REVIEW

Therapeutic interventions to reduce the risk of progression from prediabetes to type 2 diabetes mellitus

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Abstract: Clinical trials have demonstrated that it is possible to prevent diabetes through lifestyle modification, pharmacological intervention, and surgery. This review aims to summarize the effectiveness of these various therapeutic interventions in reducing the risk of progression of prediabetes to diabetes, and address the challenges to implement a diabetes prevention program at a community level. Strategies focusing on intensive lifestyle changes are not only efficient but cost-effective and/or cost-saving. Indeed, lifestyle intervention in people at high risk for type 2 diabetes mellitus (T2DM) has been successful in achieving sustained behavioral changes and a reduction in diabetes incidence even after the counseling is stopped. Although prediabetes is associated with health and economic burdens, it has not been adequately addressed by interventions or regulatory agencies in terms of prevention or disease management. Lifestyle intervention strategies to prevent T2DM should be distinct for different populations around the globe and should emphasize sex, age, ethnicity, and cultural and geographical considerations to be feasible and to promote better compliance. The translation of diabetes prevention research at a population level, especially finding the most effective methods of preventing T2DM in various societies and cultural settings remains challenging, but must be accomplished to stop this worldwide epidemic.

Keywords: lifestyle, T2DM, intervention, prevention

Introduction

The prevalence and the incidence of type 2 diabetes mellitus (T2DM) has rapidly increased over the past several decades and is now attaining epidemic proportions worldwide, paralleling the increase in obesity prevalence, particularly in developing countries.[1–4] T2DM is increasing most rapidly in the People's Republic of China, India, and the Middle East,[1,2] but is also rising in low- and middle-income countries around the world, as well as in North America and Europe.[3,4] Moreover, the global prevalence of diabetes is estimated to rise from 382 million to 592 million by 2035.[4] Recent analysis of the economic impact of diabetes in the US has demonstrated that in 2012 the estimated total economic cost of the disease was US$245 billion, a 41% increase from the previous estimate of US$174 billion in 2007.[5]

Prediabetes is defined as a state of abnormal glucose homeostasis characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both (Table 1).[6,7] Plasma glucose levels in this range increase the risk of developing frank diabetes, defined as fasting glucose level $\geq$126 mg/dL or 2-hour prandial glucose $\geq$200 mg/dL.[8]

Table 1 Classification of glucose tolerance states

Glucose tolerance states	Fasting plasma glucose level (mg/dL)	2-hour plasma glucose after a 75 g glucose load on OGTT (mg/dL)
IFG	100–125	<200
Isolated IFG	100–125	<140
IGT	<126	140–199
Isolated IGT	<100	140–199
Combined IFG/IGT	100–125	140–199
NGT	<100	<140

Note: Data from Nathan et al.[7]
Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

Prediabetes is a disease

Microvascular and macrovascular damage starts during prediabetes and is associated with an increased risk of cardiovascular disease early in the progression to T2DM.[9] Elevated glucose levels damage endothelial cells, which can lead to microvascular disease.[10] Microalbuminuria is an excellent indicator of microvascular injury and affects twice as many subjects with prediabetes than normoglycemic subjects.[11] It is associated with both chronic kidney disease, as well as macrovascular complications.[12] In the National Health and Nutrition Examination Survey, 17.7% of subjects with prediabetes based on IFG had chronic kidney disease, compared with 10.6% without diabetes or prediabetes.[13] In the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study, the prevalence of diabetic polyneuropathy was approximately increased twofold in those individuals with IFG and IGT as compared with the normal subjects.[14] There are also data suggesting increased presence of retinal changes in patients with prediabetes.[15] Taken together, these observations demonstrate that prediabetes is associated with health risk and economic burdens, as it can adversely impact multiple target organs. However, this condition has not been adequately addressed by regulatory agencies in terms of prevention or management, since prediabetes is not framed as a disease but rather as a risk or a "pre" stage for diabetes.[16]

Risk factors for the progression to diabetes and screening

An interaction of genetic predisposition, together with lifestyle and behavior, advancing age, environmental risk factors, and low education level, contributes to the risk of T2DM.[6,17–19] The consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinology describe certain characteristics and concomitant conditions that increase the risk of progression to diabetes, including family history, age, obesity, dyslipidemia,

ethnicity, inactivity, and prediabetes status.[6] Other interesting conditions can also predispose to diabetes (Table 2). Long-term antidepressant therapy, the use of which is increasing, appears to enhance the risk of T2DM,[20–22] although more investigation is needed to confirm this association.[23] The recently described condition of "new onset diabetes after transplant" is a consequence of organ transplantation due to exposure to glucocorticoids and other immunosuppressive agents.[24] New onset diabetes after transplant is associated with increased mortality and morbidity, and pretransplant screening for risk factors is highly recommended.[25] The intrauterine environment (shortage or excess of nutrients) is another condition related to T2DM. Low birth weight is associated with nutritional deprivation in utero, which predisposes to the "thrifty phenotype"[26] leading to obesity, insulin resistance, and reduced β-cell mass in later life. On the other hand, intrauterine hyperglycemia is not only associated with increased perinatal morbidity and mortality, but also with increased lifelong risk for the exposed offspring of obesity, metabolic and cardiovascular diseases, and earlier development of T2DM.[27,28] Disruption of the circadian rhythm occurs in obesity, diabetes, and cardiovascular disease and is another factor that increases risk for diabetes.[29] Transcriptional alterations of the circadian locomotor output cycles kaput (CLOCK) genes in metabolic tissues lead to blunting of rhythms of glucose tolerance and insulin sensitivity.[30] In adipose tissue, this results in local inflammation that may contribute to worsening of insulin resistance.[31]

Table 2 Characteristics and concomitant conditions that increase the risk of progression to diabetes

Characteristics and conditions
- Family history of diabetes
- Cardiovascular disease
- Excessive weight or obesity
- Sedentary lifestyle
- Non-white ancestry
- Previously identified IGT, IFG, HbA$_{1c}$ ≥5.7%, and/or metabolic syndrome
- Hypertension
- Increased levels of TG, low concentrations of HDL-C, or both
- History of gestational diabetes
- Delivery of a baby weighing >9 lb (4 kg)
- Polycystic ovary syndrome
- Antipsychotic therapy for schizophrenia and severe bipolar disorder
- Antidepressant therapy
- NODAT
- Intrauterine environment

Abbreviations: HbA$_{1c}$, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NODAT, new onset diabetes after transplant; TG, triglycerides.

International societies recommend frequent screening for diabetes among high risk individuals; however, the definition of high risk and types of risk assessment differ, as some include demographic and medical history information, while others consider measures of glycemia or oral glucose tolerance testing.[32,33] Furthermore, different cohort studies indicate that diabetes risk increases at a fasting plasma glucose (FPG) below currently recommended thresholds for diagnosis of prediabetes.[34,35] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus examined the sensitivity and specificity of a wide range of FPG values from several studies (103 mg/dL in a Dutch population, 97 mg/dL in a Pima Indian population, 94 mg/dL in a Mauritius population, and 94 mg/dL in a San Antonio population) in order to identify the best cut point to optimize the prediction of diabetes, which was then set at 100 mg/dL.[8,36] Results from an intravenous glucose tolerance test study demonstrated that the first-phase insulin secretion begins to decrease once FPG values increase above 90–97 mg/dL,[36] supporting the cutoff point for FPG established by the American Diabetes Association. Measurement of IGT may be a better parameter than IFG to identify individuals at risk for macrovascular complications,[37,38] as IGT is more sensitive at identifying prediabetic and diabetic individuals.[39] IGT identifies a larger number of individuals who might develop diabetes as it is more common than IFG in most populations.[8,40]

Both IFG and IGT are insulin resistance states differing in the tissue etiology of the insulin resistance.[41–43] While IFG is characterized by predominantly hepatic insulin resistance and normal muscle insulin sensitivity, IGT shows normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance.[7] Both IFG and IGT are associated with impairment of insulin secretion.[44] Individuals with IFG have severe impaired early insulin responses to the oral glucose tolerance test and improvements in insulin secretion during the second phase of the test, while individuals with IGT have impaired early and late phase of insulin secretion.[15,45–47] Progressive β-cell loss characterizes the development of T2DM. In the Insulin Resistance Atherosclerosis Study, β-cell function was compromised by as much as 40% in patients with IGT and 80% in patients with diabetes.[48] Whether these differences impact strategies to prevent diabetes requires further investigation. However, IGT and IFG have different implications for atherosclerotic cardiovascular disease, in which IGT is associated with metabolic syndrome and is a strong predictor of cardiovascular disease.[49]

Screening for IFG/IGT is highly recommended, and the most efficient sequence of testing would be an FPG followed by a 2-hour plasma glucose after a 75 g glucose load to demonstrate the presence of combined IFG/IGT.[7] Screening for prediabetes in the overweight and obese populations has been demonstrated to be cost-effective.[50] More novel approaches may include the preDx® (Tethys Bioscience Inc, Emeryville, CA, USA) test, which represents a collection of variables (glycated hemoglobin [HbA$_{1c}$], adiponectin, C-reactive protein, ferritin, glucose, interleukin-2 receptor A, and insulin) that have better predictive value than any single variable, which is clinically available, and a metabolomics analysis, which has suggested that glycine, lysophosphatidylcholine, and acetylcarnitine levels in plasma predict progression to diabetes.[51–53]

Diabetes prevention

The westernization of lifestyle characterized by decreasing physical activity and a dietary pattern with high intake of foods rich in hydrogenated fat, refined grains, and red meat is related to the increase in obesity, T2DM, and cardiovascular diseases. High saturated fat intake is associated with higher risk of IGT.[54] Dietary changes including reduction of total and saturated fat and increased dietary fiber intake, along with physical activity and weight loss, can reduce the incidence of T2DM.[55] Lifestyle modification focusing on improving dietary quality, physical activity, and medical intervention improves glycemic control and other cardiovascular risk factors, and is the preferred first-line treatment for the management of T2DM. Several trials have demonstrated that it is possible to prevent diabetes through lifestyle and/or medication intervention (Table 3); however, effective therapeutic strategies based on lifestyle changes, weight reduction, increasing physical activity, and eating a balanced diet are often unsuccessful due to poor compliance.[56] Pharmacological interventions using different antidiabetic drugs, especially agents that improve insulin sensitivity, can prevent or at least slow the progression of prediabetes to diabetes. Bariatric surgery has also been shown to slow the progression to diabetes. Interventions should consider sex, age, ethnicity, and cultural and geographical characteristics to be feasible and to promote better compliance. Also, interventions must address education of both children and adults, food availability, and advertising, and the health system should provide incentives to encourage adoption of effective intervention for diabetes prevention. Furthermore, individual countries should develop and evaluate cost-effective, setting-specific diabetes-risk identification and prevention strategies based on their available resources.[57]

Table 3 Lifestyle and pharmacological interventions to prevent type 2 diabetes mellitus

Study	N	Intervention	Treatment	Risk reduction
Da Qing[61,62]				
IGT	577	Diet and exercise	6 years	34%–69%
			20 years	
Finnish DPS[19,55]				
IGT	522	Diet and exercise	3 years	58%
			7 years	
DPP[66,77]				
IGT	3,234	Diet, exercise, and metformin	2.8 years	31%–58%
			10 years	
IDPP[63]				
IGT	531	Diet, exercise, and metformin	3 years	26.4%–28.4%
DREAM[139]				
IGT	5,269	Rosiglitazone	3 years	60%
STOP-NIDDM[130,132]				
IGT	1,429	Acarbose	3.3 years	21%
ACT NOW[137,138]				
IFG	~600	Pioglitazone	3.75 years	72%

Abbreviations: ACT NOW, Actos Now for the Prevention of Diabetes; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial; IDPP, Indian Diabetes Prevention Programme; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; STOP-NIDDM, Study to Prevent Non-insulin Dependent Diabetes.

Lifestyle modification and the progression of prediabetes

The worldwide surge in the prevalence of T2DM and obesity and the importance of prevention and control of noncommunicable diseases, as stated by the World Health Organization (WHO),[58] increase the need for prevention strategies focusing on intensive lifestyle changes, as they are proven to be either cost-saving or cost-effective.[59,60] Many randomized, controlled clinical trials have demonstrated a clinically significant impact of lifestyle changes in the prevention of diabetes among high risk individuals.[55,61–66] The Da Qing IGT and Diabetes Study evaluated 577 subjects with IGT who were randomized to a control group or to one of three active treatment groups (diet only, exercise only, or diet plus exercise). After a 6-year follow-up period, it was found that the diet, exercise, and diet-plus-exercise interventions were associated with 31%, 46%, and 42% reduction in risk of developing diabetes, respectively.[61] The Finnish Diabetes Prevention Study (DPS) showed that it is possible to achieve primary prevention of T2DM by changing lifestyle (diet and exercise) in subjects with IGT (n=522), reducing the risk of diabetes by 58% in the intervention group.[55] The participants were randomly allocated either into the control group or an intensive lifestyle intervention group, and the cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group.[65] The Diabetes Prevention Program (DPP) Research Group randomized 3,234 individuals with IFG and IGT to receive placebo, metformin, or a lifestyle intervention program, and after an average of 2.8 years, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years,

respectively.[66] These clinical trials establish the potential to prevent T2DM in high-risk individuals through a lifestyle intervention focusing on achievement and maintenance of weight reduction by consuming a healthy diet and increasing physical activity. Weight loss has the greatest effect in preventing and treating T2DM.[66,67] However, results from the Da Qing IGT and Diabetes Study showed a beneficial effect even with relatively small reduction in body mass index (BMI), as participants were generally lean. Thus, other lifestyle issues are important to the pathogenesis of T2DM, despite the fact that weight may work as a summary indicator of several dietary and activity factors.[60] Overall, these data highlight the importance of tailoring lifestyle interventions to prevent T2DM within distinct populations.

In the Finnish DPS, post hoc analyses showed that adopting a diet with moderate fat and high dietary fiber content,[65] in addition to weight loss and increased physical activity,[68] was independently associated with diabetes risk reduction. Thus, an appropriate strategy of diet and physical activity that promotes weight loss can prevent diabetes. The most successful nutritional strategy for both prevention and treatment of T2DM is one that the individual can adapt and follow permanently.[69] Extreme dietary restriction and avoidance of certain food groups, such as carbohydrates or sources of fats, might be efficient for weight loss in the short-term but may not be sustainable in the long-term.[70] A dietary plan should take into consideration culture, food availability, and personal preferences, and yet follow recommendations that encourage a high intake of fruit and vegetables, unrefined grains with natural high fiber content, vegetable oil with low content of saturated fat (such as olive

oil), nuts, legumes, low-fat dairy and fish as sources of protein, and limit the intake of highly processed foods.[71]

Physical inactivity is an important lifestyle factor related to chronic disease morbidity and premature mortality worldwide.[72,73] Interventions focusing on increasing physical activity improve glucose tolerance and reduce the risk of T2DM in high-risk individuals,[74] regardless of bodyweight.[68,75] The WHO recommendation on physical activity for adults is at least 150 minutes per week of moderate-intensity aerobic physical activity, or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate and vigorous-intensity activity. Physical exercises can be performed in multiple shorter bouts, of 10 minutes each, then adding together the time spent during each of these bouts until meeting the goal of 150 minutes of physical exercise per week, eg, 30 minutes of moderate-intensity activity five times per week.[76] Also, the recommendations suggest that adults perform muscle-strengthening activities two or more days per week involving all major muscle groups.[76] The Diabetes Prevention Program lifestyle intervention demonstrated beneficial effect on glycemic control in those with prediabetes with 150 minutes per week of moderate-intensity exercise.[66]

Sustained benefits of lifestyle modification

Lifestyle interventions are effective in sustaining behavioral changes that result in long-term reduction in diabetes incidence. The extended follow-up of the Finnish DPS assessed whether the originally achieved lifestyle changes and risk reduction remained after discontinuation of active counseling. The investigators found that beneficial lifestyle changes achieved by participants in the intervention group were maintained after the discontinuation of the intervention, and the marked reduction in the cumulative incidence of T2DM was sustained.[65] Likewise, the 10-year follow-up of the DPP showed that the cumulative incidence of diabetes remained lowest in the lifestyle intervention group.[77] The 20-year follow-up of the Da Qing IGT and Diabetes Study revealed that participants in the intervention group spent an average of 3.6 fewer years with diabetes than those in the control group, and diabetes could be prevented or delayed for up to 14 years after the active intervention.[62] However, there was no significant difference between the intervention and control groups in the rate of first cardiovascular events.[62] Similar results were found in the Finnish DPS 10-year follow-up, where mortality and cardiovascular morbidity were not different between the intervention and control groups.[19]

Implementing lifestyle modification at a community level

It has been a challenge to translate the message of these successful intervention trials preventing T2DM at a population level, particularly identifying the most effective methods of prevention in various societies and cultural settings.[78] The resources available at a clinical practice are typically limited when compared with experimental settings, which could be an important factor influencing translation and delivery of evidence-based diabetes prevention programs.[57,79,80] Many national and local authorities and health care providers around the world have started programs and activities to prevent T2DM and its complications,[79,81–86] and a European group of experts has prepared evidence-based guidelines on T2DM prevention,[87] a toolkit for diabetes prevention,[88] and guidelines to evaluate quality indicators for the prevention of T2DM.[89] The toolkit for the prevention of diabetes (IMAGE project) is a practical guideline that includes all the necessary information to build a T2DM prevention program (management, financial, intervention, quality assurance aspects, and how to translate this knowledge into practice).[88] The major challenge now is to disseminate these guidelines and implement them at different settings and levels in the community.[90]

Several community-based studies involving primary care and occupational health care have found significant reductions in T2DM risk factors through lifestyle intervention programs.[83,91–95] However, it has not been possible to evaluate the impact of these interventions on the incidence of diabetes, as most of the studies were small, with follow-up limited to just 1 year. The Finnish National Diabetes Prevention Program (FIN-D2D) was implemented in the Finnish primary health care system, with strategies of implementing screening and lifestyle interventions in individuals at high risk of T2DM as part of routine primary care.[82,83] After 1 year, the FIN-D2D group reported that recruiting high-risk subjects for the program was found to be simple and the program was easy to use, and a moderate weight loss was effective to reduce the risk of developing T2DM.[83] The Active Prevention in High-Risk Individuals of Diabetes Type 2 in and Around Eindhoven (APHRODITE) study is a low intensity and low cost intervention that investigated the effectiveness and feasibility of T2DM prevention through lifestyle intervention in Dutch general practice. The study showed that T2DM could be significantly reduced by lifestyle counseling.[85] Three other community studies, Diabetes Education and Prevention with a Lifestyle Intervention Offered at the YMCA (DEPLOY),[92] Prevention of Diabetes Self-management Program (PREDIAS),[93] and the Australian Great Green

Triangle (GGT) Diabetes Prevention Study[94] also showed beneficial effects of lifestyle on risk factors for T2DM. The DEPLOY study compared the results of two different lifestyle intervention approaches in adults who attended a diabetes risk-screening event at one of two semi-urban YMCA facilities. Study participants (n=92) were allocated to a group-based DPP lifestyle intervention delivery by the YMCA or standard advice alone (controls). Results showed that YMCA wellness instructors can be trained to deliver a group-based DPP lifestyle intervention, and the body mass changes after 6 and 12 months in the intervention group were similar to the DPP study.[92] The PREDIAS program randomly assigned 182 individuals at high risk for T2DM to either an intervention program consisting of 12 group sessions aimed at lifestyle modification, or a control group who received the same written information but did not attend any group sessions. The lifestyle program was able to reduce diabetes risk by promoting weight loss and modifying eating behavior and physical activity significantly.[93] The GGT Diabetes Prevention Project was implemented in a primary health care setting in Australia with 237 individuals using the intervention model based on the Finnish DPS. Results showed significant changes in weight, waist circumference, glucose and lipids, and psychological measures.[94] Although the results of these studies are encouraging, there were challenges in recruiting individuals at high risk, suggesting that a range of different approaches may be needed to engage people that are at risk for developing diabetes.[57] The DE-PLAN (Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutrition intervention) in Greece identified high-risk individuals through a questionnaire that required minimal effort to complete and found that recruitment from workplaces was more successful when compared with recruitment from primary care centers.[95]

The outcomes of the studies were related to the participant's initial risk profile, in which those with a less favorable profile had more improvement and increased motivation to lose weight, eat healthier, and exercise more. Strategies to support behavior change still need improvements as individuals from different backgrounds and cultures might need distinct actions to support lifestyle changes.[71] Partner support is an important factor for successful behavioral change, and the level of the health professional experience (ie, nurse practitioner) may facilitate the intervention success.[85] Social support is also related to effectiveness of behavior changes, especially in weight-loss programs,[87] while lack of family support can be a major barrier for achieving[86] and maintaining[96] behavior change in intervention programs to prevent T2DM.

Recently, two large community health centers in Massachusetts were assessed for translating evidence-based diabetes intervention to disadvantaged groups. The study demonstrated suboptimal quality of care for T2DM prevention, including lack of information of factors associated with diabetes risk on more than half of the medical records reviewed, and limited documentation of counseling and criteria for the interventions on risk factors. Providers recognized patient's cultural traditions, attitudes, and low motivation for the intervention as important challenges, while patients expressed interest and were concerned about their diabetes risk, even though expressing limited ability to initiate and maintain lifestyle changes. This study showed that translation efforts are needed to implement interventions in real world community health centers to prevent diabetes in individuals at risk.[86] High quality training for providers is essential for implementing a successful intervention program, which should include knowledge about the relationship between lifestyle behavior and the progression of T2DM, skills for assessing diet and physical activity, and techniques for supporting the initiation and maintenance of behavioral changes.[71,87,95,97] Developing a research team that shares racial, ethnic, and cultural backgrounds with the population being served can facilitate development of successful recruitment strategies, influence the retention of participants, and enhance trust in the outcomes of study.[80] It is important that there are members that guide teams in community intervention programs that are from the same neighborhoods, share the same or similar demographic and comorbid conditions, and/or have a vested interest in the issues being addressed in the program.[79,80,98,99]

Community-based changes

Multiple external barriers to lifestyle changes, limited understanding of diabetes risk and prevention,[79] and limited behavior change skills are important challenges that interfere with the effective implementation of diabetes prevention programs on a larger scale.[57] Barriers to effective program implementation include geographical location; vernacular; language; culture (racial, ethnic, organizational structure-bureaucratic, and mission); and whether the community is open to new approaches, while not discarding traditional rituals and customs.[98] Community-based participatory programs can address barriers via multiple levels promoting collaborative relationships between community members, educators, clinicians, researchers, university programs/interns, and agencies, and results in healthy lifestyle behaviors in the designated population. This strategy not only provides insight into barriers and potential solutions, but

helps promote individualization and buy-in of programs from all corresponding parties, providing greater access and trust with vulnerable and hard to access individuals in the community and, thus, facilitates the sustainability of programs.[100–116]

Public awareness regarding prediabetes and diabetes needs to be disseminated at various levels from educating the appropriate government representatives and community leaders and raising awareness through community events including town hall meetings, health fairs, and seminars at school meetings, community centers, and clinics. Prevention and management programs can be held for children from 4 to 18 years of age during summer and after-school programs; programs for the elderly can be held at senior centers or nutrition centers; diabetes and pregnancy programs can be held at clinic locations; and diabetes screenings, education, and management programs can be presented at community centers, churches, and clinics.[102]

Another strategy to increase partnerships in the community is to train the next generation of researchers, educators, and clinicians from outlying colleges and universities which can defray some costs of intervention programs while concurrently disseminating these programs into the community. Professors often find it difficult to locate placements for their students in real clinical life scenarios whereby they can apply the conceptual knowledge and skills that they have been taught. Specific measurable goals and projects need to be carefully outlined for each student so that they are trained in their respective course syllabus requirements and develop knowledge and skills beyond the classroom while still achieving and sustaining the goals of the community program.[117,118]

With community participation and buy-in, innovative and individualized approaches can provide the foundation toward decreasing health disparities in minority and other vulnerable populations that are disproportionately afflicted with obesity and diabetes. Although the process can be slow, taking months to years to formulate these relationships, they are worth the effort to create solid changes and sustainability of program goals and strategies.[80,111,112,119–125]

Pharmacotherapy and the progression of prediabetes

Randomized clinical trials listed in Table 3 have demonstrated that both lifestyle changes and pharmacological intervention can reduce the risk of T2DM in high-risk individuals. Table 4 summarizes the classes of medications reviewed below, their mechanism of action and the trials demonstrating the benefit.

Biguanides

The two major intervention studies that included metformin, which suppresses hepatic glucose production, reportedly by stimulating the AMPK (adenosine monophosphate-activated protein kinase) pathway in the liver,[126] were the DPP study performed in the United States and the Indian Diabetes Prevention Programme (IDPP-1) study performed in India. In the DPP trial, 1,073 participants with IGT were allocated to 850 mg of metformin twice a day and 1,082 participants were allocated to placebo, and were followed-up for a median period of 2.8 years. At the end of the study, metformin reduced the incidence of T2DM by 31% compared with placebo.[66] After the end of the original study, a 10-year follow-up was

Table 4 Pharmacologic therapy in the prevention of T2DM

Therapeutic intervention	Mechanism of action	Result of trial	Study
Biguanides	AMPK activation	Reduction in the incidence of T2DM	Knowler et al[66] Ramachandran et al[63]
Alpha glucosidase inhibitors	Slow intestinal carbohydrate absorption	Reduction in the incidence of T2DM	Chiasson et al[130]
Lipase inhibitors	Slow intestinal fat absorption	Reduction in the incidence of T2DM Promotion of weight loss	Torgerson et al[142]
DPP-4 inhibitors	Increase GLP-1 levels	Improvement in glycemic control	Rosenstock et al[153]
Thiazolidinediones	Activation of PPAR-γ	Improvement in insulin sensitivity Prevention on the progression to T2DM	Buchanan et al[135] Xiang et al[136] Defronzo et al[137] DeFronzo et al[138] Gerstein et al[139]
GLP-1 receptor agonist	Activation of GLP-1 receptor	Decrease in A_{1c} Promotion of weight loss	Rosenstock et al[158] Astrup et al[159]
Sympathomimetic amines	Appetite suppressant	Promotion of weight loss	Gadde et al[171] Garvey et al[172]

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; DPP-4, dipeptidyl peptidase-IV; GLP, glucagon-like peptide; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus.

offered to the active participants who continued to follow the original study protocol. Diabetes incidence was reduced by 18% in the metformin group in comparison with placebo after 10 years from the initial randomization.[77] The IDPP-1 study showed a 25% relative reduction in T2DM for those who used metformin 250 mg twice a day.[63] A meta-analysis of 31 randomized studies including 4,570 participants with at least 8 weeks of metformin use showed that the incidence of T2DM was reduced by 40%, with an absolute risk reduction of 6%.[127] Metformin therapy is able to improve the activation of CLOCK genes in some but not all peripheral tissues. New therapies are needed to act either on the central and/or the peripheral CLOCKs to prevent the alterations in circadian rhythm thereby preventing the progressive insulin resistance and loss of β-cell function that leads to T2DM.[128]

Alpha glucosidase inhibitors

Another antihyperglycemic agent for treating T2DM is the alpha-glucosidase inhibitor acarbose, which slows carbohydrate absorption and decreases postprandial hyperglycemia.[129] Although its use is not generally associated with weight loss, the mechanism of action is to decrease carbohydrate breakdown and thereby absorption, thus decreasing the workload on the pancreas. The Study to Prevent Non-insulin Dependent Diabetes (STOP-NIDDM) was carried out in 1,429 participants with IGT randomized to 100 mg of acarbose or placebo, three times a day for a mean period of 3.3 years. The relative reduction of T2DM was 35.8% in the acarbose group when compared with placebo. The study also showed surprising relative reductions in myocardial infarction (91%) and new onset hypertension (34%) in treated IGT patients.[130–132]

Thiazolidinediones

Experimental and clinical evidence suggest that thiazolidinediones improve insulin sensitivity, restore pancreatic β-cell function, promote fat removal from the liver, and attenuate inflammation.[133,134] Troglitazone was tested in the Troglitazone in Prevention of Diabetes Study (TRIPOD) in high-risk Hispanic women. Treatment with troglitazone delayed or prevented the onset of T2DM, and the protective effect was associated with the preservation of pancreatic β-cell function and appeared to be mediated by a reduction in the secretory demands placed on the β-cell by chronic insulin resistance.[135] The Pioglitazone In Prevention Of Diabetes (PIPOD) study was conducted to evaluate β-cell function, insulin resistance, and the incidence of diabetes during treatment with pioglitazone in Hispanic women with prior gestational diabetes who had completed participation in the TRIPOD study. Comparison of changes in β-cell compensation for insulin resistance across the TRIPOD and PIPOD studies revealed that pioglitazone stopped the decline in β-cell function that occurred during placebo treatment in the TRIPOD study and maintained the stability of β-cell function that had developed during troglitazone treatment in the TRIPOD study.[136] Pioglitazone use to prevent progression of diabetes was observed for an average of 3.75 years in the randomized placebo-controlled study ACT NOW (Actos Now for the Prevention of Diabetes), in which 602 patients with IGT received either 45 mg/day pioglitazone or placebo. As compared with placebo, pioglitazone reduced the risk of conversion of IGT to T2DM by 72%, but was associated with significant weight gain and edema.[137,138] Rosiglitazone was tested alone in two randomized studies: the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM trial)[139] and the Canadian Normoglycemia Outcomes Evaluation (CANOE).[140] The DREAM trial recruited 5,269 patients with IFG, IGT, or both, and demonstrated that rosiglitazone was highly effective in reducing the incidence of T2DM by 60% in comparison with placebo.[139] In order to assess the overall cardiovascular safety of rosiglitazone, when added to metformin or sulfonylurea treatment, the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) demonstrated that rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.[141] The CANOE study included 207 patients with IGT who received a combination of rosiglitazone (2 mg) and metformin (500 mg) twice daily for a median period of 3.9 years. The low-dose combination therapy with rosiglitazone and metformin was highly effective in the prevention of T2DM, with a low incidence of clinically relevant adverse effects. Relative and absolute risk reduction of T2DM in the active treatment group was 66% and 26%, respectively, compared with placebo.[140]

Lipase inhibitors

The lipase inhibitor orlistat was utilized in the Xenical-based Prevention of Diabetes in Obese Subjects study, a double-blind, prospective study, that randomized 3,305 obese patients to lifestyle changes plus either orlistat 120 mg or placebo, three times daily for 4 years. Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a 37.3% decrease in the risk of developing diabetes over the 4 years and produced greater weight loss in this clinically representative obese population. In addition, independent of

orlistat or placebo treatment, the relative risk of developing T2DM was greater in the patients with IGT than in those with normal glucose tolerance.[142]

Insulin

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) was the first study to evaluate the effect of early treatment with basal insulin compared with standard treatment, in a large multinational multicenter randomized trial of individuals with prediabetes and early T2DM who had high cardiovascular risk. The trial demonstrated that microangiopathy was reduced in individuals with HbA_{1c} >6.4% and that glycemic control prevents diabetes progression for 5 years by keeping HbA_{1c} around 6.5%.[143] Results from the DPPOS (Diabetes Prevention Program Outcome Study) show a 56% reduction in diabetes incidence in high-risk individuals who revert to normal glucose regulation, no matter how this reversion is achieved, as long as the intervention is early (prediabetes) and can restore normal glucose regulation.[144]

Bile acid sequestrants

In small studies, several newer agents were administered to patients with prediabetes, but not for diabetes prevention. The bile acid sequestrant colesevelam has been shown to improve insulin sensitivity and β-cell function similarly in subjects with prediabetes (IFG) and T2DM.[145] Although the mechanism of action is unknown, the observation that A_{1c} improved after colesevelam treatment in the lipid-lowering trials led to studies of glucose regulation. After demonstration of improvement in oral glucose tolerance, a randomized study was performed with 216 adults with untreated prediabetes. Participants were randomized 1:1 to colesevelam 3.75 g/day or placebo. Treatment with colesevelam was associated with a significant reduction in A_{1c} and a greater number of subjects attaining a normal FPG and an A_{1c} <6.0% compared with placebo.[146] A Hispanic subgroup was analyzed from this study (colesevelam, n=77; placebo, n=76) in whom they found a significant mean reduction in both A_{1c} and FPG levels with colesevelam ($P \leq 0.02$ for both). A FPG level <100 mg/dL was achieved in 44% of colesevelam recipients, compared with 23% of placebo recipients ($P < 0.05$).[147]

Dipeptidyl peptidase-IV (DPP-4) inhibitors

DPP-4 inhibitors, whose primary mechanism of action is enhancement of the activity of endogenous glucagon-like peptide (GLP)-1 by preventing its degradation, improve gly-

cemic control in hyperglycemic patients.[148–150] GLP-1 stimulates insulin secretion and inhibits glucagon secretion, but is not active when the plasma glucose level falls to 60 mg/dL or less, thus DPP-4 inhibitors do not cause hypoglycemia.[151,152] The first evidence regarding the effects of a DPP-4 inhibitor in a prediabetic population was a 12-week, double-blind, randomized, parallel-group study comparing vildagliptin (50 mg once daily) and placebo, conducted in 179 subjects with IGT (2-hour glucose 9.1 mmol/L, A_{1c} 5.9%). The known effects of vildagliptin on incretin levels and islet function in T2DM were reproduced in subjects with IGT, with a 32% reduction in postprandial glucose and no evidence of hypoglycemia or weight gain.[153]

GLP-1 receptor agonists

Subcutaneous injection of native GLP-1 in people with uncontrolled T2DM can reduce both A_{1c} and bodyweight.[154] The mechanism of the weight loss has been proposed as a combination of decreased food intake due to GLP-1 effects on gastrointestinal motility and direct effects of GLP-1 on the central nervous system. These data have led to speculation that GLP-1 treatment of prediabetes could also facilitate weight loss and improve A_{1c}, thereby slowing the progression to T2DM.[155,156] Data from animal models have shown that treatment with the GLP-1 human analog liraglutide can prevent the progression not only from prediabetes to diabetes but also prevent high-risk animals from developing prediabetes. Studies in prediabetic rats have demonstrated that 12 weeks of treatment was associated with restoration of islet structure and reversal of IFG, IGT, abnormal lipid profile, and inflammatory markers.[157] Human studies using exenatide or liraglutide have demonstrated significant weight loss and glucose tolerance improvement in patients with IFG or IGT, with the beneficial effects apparent by 20–24 weeks and, in the case of liraglutide, sustained for as long as 2 years of treatment.[158,159] Additional trials are ongoing in different populations, such as the Effects of Exenatide on Post-Prandial Glucose Excursions and Vascular Health in Obese/Pre-Diabetic Young Adults (Clinical Trials NCT00845559).[160]

Bariatric surgery prevents progression to diabetes

Although this review is focused on lifestyle modification and pharmacologic treatment on the prevention of diabetes, bariatric surgery should be considered as a complement to any pharmacologic agent. Initial retrospective studies have suggested that bariatric surgery prevents progression to T2DM, albeit in low-risk populations.[161–163] While surgery

is not able to "cure" T2DM, some do consider it a near cure, with the marked improvements in A_{1c} accompanied by decreases in number of medications and/or insulin doses.[162] These responses are now referred to as "remission." This benefit is likely to extend to individuals with prediabetes. Bariatric surgery, as compared with usual care, reduces the long-term incidence of T2DM by 78% in obese individuals and by 87% in individuals with IFG.[161] Again, it is not known whether the benefits are merely due to weight loss. The possibility that bariatric surgery has a direct effect on insulin resistance has long been debated due to the observation that insulin requirements decrease dramatically in the first 12–24 hours after surgery, prior to the onset of weight loss, and are more pronounced than benefits observed with typical intra-abdominal surgeries. The type of surgery is also under close scrutiny to determine whether structural alterations in the gastrointestinal anatomy have differential impacts on glucose regulation.[161–163]

Transoral gastroplasty (TOGA) is a safe and less invasive procedure than traditional bariatric surgery. Leccesi et al[164] studied the effects of TOGA on the risk of progression from prediabetes to overt T2DM or on regression from diabetes or prediabetes to a lower risk category. The study enrolled 50 subjects aged 18–60 years with a BMI between 35 and 55 kg/m². TOGA improved glucose disposal, with regression of diabetes to normal glucose tolerance or IGT and regression of IGT and IFG to normal glucose tolerance in half of the cases. Interestingly, regressors showed a much larger increase of GLP-1 levels than progressors.

Other newer agents may be useful in prediabetes

The quick-release formulation of bromocriptine, known commercially as Cycloset® (VeroScience, LLC, Tiverton, RI, USA) (bromocriptine mesylate), also has potential for treating prediabetes, as its unique mechanism of action is mediated through resetting central circadian organization of monoamine neuronal activities, thereby improving the alterations in hepatic glucose production, lipid synthesis, and mobilization associated with obesity and insulin resistance.[165] Bromocriptine is a sympatholytic dopamine D2 receptor agonist that can exert inhibitory effects on serotonin turnover in the central nervous system.[166]

Specifically, bromocriptine reduces ventromedial, arcuate, and paraventricular hypothalamic drive for increased hepatic glucose production, lipid synthesis and mobilization, and insulin resistance.[167] Administration in the early hours of the light cycle prevents or reverses seasonal weight gain, insulin resistance, and hyperinsulinemia, as well as decreases endogenous (hepatic) glucose production in mammals.[168–171] Through improving the underlying disease process of lipotoxicity and insulin resistance, it is likely that quick-release bromocriptine would be beneficial in prediabetes; thus, an intervention trial is warranted with this interesting agent.

Sustained weight loss has been demonstrated to improve β-cell function; therefore, the use of medications to facilitate and, perhaps, maintain weight loss would be expected to improve insulin resistance and preserve or enhance β-cell function. It is not known whether any of the currently available weight loss agents have any intrinsic benefit in preventing the progression from prediabetes to diabetes. The mechanistic data from the available agents, phentermine, topiramate, and lorcaserin, do not suggest a benefit to β-cell function or insulin resistance beyond that of weight loss. However, registration trials are required to assess metabolic parameters so there are data related to the impact on glucose changes in the obese subjects. The impact on glucose control was assessed in a 56-week Phase 3 trial of 2,487 subjects who were overweight or obese (aged 18–70 years), with a BMI of 27–45 kg/m² and two or more comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity). Subjects were randomized to placebo, once-daily phentermine 7.5 mg plus topiramate 46.0 mg, or once-daily phentermine 15.0 mg plus topiramate 92.0 mg in a 2:1:2 ratio in 93 centers in the USA. The combination of phentermine and topiramate, with office-based lifestyle interventions, was associated with a significant decrease in A_{1c} (−0.4%) compared with the control group (−0.1%).[172] These benefits were sustained in the double-blind 52-week extension study, where the annualized incidence rates for progression to T2DM among subjects without diabetes at baseline were 3.7%, 1.7%, and 0.9% in the placebo, 7.5/46 mg, and 15/92 mg treatment groups, respectively. These data indicate a 54% reduction in the progression to T2DM in subjects receiving 7.5/46 mg and a 76% reduction in subjects taking 15/92 mg, compared with placebo.[173] The authors attribute the lower rates of incident diabetes with phentermine plus topiramate to the weight loss, without suggesting a direct effect of the combination of the phentermine plus topiramate.[174,175] Garvey et al[174] recently demonstrated significant weight loss and reduced progression to T2DM in subjects with prediabetes and/or metabolic syndrome at baseline over 108 weeks' treatment with phentermine and topiramate extended-release. Subjects receiving either 7.5 mg of phentermine plus 46.0 mg of

topiramate or 15.0 mg of phentermine plus 92.0 mg of topiramate experienced 10.2% and 12.1% weight loss and a reduction of 70.5% and 78.7% in the incidence rate of T2DM, respectively.[174]

The exact mechanism of action for lorcaserin is not clearly understood, but it is believed to act as an agonist at central serotonin subtype 2C (5-HT2C) receptors located on hypothalamic pro-opiomelanocrotin neurons. Lorcaserin shows high selectivity for the 5-HT2C receptor subtype, with minimal activity at 5-HT2B or 5-HT2A receptor subtypes. Agonism of the 5-HT2C receptor is believed to reduce food intake and increase satiety, leading to weight loss. Earlier anti-obesity agents, such as dexfenfluramine, were withdrawn from the market because of an association with valvular heart disease thought to be caused by agonism at the 5-HT2B receptor. There is no data specifically reporting the impact of lorcaserin on prediabetes. The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) trial showed a statistically significant improvement in FPG and A_{1c} in subjects with T2DM when treated with lorcaserin versus placebo for 52 weeks.[175] The BLOSSOM (Behavioral modification and Lorcaserin Second Study for Obesity Management) and BLOOM trials did show improvements in glucose after 52 and 104 weeks, respectively, of therapy but both specifically excluded people with known T2DM and did not report glucose-related data on prediabetes subgroups.[176,177] Nonetheless, the lifestyle intervention trials have shown that loss of as little as 5%–10% of bodyweight can have beneficial effects on preventing the development of T2DM; thus, one would predict that the weight loss demonstrated with lorcaserin will have a similar beneficial effect.

Conclusion

We are facing a global epidemic of T2DM and obesity. Studies indicate T2DM can be prevented in high-risk individuals through lifestyle modification, pharmacologic interventions, and bariatric surgery. However, the translation of this research to a population level, especially finding the most effective methods of preventing T2DM in various societies and cultural settings is challenging, but is a crucial priority. Public health programs focused on increasing personal awareness of risk, community support and education, and government resources are necessary to slow the progression of prediabetes to T2DM. Importantly, health care systems need to recognize "prediabetes" as a disease and to use this term to promote programs that are culturally and geographically appropriate. Further research is needed to determine how early interventions should be implemented and sustained.

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