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ORIGINAL RESEARCH

Effect of pharmaceutical care interventions on glycemic control in patients with diabetes: a systematic review and meta-analysis

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Purpose: Diabetes is a chronic lifelong condition, and adherence to medications and self-monitoring of blood glucose are challenging for diabetic patients. The dramatic increase in the prevalence of diabetes is largely due to the incidence of type 2 diabetes in low- and middle-income countries (LMIc) besides high-income countries (HIc). We aimed to evaluate whether pharmacist care (PC) service model in LMIc and HIc could improve clinical outcomes in diabetic patients by performing a meta-analysis.

Methods: PubMed, Embase, and ProQuest Dissertations Unlimited Published Literature database were searched to find publications pertaining to pharmacist-led intervention in patients with diabetes. The inclusion criteria were as follows: 1) randomized controlled trials, 2) confirmed diabetic patients (type 1 or type 2), 3) pharmaceutical care intervention by clinical pharmacist or/and multidisciplinary team, and 4) reporting HbA1c at baseline and end of study or the mean change in these values.

Results: A total of 37 articles were included in the meta-analysis. The overall result was significant and in favor of PC intervention on HbA1c change (standard difference in mean values [SDM]: 0.379, 95% CI: 0.208–0.550, $P<0.001$). The stratified meta-analysis showed that PC was significant in both HIc (n=20; SDM: 0.351, 95% CI: 0.207–0.495) and LMIc (n=15; SDM: 0.426, 95% CI: 0.071–0.780). More than 6 months is needed to obtain adequate effects on clinical diabetes parameters.

Conclusion: Our study presented that an adequate duration of pharmacist-led pharmaceutical care was effective in improving HbA1c in patients with diabetes in both LMIc and HIc.

Keywords: pharmacist care, multidisciplinary team care, diabetes, high-income country, low- and middle-income country

Introduction

Diabetes is a serious and chronic disease that can lead to various complications and premature death. According to the "Global Report on Diabetes (2016)" by World Health Organization (WHO), the number of diabetic adults has quadrupled to 422 million since 1980. This recent dramatic rise is largely due to the incidence of type 2 diabetes in low- and middle-income countries (LMIc). In all, 43% of deaths in a total or 3.7 million deaths related to diabetes in 2012 is attributable to higher than optimal blood glucose, and this occurs before the age of 70,[1] which is much shorter than the life expectancy of 81.3 mean years among the Organisation for Economic Co-operation and Development (OECD) countries in 2015.[2] Since diabetes is a chronic lifelong condition, adherence to medications and self-monitoring of blood glucose are quite challenging to the patients. Blood glucose concentration is a sensitive marker

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affected by numerous outer environments such as food intake, exercise, stress and medication.[3] On the contrary, HbA1c concentration in the blood reflects the average blood glucose over the previous 8–12 weeks. The HbA1c level can predict the clinical outcome of microvascular[4,5] and macrovascular complications[6] as well, and the American Diabetes Association (ADA) recommend that HbA1c should be measured at regular intervals in all patients with diabetes.[7] Thus, many researches on diabetes management are using HbA1c as a surrogate marker for clinical outcomes. There have been numerous efforts to implement pharmaceutical care in diabetic patients to improve disease outcomes. Improved management with the consistent support of multidisciplinary pharmaceutical care services can lead to better control of diabetes and fewer complications.[8] For example, in Medication Therapy Management (MTM), a range of services including education, counseling, and assessing each medication and medication-related problems are provided to patients by clinical pharmacists to optimize and improve therapeutic outcomes in the USA.[9] Together with hospital-based clinician-monitored programs, pharmacist-led community/hospital-based pharmaceutical care programs can be designed in an effort to achieve better glycemic, metabolic outcome and blood pressure control in this patient group.[10]

A recent meta-analysis[11] and a systematic review[12] of pharmacist for blood pressure and cardiovascular diseases showed that the implementation of a pharmacist care (PC) model provided improvement in outcomes. The systematic analysis and meta-analysis of PC for diabetic patients showed positive impact on HbA1c outcomes.[13–15] However, recent studies reported no significantly different clinical parameters between the PC group and usual care (UC) group,[16–18] rendering the need to reevaluate PC. Moreover, they did not present the effectiveness of PC in LMIc apart from high-income countries (HIc). Since the 2016 report of WHO revealed a considerable increase in the number of diabetic patients in LMIc, thus we aimed to evaluate whether the PC service model in HIc and LMIc could improve the clinical outcomes of diabetic patients by performing a meta-analysis including the up-to-date studies.

Methods

Search strategy

A systematic review protocol conforming to the Effective Practice and Organization of Care (EPOC) guideline was developed and prepared following the PRISMA recommendations.[19] Electronic databases of PubMed, Embase, and ProQuest Dissertations Unlimited Published Literature database were searched by using the following keywords: "diabetes", "diabetes mellitus", "type one diabetes", "type two diabetes", "diabetes type 1", "diabetes type 2", "community pharmacy", "community pharmacies", "community pharmacist", "community pharmacists", "pharmacy", "pharmacist", "hospital pharmacy", "hospital pharmacist", "hospital pharmacists", "pharmacy services", "pharmacist intervention", "pharmaceutical care", "pharmac*". A manual review was performed to search for unindexed articles in the *Journal of Research in Medical Sciences*, *Journal of American Pharmacists Association* and reference lists of related articles.

Inclusion and exclusion criteria

The literature search was performed to include studies published up to July 27, 2017, by two independent reviewers. Any disagreement was resolved by discussion among the two reviewers and a third researcher. The inclusion criteria for full-text review were as follows: 1) randomized controlled trial (RCT); 2) confirmed adult diabetic patients (type 1 or type 2); 3) pharmaceutical care intervention by clinical pharmacist or/and multidisciplinary team (PC includes working in cooperation with the patient and other health care providers to assess, monitor, initiate, and modify medication use and to provide education service to health care professionals as well as to the patients); and 4) each article should have reported HbA1c or fasting blood glucose (FBG) level at baseline and end of study or the mean change in these values.

The exclusion criteria were as follows: non-English language, editorials, commentaries, narrative reviews, clinical practice guidelines, conference abstracts, and literature not in peer-reviewed journals. The same reviewers independently evaluated the full text of all identified studies in the first stage of screening and resolved any disagreements.

Outcome assessment

HbA1c concentration in the blood reflects the average blood glucose over the previous 8–12 weeks. The HbA1c level can predict the clinical outcome of microvascular[4,5] and macrovascular complications[6] as well, and ADA recommend HbA1c to be measured at regular intervals in all patients with diabetes.[7] Thus, HbA1c has been utilized as an additional stable criterion for assessing glucose control. In this aspect, we chose the difference of HbA1c change and the proportion of patients achieving target HbA1c level ($<7\%$) between two groups as the main outcome measure.

Data extraction

The following information was extracted from the full text of included studies by two independent researchers: first author, year of publication, study type, country of study site, disease type of patients, age, service providers, intervention type, and laboratory data pertaining to HbA1c and the number of patients achieving HbA1c goal. The income levels were searched to pool outcomes by income level using the data from the World Bank Group.[20] The duration of intervention was stratified and designated as 1 (<6 months), 2 (≥6 and <12 months), and 3 (≥12 months).

Quality score assessment

The quality of individual study was assessed by two independent reviewers using the EPOC risk of bias tool. This risk of bias tool is used when the clinical trials involve patient care, educational intervention, patient performance measure, health care quality measure.[21] The standard risk of bias tool includes assessment of domains such as allocation concealment, baseline outcome, baseline characteristics, blinding, and selective reporting.

A domain with a low risk of bias is indicated by "low" and that with a high risk of bias is indicated by "high". If a particular domain has ambiguity or uncertainty due to lack of information, then it is indicated as "unclear".

Statistical analyses

The association between HbA1c levels after PC intervention and clinical outcomes was evaluated quantitatively by meta-analysis. The pooled OR were calculated for the included articles stratified by income status of the countries and duration of follow-up (3–5 months, 6–11 months, and ≥12 months). The primary outcome of this study was to evaluate the association between PC and HbA1c change.

Between-study heterogeneity was assessed by Q-statistic (heterogeneity was considered statistically significant if $P<0.1$)[22] and quantified by I^2 value. Both fixed- and random-effects models were used to combine the aggregate data determined by the I^2 value. When I^2 was >50%, the random-effects model was used for analysis. Potential publication bias was assessed using the Egger's linear regression test.[23]

Statistical analyses were performed using Comprehensive Meta-Analysis (ver 3; Biostat, Inc., Engelwood, NJ, USA) and IBM SPSS (ver 21; IBM Corporation, Armonk, NY, USA). All tests were two sided, and $P<0.05$ was considered as significant unless otherwise specified.

Results

PRISMA flow for study selection

As shown in Figure 1, of the 3,794 publications identified, 35 publications were found eligible for meta-analysis.

Among the identified publications, 3,465 articles were excluded as inappropriate by title and abstract review. In all, 82 articles were eligible for full-text review. After excluding studies with no pharmacist intervention (n=2), inadequate information (n=10), non-RCT studies (n=41), and non-adult studies (n=2), 27 articles were finally selected. Upon searching for the reference review, 10 additional articles were found to be eligible for meta-analysis; therefore finally, 37 studies were included in the meta-analysis.

Overall review

In all, 14 articles were published in the North American region (USA [n=13] and Canada [n=1]), three in the European region (UK, Spain, and Belgium), eight in Asia (Thailand [n=3], Hong Kong, Taiwan, Malaysia, Pakistan, and India), six in the Middle East (Jordan [n=2], Iraq, Iran [n=2], and UAE), three in Brazil, and three in Australia. Brazil, Iran, Iraq, Malaysia, Pakistan, Thailand, Jordan, UAE, and India were classified as LMIc.[20] The intervention period was stratified as follows: intervention period <6 months (n=7), between 6 and 12 months (n=10), and ≥12 months (n=12). All the trials were conducted in ambulatory settings, including private clinic, hospital-based clinic, community pharmacies, and nationwide health care system or regional health care system (Table 1).

All 37 studies included 2,961 PC and 2,899 UC patients. The overall period of pharmacist intervention was mean 9.07 months (SD 5.73) ranging from 3 to 32 months. In 27 studies, >100 diabetic patients were enrolled, and in 15 studies, the follow-up period was ≥12 months. The interventions were given from 2-week to 3-month interval, and several studies did not report the interval. The PC was conducted by pharmacists in 24 studies and MTC in 13 studies. The PC program consisted of information on disease and medications, adherence education, survival skills regarding hypo- and hyperglycemia incidence, and insulin injection skills. The delivery type of education or intervention was face-to-face intervention, telephone counseling, or group appointments, meeting, or education sessions. Adjunctive tools such as booklets, disease or medication information sheets, pillbox, and stickers were provided in many studies (Table 1).

The overall pooled analysis for HbA1c change included 35 articles out of total 37 studies (Table S1). Owing to the

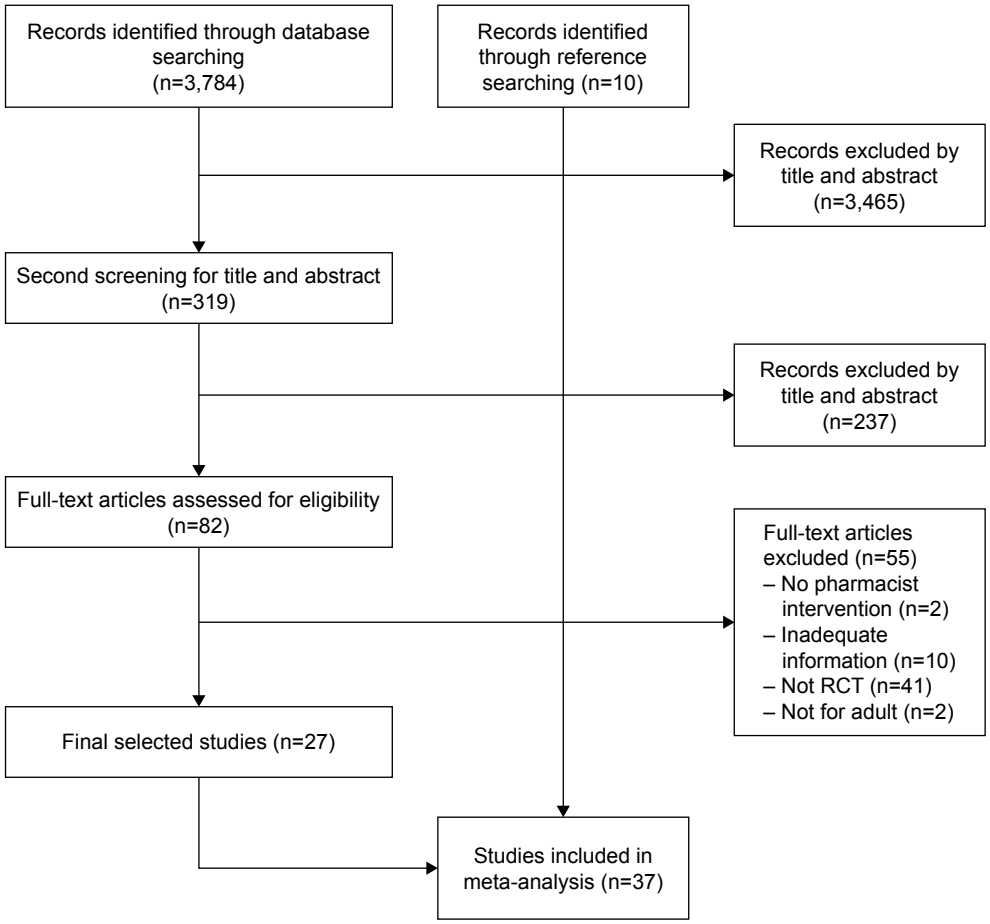

Figure 1 PRISMA flow diagram of selected publications in systematic review and meta-analysis.
Abbreviation: RCT, randomized controlled trial.

Table 1 Characteristics of randomized controlled studies included in the final analysis

Study ID	Country	Patients	PC/UC (n)	Setting	Care initiative	Intervention type	Duration (months)	Clinical outcomes
Jaber 1996[42]	USA	T2DM	17/22	University-affiliated internal medicine outpatient clinic	Pharmacist	Dosage evaluation, patient education, training on hyper- and hypoglycemia, medication counseling, dietary regulation and exercise plan, and self-monitoring of blood glucose	4	HbA1c, FBG
Clifford 2002[43]	Australia	T1DM, T2DM	48/25	Hospital	MTC	Education and a brochure on risk factors, point-of-care cholesterol measurement, referral to their physician, and drug monitoring	6	HbA1c
Raji 2002[44]	USA	T1DM, T2DM	50/56	Veterans health care system	MTC	3.5 day-structured curriculum, disease education, group discussion, lifestyle management by direct counseling or telephone intervention, and newsletter provided	12	HbA1c
Choe 2005[45]	USA	T2DM	29/36	University-affiliated primary care clinic	Pharmacist	Medication review and reconciliation, telephone intervention, lifestyle management, and self-monitoring blood glucose	12	HbA1c

(*Continued*)

Table 1 (*Continued*)

Study ID	Country	Patients	PC/UC (n)	Setting	Care initiative	Intervention type	Duration (months)	Clinical outcomes
Clifford 2005[46]	Australia	T2DM	92/88	Fremantle Diabetes Study	Pharmacist	Bimonthly newsletter, educational pamphlets, pharmacotherapeutic intervention, diet, exercise, and compliance with home blood glucose monitoring	12	HbA1c
Rothman 2005[47]	USA	T2DM	112/105	University of North Carolina General Internal Medicine Practice	Pharmacist	Intensive education and counseling, medication management, and applying evidence-based treatment algorithms	12	HbA1c
Suppapitiporn 2005[48]	Thailand	T2DM	180/180	Hospital	Pharmacist	Patient counseling, drug education, special medication container, and booklet provided	6	HbA1c, FBG
Fornos 2006[49]	Spain	T2DM	56/56	14 community pharmacies	Pharmacist	Pharmacotherapy follow-up program, adherence education, and medication reconciliation	14	HbA1c, FBG
Scott 2006[50]	USA	T2DM	76/73	Community Health Center	MTC	Group session appointment, medication review, aspirin therapy and influenza vaccination education, lifestyle management, and telephone follow-up	9	HbA1c, FBG
Krass 2007[51]	Australia	T2DM	149/140	Quality care pharmacy program affiliated to 56 pharmacies	Pharmacist	Review of self-monitoring of blood glucose, disease, medication, and lifestyle education	6	HbA1c
Phumipamorn 2008[52]	Thailand	T1DM, T2DM	67/68	30-bed community hospital	Pharmacist	Medication adherence, lifestyle management, and leaflet provided	10	HbA1c
Al Mazroui 2008[53]	UAE	T2DM	117/117	Military hospital	MTC	Drug education, lifestyle management, leaflet, and medication reconciliation	12	FBG
Edelman 2010[16]	USA	T1DM, T2DM	133/106	Two VA medical centers	MTC	Group medical clinic participation, disease education, disease, and medication review	12.8	HbA1c
Farsaei 2011[26]	Iran	T2DM	87/87	One outpatient clinic	MTC	Education and telephone counseling	3	HbA1c, FBG
Jameson 2010[18]	USA	T1DM, T2DM	52/51	AHPN	Pharmacist	Individualized education regarding diabetes self-management (diet, exercise, blood glucose level testing, medications, and insulin), early switching to insulin therapy after failure of two oral medications	12	HbA1c
Kirwin 2010[54]	USA	T1DM, T2DM	150/151	Four medical clinics	MTC	Medication review and treatment recommendation letter to physician	10	HbA1c, LDL
Taveira 2010[55]	USA	T2DM	58/51	VA medical center	MTC	Patients' didactic education and behavioral and pharmacological intervention by pharmacist	4	HbA1c
Cohen 2011[56]	USA	T2DM	50/49	VA medical center	MTC	Four once weekly 2-hour sessions of education and behavioral and pharmacologic intervention review	6	HbA1c
Mehuys 2011[57]	Belgium	T2DM	153/135	66 community pharmacies	MTC	Disease education, lifestyle management, medication adherence, and regular checkup reminding	6	HbA1c, FBG

(*Continued*)

Table 1 (*Continued*)

Study ID	Country	Patients	PC/UC (n)	Setting	Care initiative	Intervention type	Duration (months)	Clinical outcomes
Obreli-Neto 2011[27]	Brazil	T1DM, T2DM	97/97	Public primary health care unit	MTC	Group discussion, drug education, lifestyle management, patients' counseling, and medication reconciliation	36	HbA1c, FBG
Simpson 2011[58]	Canada	T2DM	131/129	Five primary care clinics	Pharmacist	Medication review and implementation of guideline concordant recommendations	12	HbA1c
Siriam 2011[59]	India	T2DM	60/60	Multi-specialty tertiary care teaching hospital	Pharmacist	Medication counseling, dietary regulation, exercise, and lifestyle modifications	3	HbA1c, FBG
Ali 2012[60]	UK	T2DM	23/23	Two community pharmacies	Pharmacist	Lifestyle management, medication review, disease education, and medication reconciliation	12	HbA1c
Chan 2012[61]	Hong Kong	T2DM	51/54	250-bed public convalescent hospital	Pharmacist	Disease education, medication adherence, and provided color stickers to identify drugs	9	HbA1c, FBG
Jacobs 2012[62]	USA	T2DM	72/92	Ambulatory general internal medicine setting	Pharmacist	Medication review, physical assessment, patients' counseling, disease education, and lifestyle management	12	HbA1c
Jarab 2012[35]	Jordan	T2DM	85/86	762-bed RMS hospital	Pharmacist	Structured patient education and discussion about type 2 diabetes, risks and types of complications from diabetes, prescribed drug therapy, and proper dosage	6	HbA1c
Kraemer 2011[5]	USA	T1DM, T2DM	36/31	Several employer-based health care plans	Pharmacist	Disease education, patients' counseling, and referral to physician	12	HbA1c, FBG
Mahwi 2013[28]	Iraq	T2DM	62/61	Diabetic center	Pharmacist	Drug therapy problems and compliance by pill count and Morisky–Green test for drug adherence	4	HbA1c, FBG
Mourao 2013[34]	Brazil	T2DM	50/50	Six primary health care units integrated into the Brazilian public health system	Pharmacist	Patient education and/or pharmacotherapy changes	6	HbA1c
Samtia 2013[29]	Pakistan	T2DM	174/168	Diabetes clinics	Pharmacist	Disease education, drug education, and monitoring	5	HbA1c, FBG
O'Connor 2014[63]	USA	T1DM, T2DM	92/103	Kaiser Permanente Health Group	MTC	Protocol-structured telephone call and medication adherence reinforcement method	6	HbA1c
Chung 2014[64]	Thailand	T2DM	120/121	Major teaching hospital	Pharmacist	Medication review, solving drug-related problem, education on diabetes, hypertension, and hyperlipidemia	12	HbA1c, FBG
Cani 2015[31]	Brazil	T2DM	41/37	Teaching hospital	Pharmacist	Individualized pharmaceutical care plan	6	HbA1c
Jahangard-Rafsanjani 2015[32]	Iran	T2DM	51/50	Community pharmacy	Pharmacist	Blood glucose self-monitoring device, special logbook and education pamphlets, and medication reconciliation	5	HbA1c

(*Continued*)

Table 1 (*Continued*)

Study ID	Country	Patients	PC/UC (n)	Setting	Care initiative	Intervention type	Duration (months)	Clinical outcomes
Wishah 2015[30]	Jordan	T2DM	52/54	University hospital	MTC	Structured patients' education and counseling for disease, medication, and lifestyle modification	6	HbA1c, FBG
Chen 2016[65]	Taiwan	T2DM	50/50	Hospital	Pharmacist	Assessment of adherence, pillbox, insulin injection technique, and medication regiment appropriateness (medication reconciliation)	6	HbA1c
Lim 2016[33]	Malaysia	T2DM	39/37	Hospital	Pharmacist	Booklet for disease and medication information, medication counseling, and education	32	HbA1c

Abbreviations: PC/UC, pharmacist care/usual care; T2DM, type 2 diabetes mellitus; FBG, fasting blood glucose; T1DM, type 1 diabetes mellitus; MTC, Multidisciplinary Team Care; VA, Veterans Affairs; AHPN, Advantage Health Physician Network; RMS, royal medical services; LDL, low density lipoprotein.

high I^2 value (89.380), the random-effects model was used. The result was significant and in favor of pharmacist-led intervention on HbA1c change (standard difference in mean values [SDM]: 0.379, 95% CI: 0.208–0.550, P=0.001), indicating the positive effect of pharmacist intervention in the improvement of clinical parameters in diabetes patients. The HbA1c level was 37.9% more reduced in the PC group than in the UC group (Figure 2).

The proportion of patients achieving HbA1c goals was evaluated using eight articles that reported targeted outcomes out of total 37 included studies (Table S2). All the seven studies set the HbA1c target <7%, and the pooled result for the

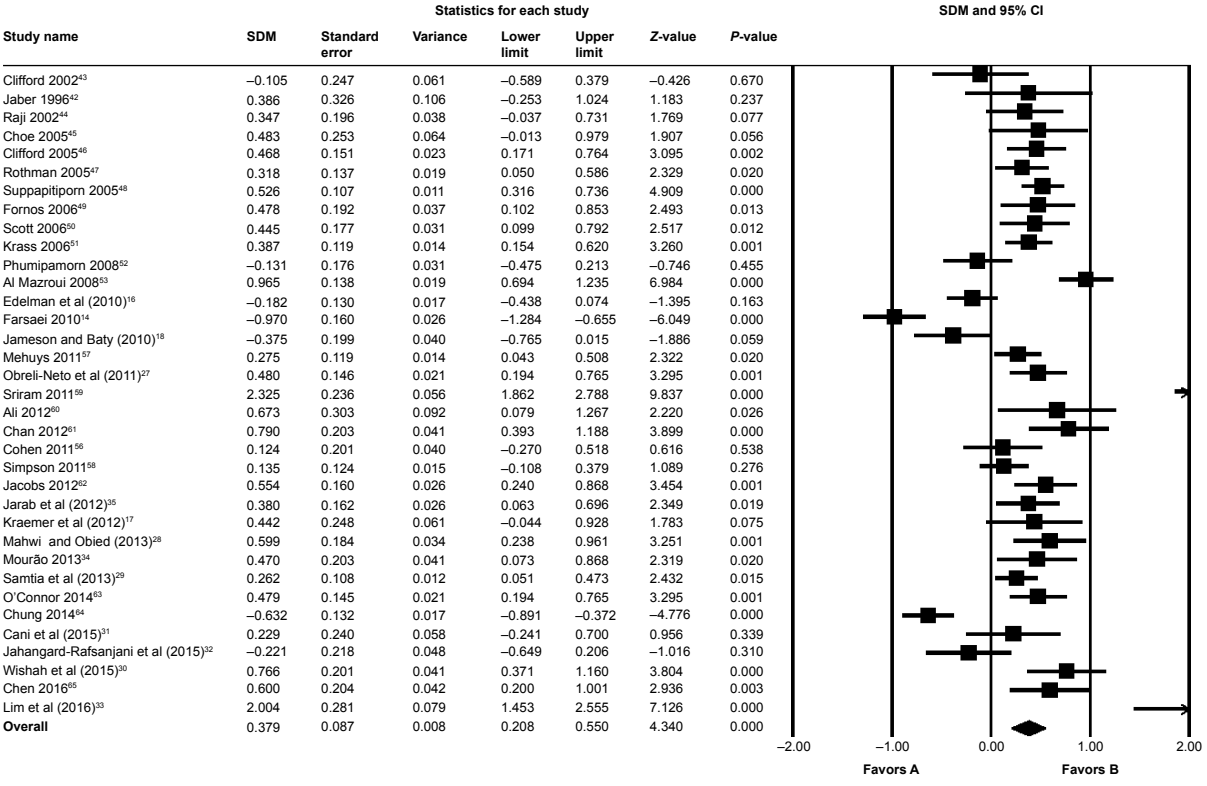

Figure 2 The overall comparison of PC and UC on the improvement of HbA1C level changes.
Abbreviations: PC, pharmacist care; UC, usual care; SDM, standard difference in mean values.

articles was significant and in favor of pharmacist intervention (OR: 2.48, 95% CI: 1.430–4.299, *P*=0.001). Approximately three times more patients achieved their HbA1c goal in the PC group compared to that in the UC group (Figure 3).

Group analysis for income status and intervention period

The stratified meta-analysis showed that PC was significant in both 20 HIc (SDM: 0.351, 95% CI: 0.207–0.495) and 15 LMIc (SDM: 0.426, 95% CI: 0.071–0.780; Figure 4A). The analysis for intervention period showed that interventions <6 months did not affect the clinical parameters of the patient (*P*=0.333). In the second group, 6–12 months of pharmacist intervention showed an improved effect, and the patients exhibited 36.4% more mean HbA1c level changes than the UC group (*P*<0.001). The longest intervention period of ≥12 months exhibited better effect on HbA1c reduction, with 38.8% more change in levels of HbA1c than the UC group (*P*=0.006; Figure 4B).

Risk of bias score assessment by EPOC

The quality score of each study was graded by EPOC risk of bias tool by two independent researchers. As the selected primary literature had a low risk of bias in the domain of baseline outcome measure and characteristics, the baseline characteristics between two groups were similar. The reporting of results section had little risk either. However, the risks on blinding, allocation concealment, and contamination were high due to the nature of educational intervention studies (Table S3).

Publication bias

As widely accepted tools for publication bias, funnel plot visualization and Egger's regression method were used to detect publication bias. Overall, the funnel plot and Egger's regression (*P*=0.183) methods did not detect publication bias (Figure S1).

Discussion

In this study, we found a significant association between pharmacist-led pharmaceutical care and clinical diabetes management. This finding is corroborated by previous meta-analysis and systematic analysis for cardiovascular disease patients.[11,12] Well-trained clinical pharmacists and a medical system utilizing active pharmacist-driven patient care can improve the quality, outcomes, and efficiency of patient management. Because this analysis included 20 studies from HIc and 15 from LMIc, the group analysis by income level showed that PC intervention was helpful in improving clinical outcomes in patients with diabetes in both HIc and LMIc. The positive outcomes observed in LMIc are particularly important considering the recent increase in the number of patients with diabetes and metabolic diseases in LMIc. The rapid spread of Western diet and lifestyle, as well as the improvement of socioeconomic status in LMIc, accelerates the incidence of obesity and chronic metabolic diseases in these countries. However, the introduction of clinical PC, such as MTM or multidisciplinary team care, is relatively rare in LMIc compared to that in HIc. A recent review reported that only 12% of clinical PC service is available for drug monitoring activities in Saudi Arabia.[24] Controlling the glucose levels at a recommended level is a difficult task, and therefore, <57% of these patients achieved control of blood glucose as measured by HbA1c concentrations.[25]

A meta-analysis by Li et al[14] included 14 RCTs and reported higher mean change in HbA1c (0.68) than that in our study (0.370), and another meta-analysis by Poolsup et al[15]

Study name	OR	Lower limit	Upper limit	*Z*-value	*P*-value
Scott 2006[50]	9.450	3.052	29.261	3.895	0.000
Kirwin 2010[54]	1.261	0.795	2.000	0.986	0.324
Taveira 2010[55]	2.390	1.022	5.589	2.009	0.045
Cohen 2011[56]	2.600	1.061	6.369	2.090	0.037
Mehuys 2011[57]	1.112	0.700	1.767	0.450	0.653
Obreli-Neto 2011[27]	23.385	3.062	178.579	3.039	0.002
Chan 2012[61]	7.866	0.396	156.161	1.353	0.176
Jacobs 2012[62]	1.998	0.889	4.490	1.675	0.094
Overall	2.480	1.430	4.299	3.235	0.001

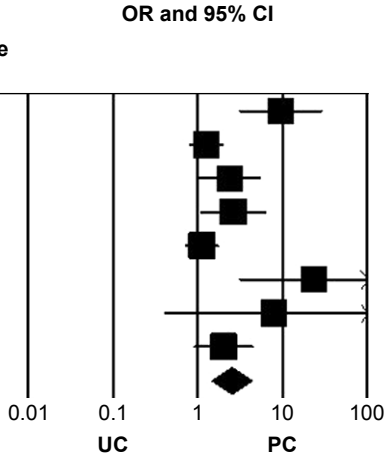

Figure 3 Meta-analysis of proportion of patients achieving target HbA1c levels between the PC and UC groups.
Abbreviations: PC, pharmacist care; UC, usual care.

included 22 RCTs and reported the same mean change of 0.68 between PC and UC groups. We tried not to include heterogeneous population and excluded the research on adolescents and gestational diabetes patients. We excluded some studies that reported inadequate information to incorporate into meta-analysis that were included in the previous meta-analyses, which might be the reason of the different result. Furthermore, we included additionally 10 recently published studies conducted in LMIc,[26–35] and this factor impacted the different results as well.

Generally, the care itself and the social/individual treatment costs of passive medical service administration are challenging. Therefore, more active and interactive multisector collaboration work is essential to manage complicated diseases such as diabetes. In addition, the length of the intervention period is important in achieving adequate effects on clinical parameter improvement.

Another important finding of this study is that the longer intervention period of >6 months showed significant impact on the clinical parameters, while the intervention period of <6 months did not. These factors suggest the need for expanded training in primary care, with at least 6 months of education and intervention, to improve the comprehensiveness and quality of care provided to the growing number of patients with diabetes.

From the aspect of intervention tools, most interventions comprise a face-to-face method between pharmacists and patients, supplemented with leaflets and telephone outreach. The growing information age has enabled the availability of high-technology information and education tool kits. To educate diabetic patients, high-technology investments should be accelerated by country-level funding as suggested by a few studies[36–38] in which the participants showed a considerable decrease in the HbA1c level and several technological

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Group by income-level	Study name	Statistics for each study: SDM	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
HI	Clifford 2002[43]	–0.105	0.247	0.061	–0.589	0.379	–0.426	0.670
HI	Jaber 1996[42]	0.386	0.326	0.106	–0.253	1.024	1.183	0.237
HI	Raji 2002[44]	0.347	0.196	0.038	–0.037	0.731	1.769	0.077
HI	Choe 2005[45]	0.483	0.253	0.064	–0.013	0.979	1.907	0.056
HI	Clifford 2005[46]	0.468	0.151	0.023	0.171	0.764	3.095	0.002
HI	Rothman 2005[47]	0.318	0.137	0.019	0.050	0.586	2.329	0.020
HI	Fornos 2006[49]	0.478	0.192	0.037	0.102	0.853	2.493	0.013
HI	Scott 2006[50]	0.445	0.177	0.031	0.099	0.792	2.517	0.012
HI	Krass 2006[51]	0.387	0.119	0.014	0.154	0.620	3.260	0.001
HI	Al Mazroui 2008[53]	0.965	0.138	0.019	0.694	1.235	6.984	0.000
HI	Edelman 2010[16]	–0.182	0.130	0.017	–0.438	0.074	–1.395	0.163
HI	Jameson and Baty 2010[18]	–0.375	0.199	0.040	–0.765	0.015	–1.886	0.059
HI	Mehuys 2011[57]	0.275	0.119	0.014	0.043	0.508	2.322	0.020
HI	Ali 2012[60]	0.673	0.303	0.092	0.079	1.267	2.220	0.026
HI	Chan 2012[61]	0.790	0.203	0.041	0.393	1.188	3.899	0.000
HI	Cohen 2011[56]	0.124	0.201	0.040	–0.270	0.518	0.616	0.538
HI	Simpson 2011[58]	0.135	0.124	0.015	–0.108	0.379	1.089	0.276
HI	Kraemer 2012[17]	0.442	0.248	0.061	–0.044	0.928	1.783	0.075
HI	O'Connor 2014[63]	0.479	0.145	0.021	0.194	0.765	3.295	0.001
HI	Chen 2016[65]	0.600	0.204	0.042	0.200	1.001	2.936	0.003
HI	**Overall**	0.351	0.074	0.005	0.207	0.495	4.776	0.000
LMI	Suppapitiporn 2005[48]	0.526	0.107	0.011	0.316	0.736	4.909	0.000
LMI	Phumipamorn 2008[52]	–0.131	0.176	0.031	–0.475	0.213	–0.746	0.455
LMI	Farsaei 2011[26]	–0.970	0.160	0.026	–1.284	–0.655	–6.049	0.000
LMI	Obreli-Neto 2011[27]	0.480	0.146	0.021	0.194	0.765	3.295	0.001
LMI	Sriram 2011[59]	2.325	0.236	0.056	1.862	2.788	9.837	0.000
LMI	Jacobs 2012[62]	0.554	0.160	0.026	0.240	0.868	3.454	0.001
LMI	Jarab 2012[35]	0.380	0.162	0.026	0.063	0.696	2.349	0.019
LMI	Mahwi and Obied 2013[28]	0.599	0.184	0.034	0.238	0.961	3.251	0.001
LMI	Mourão 2013[34]	0.470	0.203	0.041	0.073	0.868	2.319	0.020
LMI	Samtia 2013[29]	0.262	0.108	0.012	0.051	0.473	2.432	0.015
LMI	Chung 2014[64]	–0.632	0.132	0.017	–0.891	–0.372	–4.776	0.000
LMI	Cani 2015[31]	0.229	0.240	0.058	–0.241	0.700	0.956	0.339
LMI	Jahangard-Rafsanjani 2015[32]	–0.221	0.218	0.048	–0.649	0.206	–1.016	0.310
LMI	Wishah 2015[30]	0.766	0.201	0.041	0.371	1.160	3.804	0.000
LMI	Lim 2016[33]	2.004	0.281	0.079	1.453	2.555	7.126	0.000
LMI	**Overall**	0.426	0.181	0.033	0.071	0.780	2.356	0.018

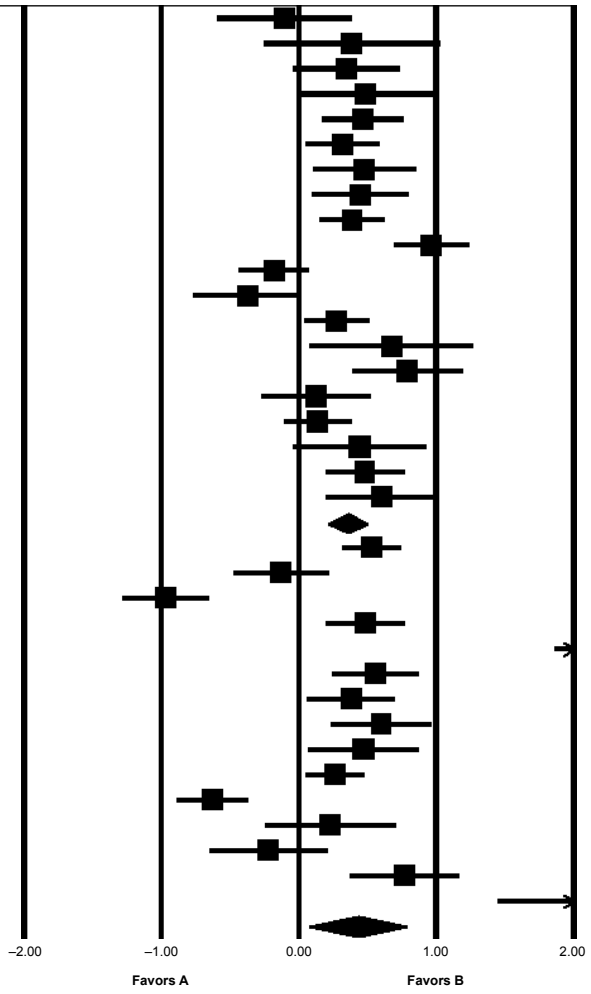

Figure 4 (*Continued*)

B

Group by period	Study name	SDM	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
1.00	Jaber 1996[42]	0.386	0.326	0.106	−0.253	1.024	1.183	0.237
1.00	Farsaei 2011[26]	−0.970	0.160	0.026	−1.284	−0.655	−6.049	0.000
1.00	Sriram 2011[59]	2.325	0.236	0.056	1.862	2.788	9.837	0.000
1.00	Mahwi and Obied 2013[28]	0.599	0.184	0.034	0.238	0.961	3.251	0.001
1.00	Samtia 2013[29]	0.262	0.108	0.012	0.051	0.473	2.432	0.015
1.00	Jahangard-Rafsanjani 2015[32]	−0.221	0.218	0.048	−0.649	0.206	−1.016	0.310
1.00	**Overall**	0.388	0.401	0.161	−0.397	1.174	0.969	0.333
2.00	Clifford 2002[43]	−0.105	0.247	0.061	−0.589	0.379	−0.426	0.670
2.00	Suppapitiporn 2005[48]	0.526	0.107	0.011	0.316	0.736	4.909	0.000
2.00	Scott 2006[50]	0.445	0.177	0.031	0.099	0.792	2.517	0.012
2.00	Krass 2006[51]	0.387	0.119	0.014	0.154	0.620	3.260	0.001
2.00	Phumipamorn 2008[52]	−0.131	0.176	0.031	−0.475	0.213	0.746	0.455
2.00	Mehuys 2011[57]	0.275	0.119	0.014	0.043	0.508	2.322	0.020
2.00	Chan 2012[61]	0.790	0.203	0.041	0.393	1.188	3.899	0.000
2.00	Cohen 2011[56]	0.124	0.201	0.040	−0.270	0.518	0.616	0.538
2.00	Jarab 1996[42]	0.380	0.162	0.026	0.063	0.696	2.349	0.019
2.00	Mourão 2013[34]	0.470	0.203	0.041	0.073	0.868	2.319	0.020
2.00	O'Connor 2014[63]	0.479	0.145	0.021	0.194	0.765	3.295	0.001
2.00	Cani 2015[31]	0.229	0.240	0.058	−0.241	0.700	0.956	0.339
2.00	Wishah 2015[30]	0.766	0.201	0.041	0.371	1.160	3.804	0.000
2.00	Chen 2016[65]	0.600	0.204	0.042	0.200	1.001	2.936	0.003
2.00	**Overall**	0.384	0.065	0.004	0.257	0.510	5.946	0.000
3.00	Raji 2002[44]	0.347	0.196	0.038	−0.037	0.731	1.769	0.077
3.00	Choe 2005[45]	0.483	0.253	0.064	−0.013	0.979	1.907	0.056
3.00	Clifford 2005[46]	0.468	0.151	0.023	0.171	0.764	3.095	0.002
3.00	Rothman 2005[47]	0.318	0.137	0.019	0.050	0.586	2.329	0.020
3.00	Fornos 2006[49]	0.478	0.192	0.037	0.102	0.853	2.493	0.013
3.00	Al Mazroui 2008[53]	0.965	0.138	0.019	0.694	1.235	6.984	0.000
3.00	Edelman 2010[16]	−0.182	0.130	0.017	−0.438	0.074	−1.395	0.163
3.00	Jameson and Baty 2010[18]	−0.375	0.199	0.040	−0.765	0.015	−1.886	0.059
3.00	Obreli-Neto 2011[27]	0.480	0.146	0.021	0.194	0.765	3.295	0.001
3.00	Ali 2012[60]	0.673	0.303	0.092	0.079	1.267	2.220	0.026
3.00	Simpson 2011[58]	0.135	0.124	0.015	−0.108	0.379	1.089	0.276
3.00	Jarab 2012[35]	0.554	0.160	0.026	0.240	0.868	3.454	0.001
3.00	Kraemer 2012[17]	0.442	0.248	0.061	−0.044	0.928	1.783	0.075
3.00	Chung 2014[64]	−0.632	0.132	0.017	−0.891	−0.372	−4.776	0.000
3.00	Lim 2016[33]	2.004	0.281	0.079	1.453	2.555	7.126	0.000
3.00	**Overall**	0.388	0.140	0.020	0.113	0.663	2.767	0.006

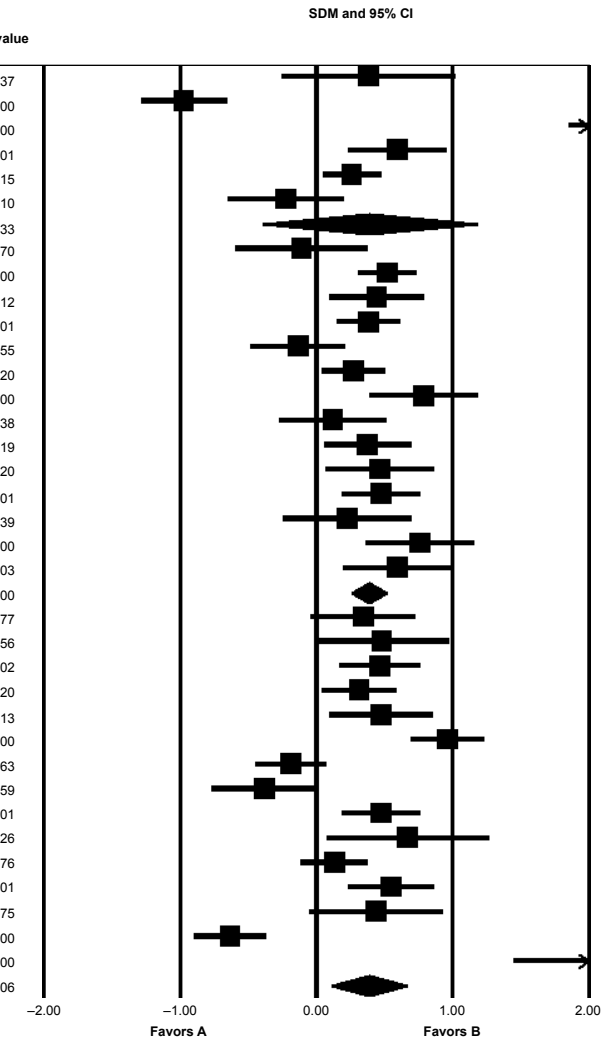

Figure 4 Effect of PC and UC in the improvement of HbA1C levels stratified by income level (**A**) and intervention period (**B**).
Abbreviations: PC, pharmacist care; UC, usual care; SDM, standard difference in mean values.

suggestions were provided. The technologies for health care providers include electronic database identifying and tracking patients and computer software designed for clinical decision support to the providers and telemedicine and telecare services, which currently equipped in HIc widely. Specific tool for patients focuses on the self-management skill improvement by the internet-, telephone- and mobile-based tools. If PC service model incorporates these high technologies into the PC, the care can produce much better clinical outcomes. Since most of the HIc have already adopted or are adopting pharmacist-led pharmaceutical care, the results of this study can encourage the utilization of pharmaceutical care in LMIc. A trend was observed in the following LMIc studies conducted in recent years: Obreli-Neto et al,[27] 2011 (Brazil); Mahwi et al,[28] 2013 (Iraq); Samtia et al,[29] 2013 (Pakistan); Cani et al,[31] 2015 (Brazil); Jahangard-Rafsanjani et al,[32] 2015 (Iran); Wishah et al,[30] 2015 (Jordan); and Lim et al,[33] 2016 (Malaysia), except for Jahangard-Rafsanjani et al,[32] 2015 (Iran) and Wishah et al,[30] 2015 (Jordan), in that all the studies showed promising outcomes for pharmacist-led pharmaceutical care strategy in diabetes care in LMIc. A study evaluating the clinical outcome of blood pressure control reported that after stopping the PC, patient behavior returned to pre-intervention level, meaning consistent PC care is needed to better contribute to patients' clinical outcome.[39]

There are some limitations to our study. The risk of bias evaluated by EPOC guideline showed that some of the included publications lack methodical robust in blinding, allocation concealment, and reporting of contaminations. These factors can be considered in future clinical studies to make the results

more reliable. The big heterogeneity of included studies is another limitation of this study. This heterogeneity is not from the clinical factor but is derived from statistical or unexplainable factors, so we adopted the random-effects model into the meta-analysis by using a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity (I^2). This model sets an assumption that the effects being estimated in the different studies are not identical but follow some distribution. Even though the random-effects model confronts some criticism but simulations have proven that this method is relatively robust even under wide range of distributional assumptions, both in estimating heterogeneity[40] and calculating an overall effect size.[41] Thus, by using random-effects model in our analysis, the heterogeneity of included studies has been overcome in our research.

Conclusion

Clinical pharmacists can make a comparative evaluation of medications based on sound knowledge of medications. The multitasking of clinical pharmacists, which includes healthy communication with health care workers and active interaction with patients, can lead to adherence to clinical therapeutic guidelines and medications. Pharmacist-led pharmaceutical care is a robust health care strategy maximizing therapeutic efficacy and improving lifelong care in diabetes patients in both HIc and LMIc.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 The changes in HbA1C between PC group and UC group

Study ID	Intervention group		Control group		Sample size		*P*-value
	Pre	Post	Pre	Post	PC	UC	
Jaber 1996[12]	11.5±2.9	9.2±2.1	12.2±3.5	12.1±3.7	17	22	0.003
Clifford 2002[13]	8.4±1.4	8.2±1.5	8.5±1.6	8.1±1.6	48	25	>0.05
Raji 2002[14]	9.9±1.3	8±1.4	9.8±1.2	8.6±1.8	50	56	0.03
Choe 2005[15]	10.1±1.8	8±1.4	10.2±1.7	9.3±2.1	29	36	0.03
Clifford 2005[16]	–0.5 (–0.7 to –0.3)		0 (–0.2 to 0.2)		92	88	0.002
Rothman 2005[17]	0.8 (0–1.7%)				112	105	0.05
Suppapitiporn 2005[18]	8.16±1.44	7.91±1.27	8.01±1.51	8.8±1.36	180	180	0.001
Fornos 2006[19]	8.4±1.8	7.9±1.7	7.8±1.7	8.5±1.9	56	56	0.001
Scott 2006[20]	8.8±1.72	7.08±1.72	8.7±0.7	8±0.7	64	67	0.012
Krass 2007[21]	8.9±1.4	7.9±1.2	8.3±1.3	8.0±1.2	125	107	<0.01
Phumipamorn 2008[22]	8.7±1.5	7.9±1.4	8.7±1.6	8.1±1.9	63	67	0.56
Al Mazroui 2009[23]	8.5 (8.3–8.7)	6.9 (6.7–7.1)	8.4 (8.2–8.6)	8.3 (8.1–8.5)	117	117	0.001
Edelman 2010[1]	9.2	8.3	9.2	8.6	133	106	0.159
	–0.33 (–0.80 to 0.13)						
Farsaei 2010[24]	9.3±1.7	7.5±1.6	8.9±1.1	9.0±1.2	87	87	>0.05
Jameson 2010[25]	–1.5 (–0.03 to –2.68)		–0.40 (0.5 to –2.10)		52	51	0.06
Cohen 2011[26]	–0.41 (–0.74 to –0.07)		–0.20 (–0.61 to 0.21)		50	49	0.028
Mehuys 2011[27]	7.7±1.7	7.1±1.1	7.3±1.2	7.2±1	153	135	0.009
Obreli-Neto 2011[3]	–0.7 (–0.9 to 0.5)		0.0 (–0.1 to 0.1)		97	97	0.001
Simpson 2011[28]	–0.15 (–0.36 to 0.05)		0.03 (–0.22 to 0.28)		131	129	<0.05
Siriam 2011[29]	8.44±0.29	6.73±0.21	9.03±0.46	8.3±0.16	60	60	0.010
Ali 2012[30]	8.2±1.65	6.6±0.59	8.1±0.97	7.5±0.64	23	23	0.001
Chan 2012[31]	–1.57%+1.50%		–0.40%+1.19%		51	54	<0.00
Jacobs 2012[32]	9.5±1.1	7.7±1.3	9.2±1	8.4±1.6	72	92	0.003
Jarab 2012[4]	–0.8 (–1.6 to 0.1)		0.1 (–0.4 to 0.7)		77	79	0.019
Kraemer 2012[5]	7.28	6.78	7.38	7.22	36	31	0.0757
	–0.5 (change in mean values)		–0.16 (change in mean values)				
Mahwi 2013[6]	11.53±1.83	9.2±2	9.97±2.75	9.5±2.1	62	61	0.001
Mourao 2013[33]	–0.6 (–1.1 to –0.02)		0.7 (0.2–1.3)		50	50	0.001
Samtia 2013[7]	8.51±1.62	7.5±1.26	8.54±1.55	8.08±1.49	178	170	0.001
O'Connor 2014[34]	–0.9±1.85		–1.08±1.78		92	103	0.001
Cani 2015[8]	9.78±1.55	9.21±1.41	9.61±1.38	9.53±1.68	34	36	0.001
Jahangard-Rafsanjani 2015[9]	7.6±1.6	6.6±1.5	7.5±1.9	7.0±1.7	51	50	0.09
Wishah 2015[10]	8.9±1.6	7.2±0.9	8.2±1.3	7.9±1.3	52	54	>0.05
Chen 2016[35]	9.22±1.7	8.39±1.2	8.94±1.5	9.37±1.5	50	50	0.002
Lim 2016[11]	10.11±0.26	9.21±0.27	9.71±0.34	9.63±0.29	39	37	0.001

Abbreviations: PC, pharmacist care; UC, usual care.

Table S2 Proportion of patients achieving HbA1c goal between PC group and UC group

Study ID	Goal	Intervention group		Control group	
		Total (n)	Event (n)	Total (n)	Event (n)
Scott 2006[20]	A1C<7%	64	24	67	4
Kirwin 2010[36]	A1C<7%	150	65	151	57
Taveira 2010[37]	A1C<7%	58	23	51	11
Cohen 2011[26]	A1C<7%	50	20	49	10
Mehuys 2011[27]	A1C<7%	153	80	135	67
Obreli-Neto 2011[3]	A1C<7%	97	19	97	1
Chan 2012[31]	A1C<7%	51	3	54	0
Jacobs 2012[38]	A1C<7%	55	19	67	14

Abbreviations: PC, pharmacist care; UC, usual care.

Table S3 Quality check for included studies (randomized controlled studies) by EPOC risk of bias

Study ID	Sequence generation	Allocation concealment	Baseline outcome measurements	Baseline characteristics	Incomplete outcome data	Blinding of participants, personnel	Protection against contamination	Selective outcome reporting	Other sources of bias
Jaber 1996[12]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear
Clifford 2002[13]	Low	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear
Raji 2002[14]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear
Choe 2005[15]	Low	Unclear	Low	Low	Low	High	Low	Low	Unclear
Clifford 2005[16]	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Unclear
Rothman 2005[17]	Low	Low	Low	Low	Low	Unclear	Low	Low	Unclear
Suppapitiporn 2005[18]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear
Fornos 2006[19]	Low	Unclear	Low	Low	Low	High	Low	Unclear	Unclear
Scott 2006[20]	Low	Unclear	Low	Low	Low	High	Low	Unclear	Unclear
Krass 2007[21]	Unclear	Unclear	Low	Low	Low	High	Low	Low	Unclear
Phumipamorn 2008[22]	Low	High	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Al Mazroui 2009[23]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Edelman 2010[1]	Low	Unclear	Low	Low	Unclear	High	Low	Low	Unclear
Farsaei 2010[24]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Jameson 2010[2]	Low	Low	Low	Low	Low	High	Unclear	Low	Unclear
Kirwin 2010[36]	Unclear	Unclear	High	Low	Unclear	Unclear	High	High	Unclear
Taveira 2010[37]	Low	Unclear	High	High	Unclear	Unclear	Unclear	High	Unclear
Cohen 2011[26]	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low	Unclear
Mehuys 2011[27]	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Obreli-Neto 2011[3]	Low	Unclear	Low	Low	High	High	Unclear	Low	Unclear
Simpson 2011[28]	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Low
Siriam 2011[29]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear
Ali 2012[30]	Low	Low	Low	Low	Low	Unclear	Low	Low	Unclear
Chan 2012[31]	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Jacobs 2012[32]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Jarab 2012[4]	Low	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear
Kraemer 2012[5]	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Mahwi 2013[6]	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Mourao 2013[33]	Low	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
Samtia 2013[7]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Chung 2014[39]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear
O'Connor 2014[34]	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Cani 2015[8]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear
Jahangard-Rafsanjani 2015[9]	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Wishah 2015[10]	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Chen 2016[35]	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Lim 2016[11]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear

Abbreviation: EPOC, Effective Practice and Organization of Care.

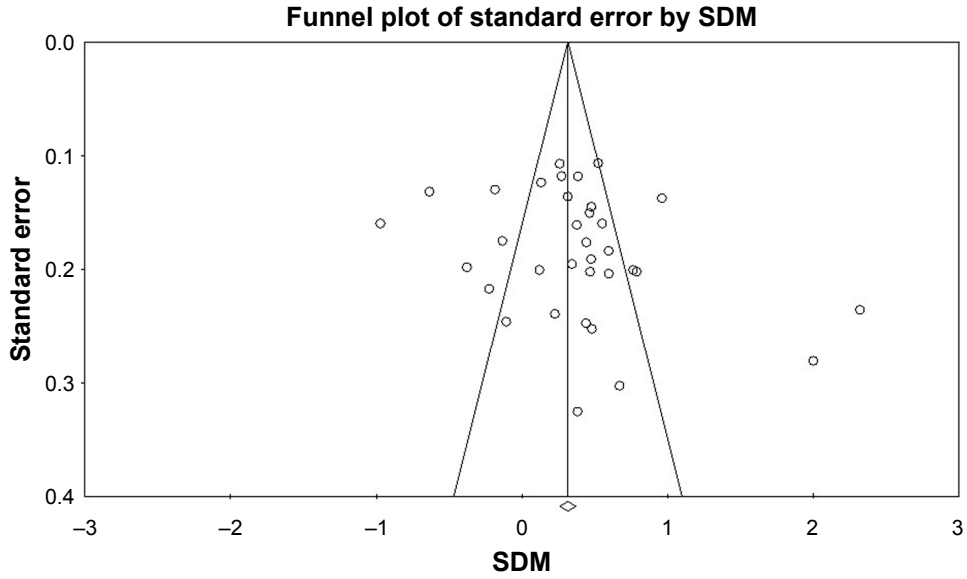

Figure S1 Publication bias visualized by funnel plot.
Abbreviation: SDM, standard difference in mean values.

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