haggar SM, Farrag WF, Kotkata FA. Effect of ketotifen in obese patients with type 2 diabetes mellitus. Journal of Diabetes & its Complications. 2015;29(3):427-32.

El-Makaky 2020

El-Makaky Y, Shalaby HK. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: a randomized controlled trial. Oral diseases. 2020;26:822-9.

El-Shamy 2018

El-Shamy FF, El-Kholy SS, Labib M, Kabel AM. Ameliorative potential of acupressure on gestational diabetes mellitus: a randomized controlled trial. Journal of complementary and integrative medicine. 2018; 16(1).

El-Sheikh 2019

El-Sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of L-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. Diabetes and metabolic syndrome: clinical research and reviews. 2019;13(1):167-73.

El- Sharkawy 2016

El- Sharkawy HM, Anees MM, Van Dyke TE. Propolis improves periodontal status and glycemic control in patients with type 2 diabetes mellitus and chronic periodontitis: a randomized clinical trial. Journal of periodontology. 2016;87(12):1418-26.

Elbarbary 2016

Elbarbary NS. Effectiveness of the low-glucose suspend feature of insulin pump during fasting during Ramadan in type 1 diabetes mellitus. Diabetes/metabolism research and reviews. 2016;32(6):623- 33.

Elbarbary 2018

Elbarbary NS, Ismail EAR, El-Naggar AR, Hamouda MH, El-Hamamsy M. The effect of 12 weeks carnosine supplementation on renal functional integrity and oxidative stress in pediatric patients with diabetic nephropathy: a randomized placebo-controlled trial. Pediatric diabetes. 2018;19(3):470- 7.

Elbarbary 2020

Elbarbary NS, Ismail EAR, Zaki MA, Darwish YW, Ibrahim MZ, El-Hamamsy M. Vitamin B complex supplementation as a homocysteine-lowering therapy for early stage diabetic nephropathy in pediatric patients with type 1 diabetes: A randomized controlled trial. Clinical Nutrition. 2020;39(1):49-56.

Embaby 2016

Embaby H, Elsayed E, Fawzy M. Insulin Sensitivity and Plasma Glucose Response to Aerobic Exercise in Pregnant Women at Risk for Gestational Diabetes Mellitus. Ethiopian journal of health sciences. 2016;26(5):409- 14.

Essien 2017

Essien O, Otu A, Umoh V, Enang O, Hicks JP, Walley J. Intensive Patient Education Improves Glycaemic Control in Diabetes Compared to Conventional Education: A Randomised Controlled Trial in a Nigerian Tertiary Care Hospital. PLoS ONE 2017;12(1):e0168835.

Fairall 2016

Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, et al. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: a Pragmatic Cluster Randomised Controlled Trial. Plos medicine. 2016;13(11):e1002178.

Fayehun 2018

Fayehun AF, Olowookere OO, Ogunbode AM, Adetunji AA, Esan A. Walking prescription of 10 000 steps per day in patients with type 2 diabetes mellitus: a randomised trial in Nigerian general practice. British Journal of General Practice. 2018;68(667):e139-e45.

Ghoneim 2013

Ghoneim EM, Abd El Ghany AA. Behavior of intraocular pressure after intravitreal injection of triamcinolone acetonide among egyptians. Ophthalmology and Therapy. 2013;2(2):121-30.

Hailu 2018

Hailu FB, Hjortdahl P, Moen A. Nurse-Led Diabetes Self-Management Education Improves Clinical Parameters in Ethiopia. Frontiers in Public Health. 2018;6:302.

Ibrahim 2014

Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Archives of Gynecology & Obstetrics. 2014;289(5):959-65.

Krawinkel 2018

Krawinkel MB, Ludwig C, Swai ME, Yang RY, Chun KP, Habicht SD. Bitter gourd reduces elevated fasting plasma glucose levels in an intervention study among prediabetics in Tanzania. Journal of Ethnopharmacology. 2018;216:1-7.

Labhardt 2011

Labhardt ND, Balo JR, Ndam M, Manga E, Stoll B. Improved retention rates with low-cost interventions in hypertension and diabetes management in a rural African environment of nurse-led care: a cluster-randomised trial. Tropical Medicine & International Health. 2011;16(10):1276-84.

Maharaj 2016

Maharaj SS, Nuhu JM. Rebound exercise: A beneficial adjuvant for sedentary non-insulin-dependent type 2 diabetic individuals in a rural environment. Australian Journal of Rural Health. 2016;24(2):123-9.

Malek 2015

Malek R, Ajili F, Assaad-Khalil SH, Shinde A, Chen JW, Van den Berg E. Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. Diabetes & Metabolism. 2015;41(3):223-30.

Marais 2018

Marais C, Hall DR, van Wyk L, Conradie M. Randomized cross-over trial comparing the diagnosis of gestational diabetes by oral glucose tolerance test and a designed breakfast glucose profile. International Journal of Gynaecology & Obstetrics. 2018;141(1):85-90.

Malipa 2013

Malipa M, Menon J. The relationship between compliance and quality of life among adolescents with diabetes mellitus type1. Medical Journal of Zambia. 2013;40(3):93-103.

Mash 2014

Mash RJ, Rhode H, Zwarenstein M, Rollnick S, Lombard C, Steyn K, et al. Effectiveness of a group diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized controlled trial. Diabetic Medicine. 2014;31(8):987-93.

Mash R, Kroukamp R, Gaziano T, Levitt N. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. Patient Education & Counseling. 2015;98(5):622-6.

Matter 2020

Matter RM, Elbarbary NS, Ismail EAR, Darwish YW, Nada AS, Banoub VP. Zinc supplementation improves glucose homeostasis in patients with Î²-thalassemia major complicated with diabetes mellitus: a randomized controlled trial. Nutrition 2020;73.

Mohamad 2009

Mohamad RH, Zekry ZK, Al-Mehdar HA, Salama O, El-Shaieb SE, El-Basmy AA, et al. Camel milk as an adjuvant therapy for the treatment of type 1 diabetes: verification of a traditional ethnomedical practice. Journal of Medicinal Food. 2009;12(2):461-5.

Moustafa 2019

Moustafa HAM, El Wakeel LM, Halawa MR, Sabri NA, El-Bahy AZ, Singab AN. Effect of Nigella Sativa oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. Endocrine. 2019;65(2):286- 94.

Muchiri 2016

Muchiri JW, Gericke GJ, Rheeder P. Effect of a nutrition education programme on clinical status and dietary behaviours of adults with type 2 diabetes in a resource-limited setting in South Africa: a randomised controlled trial. Public Health Nutrition. 2016;19(1):142-55.

Muchiri JW, Gericke GJ, Rheeder P. Impact of nutrition education on diabetes knowledge and attitudes of adults with type 2 diabetes living in a resource-limited setting in South Africa: a randomised controlled trial. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2016;21(2):26-34.

Nteleki 2015

Nteleki B, Abrahamse H, Houreld NN. Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers. Seminars in Vascular Surgery. 2015;28(3-4):172-83.

Owolabi 2019

Owolabi EO, Goon DT, Ajayi AI. Efficacy, acceptability and feasibility of daily text-messaging in promoting glycaemic control and other clinical outcomes in a low-resource setting of South Africa: A randomised controlled trial. PLoS ONE [Electronic Resource]. 2019;14(11):e0224791.

Owolabi EO, Goon DT, Ajayi AI. Impact of mobile phone text messaging intervention on adherence among patients with diabetes in a rural setting: A randomized controlled trial. Medicine. 2020;99(12):1-8.

Ragheb 2020

Ragheb SR, El Wakeel LM, Nasr MS, Sabri NA. Impact of Rutin and Vitamin C combination on oxidative stress and glycemic control in patients with type 2 diabetes. Clinical nutrition ESPEN. 2020;35:128-35.

Rashad 2017

Rashad H, Metwally FM, Ezzat SM, Salama MM, Hasheesh A, Abdel Motaal A. Randomized double-blinded pilot clinical study of the antidiabetic activity of Balanites aegyptiaca and UPLC-ESI-MS/MS identification of its metabolites. Pharmaceutical Biology. 2017;55(1):1954-61.

RezkAllah 2019

RezkAllah SS, Takla MK. Effects of different dosages of interval training on glycemic control in people with prediabetes: a randomized controlled trial. Diabetes spectrum. 2019;32(2):125- 31.

Saeed 2013

Saeed AM. Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. Clinical Ophthalmology. 2013;7:283-97.

Salem 2010

Salem MA, Aboelasrar MA, Elbarbary NS, Elhilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetology & metabolic syndrome. 2010;2(1):47.

Sodipo 2017

Sodipo OO, Adedokun A, Olusola AA. Effect of self-monitoring of blood glucose on glycaemic outcome among type 2 diabetic patients. South african family practice. 2017;59(6):208- 13.

Somanah 2012

Somanah J, Aruoma OI, Gunness TK, Kowelssur S, Dambala V, Murad F, et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. Preventive Medicine. 2012;54 Suppl:S90-7.

Steyn 2013

Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, et al. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: a randomised controlled trial. Glob Health Action. 2013;6:20796.

Takenga 2014

Takenga C, Berndt RD, Musongya O, Kitero J, Katoke R, Molo K, et al. An ICT-Based Diabetes Management System Tested for Health Care Delivery in the African Context. International Journal of Telemedicine & Applications. 2014;2014:437307.

Tawfik 2016

Tawfik MY, Mohamed RA. The impact of communicating cardiovascular risk in type 2 diabetics on patient risk perception, diabetes self-care, glycosylated hemoglobin, and cardiovascular risk. Journal of public health. 2016;24(2):153- 64.

Thuita 2020

Thuita AW, Kiage BN, Onyango AN, Makokha AO. Effect of a nutrition education programme on the metabolic syndrome in type 2 diabetes mellitus patients at a level 5 Hospital in Kenya: "a randomized controlled trial". BMC Nutr. 2020;6:30.

Tsobgny-Tsague 2018

Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, Tankeu AT, Katte JC, Dehayem MY, et al. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health. 2018;18(1):28.

Utz 2018

Utz B, Assarag B, Smekens T, Ennassiri H, Lekhal T, El Ansari N, et al. Detection and initial management of gestational diabetes through primary health care services in Morocco: An effectiveness-implementation trial. PloS one. 2018;13(12):e0209322.

van der Hoogt 2017

van der Hoogt M, van Dyk JC, Dolman RC, Pieters M. Protein and fat meal content increase insulin requirement in children with type 1 diabetes - Role of duration of diabetes. Journal of clinical and translational endocrinology. 2017;10:15- 21.

van Rooijen 2004

van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A1C in Black females with type 2 diabetes mellitus. Qjm. 2004;97(6):343-51.

Webb 2015

Webb EM, Rheeder P, Van Zyl DG. Diabetes care and complications in primary care in the Tshwane district of South Africa. Primary care diabetes. 2015;9(2):147-54.

Webb EM, Rheeder P, Roux P. Screening in Primary Care for Diabetic Retinopathy, Maculopathy and Visual Loss in South Africa. Ophthalmologica. 2016;235(3):141-9.

Webb EM, Rheeder P. A cluster-randomized trial to estimate the effect of mobile screening and treatment feedback on HbA1c and diabetes-related complications in Tshwane primary health care clinics, South Africa. Primary care diabetes. 2017;11(6):546-54.

Yakoot 2019

Yakoot M, Abdelatif M, Helmy S. Efficacy of a new local limb salvage treatment for limb-threatening diabetic foot wounds-a randomized controlled study. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2019;12:1659.

Yan 2014

Yan H, Prista A, Ranadive SM, Damasceno A, Caupers P, Kanaley JA, et al. Effect of Aerobic Training on Glucose Control and Blood Pressure in T2DDM East African Males. Isrn Endocrinology Print. 2014;2014:864897.

1.2 List of excluded studies

1.2.1 Other design (28 references)

1. Abd El Hameed AA, Shreif HE, Mowafy HE. The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. Middle east fertility society journal. 2011;16(3):204- 8.

2. Abdelaziz TS, Sadek KM. Effect of reducing medication regimen complexity on glycaemic control in patients with diabetes. Romanian Journal of Internal Medicine. 2019;57(1):23-9.

3. Agboola-Abu CF, Ohwovoriole AE, Akinlade KS. The effect of oral hypoglycaemic agents on dyslipidaemia in Nigerian patients with newly diagnosed non-insulin dependent diabetes mellitus--a prospective study. West African Journal of Medicine. 2000;19(2):126-31.

4. Assah FK, Atanga EN, Enoru S, Sobngwi E, Mbanya JC. Community-based peer support significantly improves metabolic control in people with Type 2 diabetes in Yaounde, Cameroon. Diabetic Medicine. 2015;32(7):886-9.

5. Bahramikia S, Yazdanparast R. Phytochemistry and medicinal properties of Teucrium polium L. (Lamiaceae). Phytotherapy Research. 2012;26(11):1581-93.

6. Bailey CJ, Iqbal N, T'Joen C, List JF. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes, Obesity & Metabolism. 2012;14(10):951-9.

7. Bekkouche L, Bouchenak M, Malaisse WJ, Yahia DA. The Mediterranean diet adoption improves metabolic, oxidative, and inflammatory abnormalities in Algerian metabolic syndrome patients. Hormon- und Stoffwechselforschung / Hormones et metabolisme [Hormone and metabolic research]. 2014;46(4):274- 82.

8. Bello SI, Ganiyu KA, Dakop YO, Erah PO. Pharmacist's intervention in the control of blood sugar levels in randomised diabetes patients at a primary health care setting in Benin City. Nigerian Quarterly Journal of Hospital Medicine. 2012;22(4):245-8.

9. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database of Systematic Reviews. 2017;1:CD011967.

10. Chou HS, Truitt KE, Moberly JB, Merante D, Choi Y, Mun Y, et al. A 26-week, placebo- and pioglitazone-controlled monotherapy study of rivoglitazone in subjects with type 2 diabetes mellitus. Diabetes, Obesity & Metabolism. 2012;14(11):1000-9.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1 (Numbers are manuscript pages)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary data
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	not done due to the narrative approach

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	not done due to the narrative approach
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not done due to the narrative approach
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not done due to the narrative approach
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary data, list of excluded studies
Study characteristics	17	Cite each included study and present its characteristics.	9-16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Data – Table: Risk of Bias
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Data – Tables
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 3 and 4 in the results section (page 13)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9 (study designs, participants, settings) Pages 10 – 15 (interventions) narrative description of heterogenous studies
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not done due to the narrative approach

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not done due to the narrative approach
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Only for HbA1c measures: Figures 3 and 4; others not done due to narrative approach
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17
	23b	Discuss any limitations of the evidence included in the review.	21
	23c	Discuss any limitations of the review processes used.	21-22
	23d	Discuss implications of the results for practice, policy, and future research.	17-21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8 + abstract
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8 + abstract
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	23
Competing interests	26	Declare any competing interests of review authors.	23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	In the supplement: search strategy for 6 databases, list of included and excluded studies

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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