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Clinical and humanistic outcomes of pharmaceutical care interventions in diabetes mellitus: a systematic review and meta-analysis

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ABSTRACT

Background: Diabetes mellitus is a chronic disease for which life-long medications and care are needed. Effectiveness of care is related to good glycemic control, which is desired to forestall complications.

Objective: This study evaluated the effectiveness of pharmaceutical care (PC) services provided by pharmacists in improving clinical and humanistic outcomes in diabetes mellitus patients.

Method: Five databases (PubMed/Medline, Embase, Scopus, Cochrane Central Register of Control Trials and Google Scholar) were systematically searched for randomized controlled trials (RCTs) reported in English using free text and medical subject headings keywords. Studies which had PC intervention arm, a control group, type1 and type 2 diabetes mellitus patients; clinical and/or humanistic outcomes were included. For meta-analysis, standard mean difference evaluated with random effect model at $P<0.05$ was reported. Significant heterogeneity was further evaluated with sensitivity and subgroup analyses.

Results: A total of 41 RCTs with 7,448 patients were eligible out of 1222 citations. PC intervention significantly lowered glycosylated hemoglobin, fasting blood glucose, systolic blood pressure, diastolic blood pressure, total cholesterol, and low density lipoprotein cholesterol ($P < 0.05$), with significant heterogeneity. PC intervention also improved self-care but medication adherence, disease knowledge and quality of life were not improved. PC services offered (patient education, identification and resolution of drug therapy problems, and pharmacotherapy evaluation) were not uniform across the studies.

Conclusion: The review and meta-analysis showed that PC intervention is of great benefit to improve most clinical outcomes which may result in better disease management. A call is however made for standardized pharmaceutical care intervention.

Keywords: Pharmaceutical care, diabetes mellitus, HbA1c, fasting blood glucose, quality of life, adherence

Résultats cliniques et humanistes des interventions de prise en charge pharmaceutique du diabète sucré : examen systématique et méta-analyse

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RESUME

Contexte : Le diabète sucré est une maladie chronique pour laquelle des médicaments et des soins à vie sont nécessaires. L'efficacité des soins est liée à un bon contrôle glycémique, qui est souhaitable pour prévenir les complications.

Objectif : Ainsi, cette étude a évalué l'efficacité des services de soins pharmaceutiques fournis par les pharmaciens pour améliorer les résultats cliniques et humains des patients atteints de diabète sucré.

Méthode : Des recherches systématiques dans cinq bases de données (PubMed/Medline, Embase, Scopus, Registre central des essais de contrôle de Cochrane et Google Scholar) ont visé les essais contrôlés randomisés (ECR) rapportés en anglais à l'aide de mots-clés en texte libre et médical. Les études portant sur le groupe d'intervention PC, un groupe témoin, des patients atteints de diabète sucré de type 1 et de type 2; les résultats cliniques et / ou humanistes ont été inclus. Pour la méta-analyse, la différence moyenne standard évaluée avec un modèle à effet aléatoire à $p < 0,05$ a été rapportée. Une hétérogénéité significative a ensuite été évaluée avec des analyses de sensibilité et des sous-groupes.

Résultats : Un total de 41 ECR avec 7 448 patients ont été éligibles sur 1222 citations. L'intervention du PC a abaissé de manière significative l'hémoglobine glycosylée, la glycémie à jeun, la pression artérielle systolique, la pression artérielle diastolique, le cholestérol total et le cholestérol des lipoprotéines de basse densité ($P < 0,05$), avec une hétérogénéité significative. L'intervention du PC a également amélioré les soins personnels, mais l'observance du traitement, les connaissances sur la maladie et la qualité de vie ne se sont pas améliorées. Les services PC proposés (éducation des patients, identification et résolution des problèmes de pharmacothérapie, et évaluation de la pharmacothérapie) n'étaient pas uniformes dans toutes les études.

Conclusion : La revue et la méta-analyse ont montré que l'intervention de la PC, telle qu'elle était administrée, était très utile pour améliorer la plupart des résultats cliniques, ce qui pourrait entraîner une meilleure gestion de la maladie. Un appel est toutefois lancé pour une intervention de soins pharmaceutiques standardisée.

Mots-clés : soins pharmaceutiques, diabète sucré, HbA1c, glycémie à jeun, qualité de vie, adhérence

INTRODUCTION

Diabetes mellitus is a chronic and complex lifelong disease, which requires long term care. According to the Global Report on Diabetes (2018) by World Health Organization,[1] diabetes was the seventh leading cause of death in 2016. Global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014.[1]

As with most chronic diseases, diabetes mellitus patients tend to have problems with adherence. Adherence with medication, diet, and exercise, and blood glucose self–monitoring is quite challenging for most patients with diabetes mellitus,[2] and may result in poor glycemic control. This sometimes may led to treatment failure and complications which impacts on morbidity and mortality. Poor glycemic control has been linked to the development of hyperlipidemia and hypertension.[3] Thus, the management of diabetes mellitus also takes into consideration these comorbidities and other risk factors such as obesity. The presence of these comorbidities and modifiable risk factors have been shown to speed up the development of microvascular and macrovascular complications in uncontrolled diabetes.[4]

Tight glycemic control is critical in the management of diabetes mellitus. This is the reason why the American Diabetes Association recommended regular check-up of HbA1c, a parameter that indicates glycemic control over a period of three months, to forestall the development of microvascular and macrovascular complications.[5] Thus, HbA1c is used as a surrogate marker in several studies on diabetes mellitus and to predict clinical outcome of microvascular[4, 6–10] and macrovascular complications.[4, 10] It has also been frequently employed as the primary clinical outcome in most systematic reviews and meta-analyses.[11,12]

Different types of intervention models have been used to improve economic, clinical and humanistic outcomes of the management of diabetes mellitus.[13, 14] Generally, incorporation of pharmaceutical care into patients' disease management has been declared to lead to better outcomes of the disease.[15–18] Usually, diabetes mellitus patients are managed by multidisciplinary team especially in developed health care system.[19] Several reports have laid credence to the involvement of clinical pharmacists either in hospitals or community settings in providing extra care in the form of pharmaceutical care for these patients.[20–23] Most pharmaceutical care intervention studies on diabetes mellitus patients evaluated HbA1c, fasting blood glucose (FBG), lipid profile and blood pressure as the clinical outcomes.[7, 8, 24, 25] Few examined humanistic and economic outcomes.[6, 26] Despite these available intervention studies most systematic reviews and meta-analysis only reported HbA1c as the clinical outcome. Because the presence of comorbid factors like hyperlipidemia and hypertension can complicate the management of diabetes mellitus, and if present, may increase the chances of microvascular and macrovascular complication, we therefore undertook this systematic review and meta-analysis. We synthesized the effect of pharmaceutical care interventions on the management of diabetes mellitus by evaluating the clinical outcomes (HbA1c, FBG, systolic and diastolic blood pressure, total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol) and humanistic outcomes (diabetes knowledge, self-care and quality of life) when compared with usual care.

METHODS

Search strategy

Literature search was conducted using the following databases: Pubmed/Medline, Scopus, Embase, Cochrane Central Register of Control Trials, and Google Scholar. These databases were comprehensively and systematically searched from inception to 04 December 2018. Medical subject headings (MeSH) keywords and other relevant keywords used were pharmaceutical care, diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, pharmacist, clinical outcomes, humanistic outcomes, and outcome assessment (Health care). For example, the search strategy used on Pubmed was ("Pharmaceutical Services"[MeSH] AND "Diabetes Mellitus"[MeSH]) AND "Outcome Assessment (Health Care)"[MeSH]). The search strategies were limited to randomized controlled trial (RCT) articles written in English language. References of eligible articles were searched for relevant articles, which might not have been previously identified.

Eligibility criteria

Articles were selected if they were RCTs, participants were type1 and/or type 2 diabetes mellitus patients, a pharmaceutical care intervention group prominently managed by a pharmacist, a control group which received usual care for diabetes mellitus patients, a minimum of three months study duration with reported mean and standard deviation or number of events for the measured primary and secondary outcomes. Studies were excluded if they were non-randomized controlled trials, if the pharmaceutical care

intervention group was managed by non-pharmacist, or the articles were commentaries, conference abstracts, reviews, meta-analysis, and editorials.

Outcomes measured

Primary outcomes reported for this systematic review and meta-analysis were clinical outcomes such as glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG) and Adherence (medication, exercise and diet). The secondary clinical outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDLc), and low density lipoprotein cholesterol (LDLc). Secondary humanistic outcomes included self-care, quality of life and patients' diabetes knowledge

Data extraction

Three authors SJS, ASW and FTO independently screened the articles for duplicates and title relevance. Abstracts of relevant articles were assessed using the inclusion criteria. Full texts of eligible articles were further screened and their references examined for potentially relevant articles. At each stage, discrepancies were resolved by all the authors in agreement. Study characteristics extracted from eligible studies included first author's name, year of publication, study type, country of study, site of study, diabetes type, age of participants, service providers, pharmaceutical care intervention type, clinical and humanistic parameters measured, and number of participants in the intervention and control groups. Mean and standard deviations and number of events were extracted as data endpoints for continuous and dichotomous outcomes, respectively, using standardized spreadsheets in Microsoft Excel (Windows 10).

Quality assessment

The quality of each included RCT was assessed using the Cochrane Collaboration tool by two authors SJS and FTO. Any disagreement was resolved by the third author ASW. The risk of biases assessed for each article were selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, and reporting bias. Each risk of bias was rated as “low risk”, “unclear risk”, and “high risk” according to Cochrane handbook. For quality assessment score, “low risk” was assigned a score of 1 while “unclear risk” and “high risk” were assigned zero. Articles with quality assessment score of 0 - 3 points out of the possible 6 points were adjudged to be “low quality” studies, articles with quality of assessment score of 4 to 5 were described as “moderate quality” studies while those with 6 points were said to be “high quality” studies.[11]

Quality of evidence of outcomes

Quality of evidence for each outcome reported in the included articles was graded as “high” (confident that the true effect is close to the estimate), “moderate” (moderately confident in the effect estimate but may be substantially different), “low” (confidence in the effect estimate is limited) or “very low” (very little confidence in the effect estimate) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and GRADEprofiler software (version 3.6.1, McMaster University and Evidence Prime Inc., Hamilton, Ontario, Canada, 2011). In grading the quality of evidence for each outcome, all the authors, SJS, ASW and FTO unanimously downgraded evidence based on risk of bias, inconsistency, imprecision, indirectness and publication bias. The quality of evidence for the studies were upgraded based on large effect, plausible confounding which would change the effect and dose-response gradient.[27, 28]

Data analyses

Data from included RCTs were pooled and analyzed with Review Manager (RevMan) (version 5.3.5 Copenhagen Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Continuous data were analyzed with inverse variance method using random effects model and effect estimate expressed as standard mean difference (SMD) with 95% confidence interval (CI). Dichotomous data were analyzed with Mantel-Haenszel method using random effects model and effect estimate stated as risk ratios with 95% CI. A $P<0.05$ was considered statistically significant.

Evidence of heterogeneity was determined with Cochrane's heterogeneity statistics (Q-statistics) and expressed as I^2. A $P<0.10$ for heterogeneity was considered significant and heterogeneity was further categorized as low heterogeneity ($I^2 < 25\%$), moderate heterogeneity ($I^2 >25\%$ and $\leq 50\%$) and high heterogeneity ($I^2 > 50\%$).[29] Sources of heterogeneity in the meta-analysis were investigated as publication bias visually with funnel plot. Asymmetric shape of the funnel plot indicates publication bias.

All qualified studies with mean, standard deviation (SD) and number of events were included in the meta-analysis. Studies without these data or those with data expressed as mean difference with SD, or median and

interquartile range for each of the measured outcomes were excluded from meta-analysis. Adherence in the form of diet, medical tests, exercise and clinic attendance, and self-care outcomes were described in the narrative form. Though similar data end-points were used in the RCTs reporting these outcomes, different scales were used in some of the studies to assess the outcomes. Thus, they could not be pooled for meta-analysis.

Sensitivity and subgroup analyses

Sensitivity and subgroup analyses were performed to determine the robustness of the meta-analysis. For sensitivity analyses, the effect estimate for each outcome was compared using random and fixed-effect models and study omissions. Subgroup analyses were carried out comparing included studies on the basis of length of study (≤ 6 months and > 6 months), sample size (n ≤ 150 and n >150), and country of study (developing and developed countries).

RESULTS

Study selection

A total of 1222 citations were recovered from the five databases searched, and 14 articles from references of eligible full text articles. After the removal of duplicate citations and irrelevant titles, 143 article abstracts were reviewed for the inclusion criteria. After full-text review of 58 articles emanating from the abstract screening, 41 full-text articles were eligible for inclusion in the systematic review and meta-analysis (Figure 1). The list of articles not included in the meta-analysis and the outcomes affected as described under data analyses is shown in Table 1.

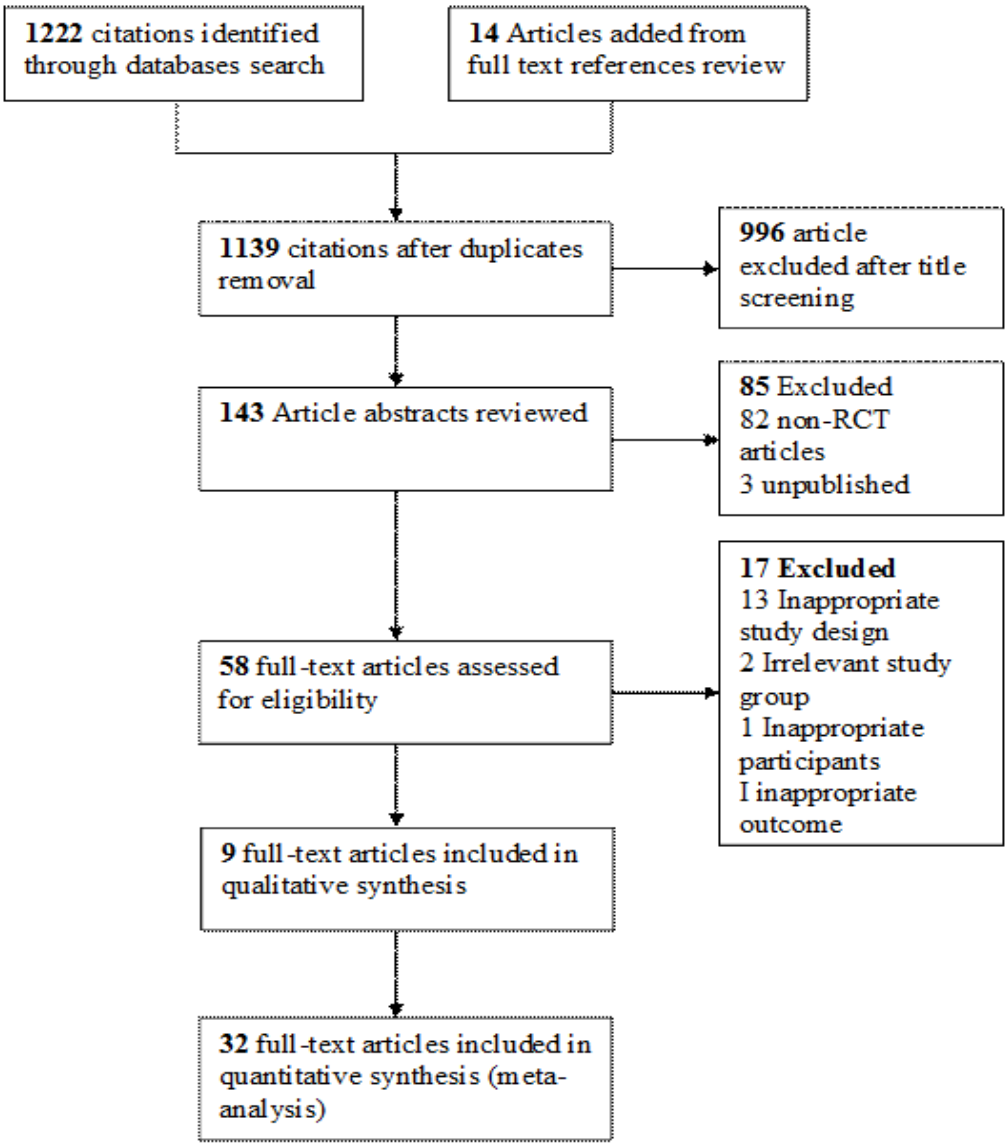

Figure 1: PRISMA flow diagram for the systematic review and meta-analysis.

Table 1: Outcomes with missing data for meta-analysis from included articles

Study	Outcomes without mean ± standard deviation for specific articles									
	HbA1c	FBG	SBP	DBP	TC	TG	HDLc	LDLc	Med Adh	Q of life
Aguiar 2016[11]		-	√	√	-	-	-	√	√	-
Al Mazroui 2009[3]	√	√	√	√	√	√	√	√	-	-
Chan 2012[30]	√	-	√	√	√	√	√	√	-	-
Clifford 2005[31]	√	√	√	√	√	√	√	-	-	-
Guirguis 2001[32]	√	-	-	-	-	-	-	-	-	-
Jaber 1996[33]	-	-	-	-	√	√	√	√	-	√
Jameson 2010[24]	√	-	-	-	-	-	-	-	-	-
Jarab 2012[34]	√	√	√	√	√	√	√	√	-	-
Kandasamy 2017[35]	-	-	-	-	-	-	-	-	-	√
Lim 2016[9]	-	-	-	-	√	√	√	√	-	-
Ramanath 2011[36]	-	√	-	-	-	-	-	-	√	-
Schapansky 2000[37]	√	-	-	-	-	-	-	-	-	-
Scott 2006[38]	√	-	√	√	-	-	√	√	-	-
Shao 2017[17]	-	-	-	-	-	√	-	-	√	-
Siaw 2017[6]	-	-	-	-	-	√	-	√	-	-
Simpson 2011[39]	-	-	-	-	√	√	-	-	√	-
Soorapan 2002[40]	-	-	-	-	-	-	-	-	-	√
Wishah 2015[16]	-	-	-	-	-	-	-	√	-	-

√ - articles without necessary data such as mean ± standard deviation or number of events in the case of Medication adherence. HbA1c – glycosyated hemoglobin, FBG – fasting blood glucose, SBP – systolic blood pressure, DBP – diastolic blood pressure, TC – total cholesterol, TG – triglyceride, HDLc – high density lipoprotein cholesterol, LDLc – low density lipoprotein cholesterol, Med Adh – medication adherence, Q of life – quality of life.

Study characteristics

The 41 articles ranged from 1996 to 2018. Most of the participants were T2DM patients while two studies had both T1DM and T2DM patients[2, 15] Jaber et al[33] had the least number of participants (39) while Al Hamarneh et al[19] had the largest number of participants (573). Most studies had pharmacist as the key anchor person for pharmaceutical care intervention arm while three studies had a collaborative team with either the physician or other health professionals involved in some components of the intervention that was relevant to their professions[6, 15, 41] Most of the included studies (75.6%) were conducted in primary, secondary and tertiary health care facilities,[2, 3, 6–9, 11, 15–18, 20–24, 30, 31, 33–36, 39–48] 22.0% in community pharmacies[19, 25, 32, 37, 38, 49–52] and 3.4% in research centers[53] as shown in Table 2. The period of study ranged from 3 months to 24 months (Table 2).

The pharmaceutical care (PC) components delivered by pharmacists in the intervention group were mainly assessment, identification and resolution of drug therapy problems, patient education on the disease, medication use, life style modification, recognition and management of hypoglycemic and hyperglycemic episodes. Others included medication adherence, provision of self-monitoring blood glucose device, medication therapy management, cardiovascular risk management, counseling on self-care, medication reviews, proper storage and administration of insulin, establishment and monitoring of pharmacotherapeutic outcomes and medication history- taking (Table 2).

Quality assessment

Figure 2 summarized the risk of bias distribution across the included studies. Due to the pharmaceutical care intervention which required face-to-face interactions or phone calls between the pharmacist and the patient, most studies could not be blinded for participants or personnel (performance bias) or outcome assessment (detection bias). However, almost all the studies lacked attrition and reporting biases. Only ten (10) out of the forty-two studies reported concealing allocation of patients to the two arms. Simpson et al [39] carried out in Canada was devoid of selection, performance, attrition and reporting biases, indicating a well-designed study. According to quality assessment score, only six of the included RCTs[30, 39, 41, 42, 50, 51] were of moderate quality while the remaining 35 RCTs were of low quality.

Table 2: Study characteristics of included randomized controlled trials

Authors, Country of study, Patient type	Age (PC/UC)	No of Participants (PC/UC)	Gender, male (%) [PC/UC]	Intervention details	Care initiator	Follow up	Site of study	Clinical outcomes Humanistic outcomes
Adibe 2014[18] Nigeria T2DM	PC= (52.4 ± 7.6); UC (52.8 ± 8.2)	PC (93); UC (99)	PC = 49 (44.55); UC = 44 (40)	Assessment of patient's specific educational needs and setting priorities for patient care, Patient education, identification and resolution of DTPs, and drug-related problems, collaboration with the physicians, PC development and implementation.	Pharmacist	12 months	Two tertiary health facilities	Fasting blood glucose, HbA1c, Systolic and diastolic blood pressure, Medication Adherence, Total Cholesterol, Triglycerides, HDLc, LDLc,
Chung 2014[22] Malaysia T2DM	PC= (59.7±9.5); UC = (58.5±8.3)	PC (120); UC (121)	PC = 50 (41.7); UC = 56 (46.3)	Patient education on diabetes, hypertension and hyperlipidemia, medications management, medication adherence, Provision and training on the use of blood glucose monitoring device and pill box,, Counseling on blood glucose level, with more stringent levels for the uncontrolled glycemia, Identification and resolution of DTPs,	Pharmacist	12 months	One major teaching hospital	Fasting blood glucose, HbA1c, Medication Adherence
Oparah 2009[2] Nigeria T2DM, T1DM	NP	PC (50); UC (49)	PC = 23 (46); UC = 23 (47)	Provision of information, training, reinforcement to help patients appreciate their responsibility in managing their conditions, Drug therapy monitoring for efficacy and safety, patient education, identification and resolution of drug therapy problems,	Pharmacist	3 months	Medical outpatient clinic	Fasting blood glucose, Systolic and diastolic blood pressure, Medication, Adherence, Diet Adherence, Test Adherence, 2-hour post prandial test, Clinic Attendance Adherence
Mehuys 2011[25] Belgium T2DM	PC= (63); UC (62.3)	PC (152); UC (135)	PC= 78 (51); UC = 72 (53.7)	Appropriate use of oral hypoglycemic agents, Patient education about T2DM, complications, ensuring medication adherence, healthy lifestyle education (diet, physical exercise and smoking cessation), regular annual eye and foot examination	Pharmacist	6 months	Sixty-six Community Pharmacies	Fasting blood glucose, HbA1c, Medication Adherence, Diet Adherence, Self-management, Knowledge of Disease
Al Hamarneh 2017[19] Canada T2DM	PC= (61.0 ±11.8); UC (61.3± 12.4)	PC (286); UC (287)	PC= 159 (55.6%); UC 162 (56.5%)	Medication therapy management: Frequent communication with physician about patient, assessment of patient, laboratory assessment (HbA1c, lipid profile), personalized cardiovascular risk assessment	Pharmacist	3 months	Fifty-six Community Pharmacies	HbA1c, Systolic and diastolic blood pressure, Total Cholesterol, HDLc, LDLc,
Shao 2017[17] China T2DM	PC= (58.86±10.59); UC (59.20±10.34)	PC (100); UC (99)	PC= 51 (51%); UC 47 (47.1%)	Diabetic management (risk of diabetes complications, suitable use and precautions of oral antidiabetes and insulin, signs and symptoms of hypoglycemia and self-management, importance of SBGM, and healthy lifestyle	Pharmacist	6 months	Endocrinology outpatient clinic of an hospital	Fasting blood glucose, 2-hour post prandial glucose level, Total Cholesterol, Triglycerides, HDLc, LDLc, Medication Adherence
Lim 2016[9] Malaysia T2DM	PC =(57±1.56); UC = (55.62±1.49)	PC (39); UC (37)	PC =18 (46.2); UC 17 (45.9)	Education on diabetes and it's medications, antidiabetic medicines and target for diabetes, lipid, blood glucose and blood pressure monitoring by pharmacist, medications management, Counseling on any inappropriate drug use, healthy lifestyle advice	Pharmacist	12 months	Outpatient clinic of an hospital	Fasting blood glucose, HbA1c, Systolic and diastolic blood pressure, Medication Adherence, Total Cholesterol, Triglycerides, HDLc, LDLc,
Korcegez 2017[48] Cyprus T2DM	PC= (61.80±10.38); UC (62.22±9.54)	PC 75); UC (77)	PC = 17(22.7); UC 20 (26)	Education and counseling on SMBG, healthy diet, physical exercise, smoking cessation, self-care, complications, medications, and treatment goals of T2DM. Revision of medications, identification and resolution of DTPs	Pharmacist	12 months	Public hospital outpatient diabetic clinic	Fasting blood glucose, HbA1c, Systolic and diastolic blood pressure, Medication Adherence, Total Cholesterol, Triglycerides, HDLc, LDLc
Guirguis 2001[32] Canada T2DM	PC= (57.1±12.4); UC=(61.9± 9.4)	PC (26); UC (23)	PC =13 (50); UC =13 (57)	Documented diabetes care with follow-up	Pharmacist	6 months	Twenty-two community pharmacies	HbA1c, participant's beliefs, attitude and confidence in managing diabetes, self-care activities, participant's expectations and satisfaction with pharmacy services
Jacobs 2012[47] USA T2DM	PC=(62.7±10.8);UC(63.0±11.2)	PC (72); UC (92)	PC= 49 (68); UC 51 (55)	Medication therapy review; Measurement of weight, height, blood pressure, pulse and foot exam, Education on pathophysiology and importance of control of diabetes; reviewing, modifying and monitoring patient's medication therapy, provision of detailed counseling on all therapies, facilitating SMBG, reinforcement of dietary guidelines and exercise	Pharmacist	12 months	Hospital clinic	HbA1c, systolic and diastolic blood pressure, LDLc, Medication use, Microvacsular screening parameters

Aguiar 2016[41] Brazil T2DM	PC= (61.1±7.9); UC (62.4±8.2)	PC= (36); UC (37)	PC= 11 (30.6); UC 13 (35.1)	Clinical Pharmacy service, Discussion of health education related issues specifically in diabetes, lifestyle, and self-monitoring of blood glucose, provision of specific information on medication adherence, adverse reactions, storage and administration, provision of educational leaflets on diabetes care, identification and resolution of drug therapy problems	Pharmacist/Physician	12 months	University Hospital-affiliated secondary care clinic	HbA1c, Systolic and diastolic blood pressure, Medication Adherence, LDLc, Adherence Score
Chen 2016[23] Taiwan T2DM	PC =(72.16±6.6); UC= (72.76±5.9)	PC (50) ; UC (50)	PC = 25 (50); UC 25 (50)	Recommendation to physicians; changes to medication regimen as approved by the physician, diabetes education, Assessment of adherence,, insulin injection technique, monthly telephone calls as required for medication counseling and adverse event surveys, personal visits to patients, if required.	Pharmacist	6 months	An hospital in the Ministry of Health and Welfare	HbA1c
Jarab 2012[34] Jordan T2DM	PC=(63.4±10.1); UC=(65.3±9.2)	PC=(77); UC=(79)	PC=49(57.6) ; UC=48(55.8)	Structured patient education on diabetes, risk and complications, possible side to effects of medications, life style management of diet, exercise and monitoring of blood glucose level, introduction of evidence-based antidiabetic and antilipidemic therapy,	Pharmacist	6 months	Outpatient diabetes clinic	HbA1c, Systolic and diastolic blood pressure, , Total Cholesterol, Triglycerides, HDLc, LDLc, Medication Adherence, Levels of self-care activities
Clifford 2005[31] Australia T2DM	PC=70.5±7.1; UC=70.3±8.3	PC=92; UC=88	PC= 47.8%; UC=56.8%	Ranking of patient's drug therapy problems; Encouragement of patient to diet, exercise and SMBG;, Establishing and monitoring pharmacotherapeutic outcomes, determining best pharmacotherapeutic solution	Pharmacist	12 months	T2DM patients from Fremantle Diabetes Study	HbA1c, Systolic and diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc,
Choe 2005[46] USA T2DM	PC=52.2±11.2; UC=51±9.0	PC=36; UC=29	PC=48.8%; UC=46.1%	Evaluation and modification of pharmacotherapy after approval by primary care physician, Education on basic self-management skills (self-care, medications and screening process); Diabetes education	Pharmacist	12 months	University affiliated primary care internal medicine clinic	HbA1c,
Fornos 2006[49] Spain T2DM	PC=62.4±10.5; UC=64.9±10.9	PC=56; UC=56	PC=24(42.9) ; UC=24(42.9)	Provision of verbal and written information about correct use, and possible adverse reactions or interactions of each drug, Educational interventions on lifestyle, to improve and maintain patient compliance, Knowledge of diabetes	Pharmacist	12 months	Fourteen community pharmacies	HbA1c, Fasting Blood glucose, Systolic and diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc, DRP
Jahangard-Rafsanjani 2014[50] Iran T2DM	PC=57.3 ±8.6; UC= 55.9 ±8.7	PC=45; UC=40	PC= 20 (51); UC= 14 (48)	Resolution of therapy-related problems; treatment adherence, Education on diet management, physical activity, and diabetes complications, Provision of blood glucose self-monitoring device and test strips for 1 month to individual patients, Discussion of medication-related problems and self-care issues at follow-up visits	Pharmacist	5 months	One community Pharmacy	HbA1c, Medication Adherence, Systolic and diastolic blood pressure, Patient satisfaction, Self-care activity
Kandasamy 2017[35] India T2DM	Grouping	PC=30; UC=30	PC=14 (46.7%); UC=10 (33.3%)	Patient counseling in local language using oral and visual methods, Use of patient information leaflet between periods of follow-up	Pharmacist	6 months	Rural areas of Kumarapalayam, Tamilnadu	Fasting blood glucose Quality of life
Sakthong 2017[8] Thailand T2DM	PC=61.0 ± 11.9; UC=58.4 ± 11.7	PC=259; UC=255	PC=102 (39.4); UC=110 (43.1)	Identification and resolution of DRNs (medicine understanding, expectation, concern) and DRPs (unnecessary drug therapy, needs for additional drug therapy, wrong drug, insufficient dosage, adverse drug reaction, excessive dosage and non-compliance), discussion of therapeutic goals, development of care plans	Pharmacist	3 months	A tertiary Public Hospital in Bangkok	Summation of drug related problem outcomes, Overall Quality of life
Schapansky 2000[37] Canada T2DM	PC= 57.1 ± 12.4 UC= 61.9 ± 9.4	PC=26 UC=23	PC= 13 (50 %) UC= 13 (57 %)	Diabetes care and education from CDE pharmacists, Identification of drug-related problems, measurement of blood sugar, recognition of education deficits and setting of goals for patient. Education of patients on diabetes and its complications, "highs" and "lows", medication use, role of diet and exercise, and SMBG. One-on-one educational sessions with patients at least once a month with follow-up on drug-related problems, review of self-care activities, and to address participants' concerns	Pharmacist	6 months	Shoppers Drug Mart Pharmacy	HBA1c, Diabetes Attitude Scale, Summary of Diabetes Self-Care Activities, Patient Expectations & Satisfaction with Pharmacy Services, and Health-Related Quality of Life
Soorapan 2002[40] Scotland T2DM	PC=65 ±10; UC=66 ±10	PC=83; UC=77	PC=40 (48); UC=42 (54)	Identification of drug related problems, provision of patient information leaflet. Peer –review of referrals prior to submission to the physician. All physician-approved referrals were implemented by the pharmacist	Pharmacist	12 months	Nine general practices in Greater Glasgow Health Board	HbA1c, systolic blood pressure, health related quality of life, DRPs and the percentage of pharmacist recommendations accepted by GP
Wishah 2014[16] Jordan T2DM	PC =(52.9±9.6); UC(53.2±11.2)	PC =(52); UC=(54)	PC=20(38.5) ; UC 26(48.1)	Assessment and management of patient's condition collaboratively by focused care plans designed by the clinical pharmacist and approved by the physician. Initiation of oral hypoglycemic agents, titration of drug therapeutic dosage, and changing the current medication due to ineffectiveness based on approval by physician. Monitoring of efficacy of medications,. Structured patient education and counseling about type 2 diabetes including risks for complications, prescribed medications, and possible side effects; importance of adherence to diabetes self-care activities.	Pharmacist	6 months	An outpatient diabetes clinic at a major teaching hospital	HbA1c, Fasting blood glucose, Medication Adherence, Total Cholesterol, Triglycerides, HDLc, LDLc, Self-care, disease knowledge

Siaw 2017[6] Singapore T2DM	PC= (59.2±8.2); UC (60.1±8.1)	PC =(214); UC =(197)	PC = 112 (52.3); UC 120 (60.9)	Patient education, identification of drug therapy problems, face-to-face visits or phone calls with board-certified pharmacotherapy clinical pharmacist specialist using established protocol.	Pharmacist/ Physician	6 months	Four outpatient healthcare institutions	HbA1c, Systolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc, Self-care, disease knowledge
Phumipamorn 2008[7] Thailand T2DM	PC = (52.27±11.15); UC(55.90±13.67)	PC= (63); UC=(67)		Reminder of hospital visits; discussion on use of medications and pill count; Education of patient on appropriate lifestyle and correct diet, use of pamphlet covering educational topics on diabetic complications, target of treatment, lifestyle changes and antidiabetic medications	Pharmacist/Physician	6 months	Outpatients attending a 30-bed community hospital	HbA1c, Systolic and diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc,
Sriram 2011[21] South India T2DM	PC=(53.65± 2.38); UC(57.98±2 .62)	PC=(60); UC=(60)		Medication counseling, instructions on dietary regulations, exercise, medication and other lifestyle issues	Pharmacist	8 months	General Medicine department of a 550-bedded tertiary care teaching hospital	Fasting blood glucose, HbA1c Quality of life, treatment satisfaction
Sarayani 2017[51] Iran T2DM	PC=(53.4±10.3); UC (56.7±11.5)	PC=(50); UC=(50)	PC=28(54.9) ; UC 31(62.0)	Phone calls to patients. Using pre-defined checklist including trend of blood glucose levels; resolving drug therapy problems, and giving appropriate referral, when needed.	Pharmacist	9 months	A referral pharmacy affiliated with a College of Pharmacy	HbA1c, Total Cholesterol, Triglycerides, HDLc, LDLc,, Self-care, disease knowledge
Al Mazroui 2009[3] UAE T2DM	PC=(48.7± 8.2); UC 49.9±8.3)	PC (120); UC (120)	PC= 84(70); UC=82(68.3)	Provision of patient education on diabetes and the medications, risk of diabetes complications, proper dosage, side effects and storage of medications, components of healthy lifestyle; management of diabetes mellitus signs and symptoms through self-monitoring	Pharmacist	12 Months	A 400-bed Military Hospital facility	Fasting blood glucose, HbA1c, Systolic and Diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc, Self-care, disease knowledge
Scott 2006[38] USA T2DM	NP	PC (64); UC (67)	PC=32 (42.1); UC=26 (35.6) baseline values	Free blood glucose monitor with test strips; Patient education on disease management, lifestyle adjustment and goal setting; Provision of nutrition and basic diabetes management at group meetings. Reminder of appointments by clinical pharmacist; referral of patients to providers to address other health concerns. SMBG, Medication reviews, therapeutic interventions including initiating aspirin therapy, administering influenza vaccinations, referring patients for therapeutic shoes, and managing medications for hypertension and dyslipidemia.	Pharmacist	9 months	An onsite pharmacy in a Community Health Center	HbA1c, Systolic and diastolic blood pressure, LDLc, HDLc, Quality of life
Simpson 2011[39] Canada T2DM	PC=(58.8±11.1); UC(59.4±12 .1)	PC (131); UC(129)	NP	Patient education, Medication assessment; Guideline-concordant recommendations formulated by pharmacists to optimize medication management of cardiovascular risk factors, implemented for patients when approved by physicians.	Pharmacist	12 months	Five primary care clinics affiliated with a Primary Care Network	HbA1c, change in predicted 10-year risk of cardiovascular disease Systolic and diastolic blood pressure, Total Cholesterol and HDLc, Triglyceride, LDLc, Self-care
Ramanath 2011[36] India T2DM	NP	PC=52; UC=48	PC=35(67.3) ; UC=24(50.0)	Educational patient information leaflet with formal counseling		3 months	Outpatient and inpatients of Medicine Department of an Hospital & Research Center.	FBG, 2HPPBG, Medication Adherence QoL
Sarkadi 2004[45] Sweden T2DM	PC= (66.4±7.9); UC(66.5±10 .7)	PC (33); UC (31)	Not reported	Patient education on disease and life style modification, practical aspects of diabetes management including choice and preparation of food, performing self-monitoring tasks, walking or jogging to decrease blood-glucose levels,	Pharmacist	24 months	Participants were self-referred, responding to advertisements in local newspapers and flyers distributed at GPs' office and a Diabetes Association	HbA1c

Adepu 2018[44] India T2DM	PC=51.29± 10.82; UC=58.05± 12.75	PC=(37); UC=(35)	PC=29 (40.27); UC=18 (25)	Educational intervention on health-related QoL and glycemic control Pharmacist-mediated structured education on disease, medication, diet, and lifestyle modification at baseline and further follow-up; use of patient information leaflet.	Pharmacist	6 months	Medicine outpatient department of an Hospital and Research Centre,	Fasting blood glucose, HbA1c; 2-hour Post Prandial blood glucose Quality of life
Chan 2012[30] Hong Kong T2DM	PC=63.2 + 9.5; UC=61.7 + 11.2	PC=(51); UC=(54)	PC=30 (58.8); UC=28 (51.9)	Education on medication adherence, knowledge and beliefs, skills, perceived health as well as cognitive functions.	Pharmacist	9 months	Diabetes clinic of a 250-bed public convalescent hospital	HbA1c, Systolic and diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc,
Clifford 2002[15] Australia T1DM, T2DM	PC= 60±12; UC=61±12	PC=(48); UC=25	PC= 28 (58%); UC= 12 (48%)	Pharmacotherapy, Medication history and counseling (proprietary, non-proprietary and complimentary)	Pharmacist with other health professional	6 months	Diabetes outpatient clinic of an Hospital	HbA1c, Patient's satisfaction QoL
Farsaei 2011[53] Pakistan T2DM	PC=52.9±8. 5; UC=53.4±9. 8	PC=87; UC=87;	PC=31.8%; UC=36.8%	Educational program on oral anti-hyperglycemic medications, diabetes knowledge, the importance of medication adherence, dietary adherence and exercise on better glycemic control, diabetes dairy log and pill box usage , giving of advice according to concerns about diabetes control, medication consultation service to improve adherence; creation of individualized patient schedule on administration times and dosage of each medication, education on how to take medications in the holy month of Ramadan	Pharmacist	3 months	An Endocrine and Metabolism Research Center	HbA1c, Fasting blood glucose
Jaber 1996[33] USA T2DM	PC=59±12; UC=65±12	PC=17; UC=22	PC=5(29.4) UC=7(31.8)	Diabetes-specific pharmacotherapeutic evaluation and dosage adjustments, comprehensive and individualized patient education regarding diabetes and its complications, training on the recognition and treatment of hypoglycemia and hyperglycemia, medication counseling, specific instructions on dietary regulation and an exercise plan, and training for self-monitoring of blood glucose (SMBG). Instructed to record date and time of any hypoglycemic events as well as symptoms they experienced during these events. Evaluation of current hypoglycemic therapies were performed during each clinic visit based on the self-tested blood glucose responses performed 4 times per day for 2 days per week. Hypoglycemic therapeutic regimens were adjusted or titrated to achieve acceptable fasting blood glucose (FBG) concentrations	Pharmacist	4 months	Urban African-American patients with NIDDM currently attending a university-affiliated general internal medicine outpatient clinic	Fasting Blood Glucose, HbA1c, Triglyceride, Total Cholesterol, HDLc, LDLc, QoL
Jameson 2010[24] USA, T2DM	PC=49.3±1 0.8; UC=49.7±1 0.9	PC=52; UC=51	PC=25 (48.9); UC=25 (49)	Assessment of adherence, barriers to optimizing blood glucose levels, and current medication regimen. Individualized education regarding diabetes self-management, including diet, exercise, blood glucose level testing, medications, and insulin following guidelines of the Management of Hyperglycemia in Type 2 Diabetes. Early switching to insulin therapy after failure of 2 oral medications. The patient's primary care physician approved any changes in medication or therapy, pharmacist was given autonomy to adjust insulin doses as needed. Subsequent visits with the pharmacist based on the need to further educate the patient about diabetes control or to monitor therapeutic changes. Follow-up visits were supplemented with telephone calls as needed for medication management.	Pharmacist	12 months	Thirteen Advantage Health Physician Network offices (3 urban, 9 suburban, and 1 rural site).	HbA1c
Rothman 2005[42] USA T2DM	PC (54±13); UC (57±11)	PC= (112); UC =(105)	PC= 49 (44); UC 46(44)	Patient education, cardiovascular and risk factors reduction, improve glycemic control, lipid profile and other clinical parameters, , address barriers to care	Pharmacist	12 months	A university General Internal Medicine Practice	HbA1c, Systolic and Diastolic blood Pressure, Triglyceride, Total Cholesterol, HDLc, LDLc, Disease Knowledge, Satisfaction, use of clinical services
Odegard 2005[43] USA T2DM	PC (51.6±11.6); UC (51.9±10.4)	PC= (43); UC =(34)	NOT CLEAR	Diabetes care plan, pharmacist-patient and pharmacist-provider communication on diabetes care progress, identification of medication-related problems, weekly in-person or telephone contact, phone follow-up	Pharmacist	12 months	A university Medicine Clinic – a nonprofit medical group, consist of 70 primary care providers based in 8 clinics serving 100 000 patients	HbA1c, Medication appropriateness, Self-reported Adherence, Appropriateness of Therapy, Medication Appropriateness Index

Mourao 2013[3] Brazil T2DM	PC (60.0±10.2); UC (61.3±9.9)	PC (50); UC (50)	NOT CLEAR	Patient education (diet and exercise) complications and treatment goals, medication management, Identification of DTPs, Individualized care plan	Pharmacist	6 months	6 Primary Health Care Units integrated into the Brazilian Public Health System	Fasting Plasma glucose, HbA1c, Systolic and diastolic blood pressure, Drug therapy problems, Total Cholesterol, Triglycerides, HDLc, LDLc
Krass 2007[52] Australia T2DM	PC (62±11); UC (Similar)	PC (149); UC (140)	Total (PC, UC 51%)	Medication review and provision of glucometer for individual participants, SMBG, education on medication adherence, lifestyle information (weight loss, increased physical activities) and foot care issues	Pharmacist	6 months	Fifty-six Community Pharmacies	HbA1c, Systolic and diastolic blood pressure, Total Cholesterol, Triglycerides, HDLc, LDLc, Quality of life scores

HbA1c= Glycosylated hemoglobin; TC= Total cholesterol; TG= Triglyceride; HDLc= High density lipoprotein cholesterol; LDLc= Low density lipoprotein cholesterol QoL= Quality of life; GP= General practice, DRP= Drug related problem. SMBG – Self Monitoring of Blood Glucose; DTP – Drug Therapy Problems; GP- General Practitioner

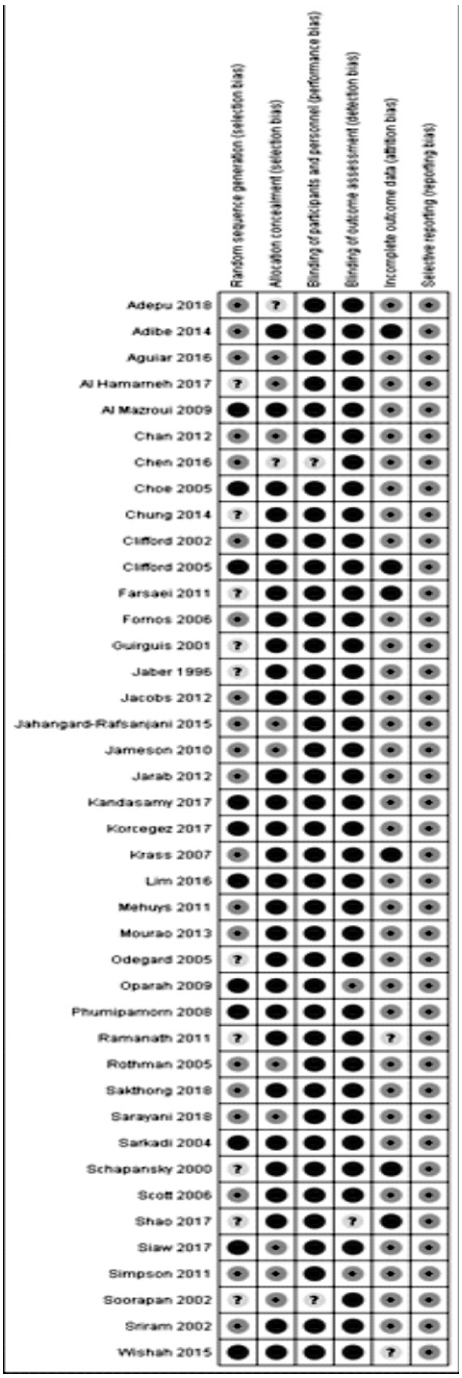

Figure 2: Risk of bias across included studies

Glycosylated hemoglobin (HbA1c)

Thirty of the studies measured HbA1c with only 21 reporting the mean and standard deviation. The pooled estimate effect of these 21 RCTs showed better reduction in HbA1c with the PC intervention group compared with the usual care group. The standard mean difference was -0.57 (95% CI = -0.89, -0.25; P = 0.0005; I^2 = 95%) (Figure 3). The quality of evidence was rated low due to considerable risk of bias and inconsistency (Table 3). Visual inspection of the funnel plot was symmetrical and did not reveal any publication bias.

Fasting Blood Glucose (FBG)

The SMD of the thirteen pooled RCTs out of the 17 included articles reporting values for fasting blood glucose (FBG) was -1.55 (95% CI: -2.24, -0.86; P < 0.0001; I^2 = 98% (P <0.00001) as seen in Figure 3. The effect of PC intervention on FBG was statistically significantly lower than the usual care group, though with high heterogeneity. The quality of evidence of the included studies is low (Table 3) and no publication bias was detected through funnel plot.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Pharmaceutical care intervention with diabetic patients showed similar reduction in SBP and significant reduction in DBP when compared with usual care. The SMD and 95% CI for SBP was -0.53 (-0.90, -0.16; P = 0.005) and for DBP, it was -0.55 (-0.93, -0.18; P = 0.004). Heterogeneity was high in both; SBP (I^2 = 94%; P <0.0000) and DPB (I^2 = 92%; P=0.004). Publication bias was not observed among the 12 and 10 RCTs pooled for the effect estimate of interventions and usual care on SPB and DBP, respectively. The quality of evidence for these two outcomes was adjudged to be low by the three authors.

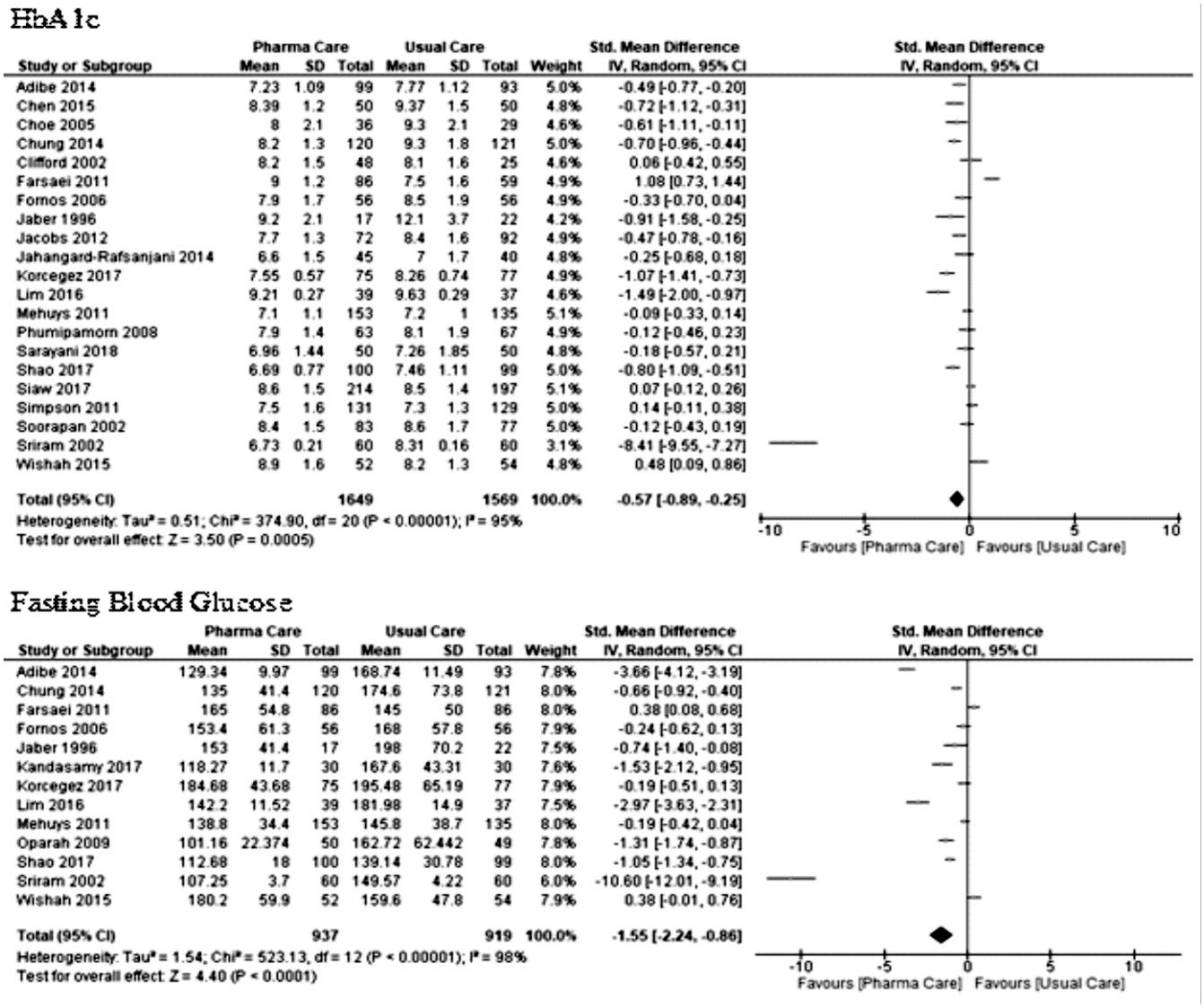

Figure 3: Forest plot for glycosylated hemoglobin (HbA1c) and fasting blood glucose

Table 3: Quality of evidence of included studies

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Pharmaceutical care (95% CI)
Glycosylated Hemoglobin (HbA1c)	3218 (21 studies) 3 – 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean glycosylated hemoglobin (HbA1c) in the intervention groups was **0.57 standard deviations lower** (0.89 to 0.25 lower)
Fasting Blood Glucose	1856 (13 studies) 3 – 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean fasting blood glucose in the intervention groups was **1.55 standard deviations lower** (2.24 to 0.86 lower)
Systolic Blood Pressure	2040 (12 studies) 3 – 24 months	⊕⊕⊖⊖ **LOW** due to risk of bias, inconsistency			The mean systolic blood pressure in the intervention groups was **0.53 standard deviations lower** (0.9 to 0.16 lower)
Diastolic Blood Pressure	1469 (10 studies) 3 – 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean diastolic blood pressure in the intervention groups was **0.55 standard deviations lower** (0.93 to 0.18 lower)
Total Cholesterol	991 (7 studies) 6 – 24 months	⊕⊕⊖⊖ **MODERATE**[1,2] due to risk of bias			The mean total cholesterol in the intervention groups was **0.29 standard deviations lower** (0.47 to 0.11 lower)
Triglyceride	792 (6 studies) 6 – 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean triglyceride in the intervention groups was **0.11 standard deviations lower** (0.4 lower to 0.19 higher)
High Density Lipoprotein Cholesterol	1251 (8 studies) 6 – 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean high density lipoprotein cholesterol in the intervention groups was **0.14 lower** (3.79 lower to 3.52 higher)
Low Density Lipoprotein Cholesterol	1309 (8 studies) 6 – 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean low density lipoprotein cholesterol in the intervention groups was **0.37 standard deviations lower** (0.73 lower to 0 higher)
Quality of Life	687 (3 studies) 3 – 6 months	⊕⊕⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision			The mean quality of life in the intervention groups was **0.27 standard deviations higher** (0.12 lower to 0.67 higher)
Disease Knowledge	172 (2 studies) 6 – 24 months	⊕⊕⊖⊖ **VERY LOW**[1,2] due to risk of bias, inconsistency, imprecision			The mean disease knowledge in the intervention groups was **2.72 standard deviations higher** (0.33 lower to 5.78 higher)
Medication Adherence	577 (4 studies) 5 – 12 months	⊕⊕⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	**OR 3.07** (1.32 to 7.15)	**Study population**	
				561 Med Adh per 1000	**236 more Med Adh per 1000** (from 67 more to 340 more)
				Moderate	
				556 Med Adh per 1000	**238 more Med Adh per 1000** (from 67 more to 344 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio; Med Adh: Medication Adherence
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[1] The studies were generally open-labeled because of the pharmaceutical care intervention that required face-to-face contact.
[2] Large heterogeneity possibly due to population difference and varied length of follow-up
[3] Different instruments and scales were used.

Lipid profile outcomes

Quality of evidence of pooled RCTs for the four lipid profile outcomes was moderate for total cholesterol and low for triglyceride, high density lipoprotein cholesterol and low density lipoprotein cholesterol (Table 3). The SMD is significant for both total cholesterol and low density lipoprotein cholesterol in favor of PC intervention group (Figure 4). However, there was moderate heterogeneity (I^2 = 51%; P = 0.06) of the 7 RCTs pooled for total cholesterol, and high heterogeneity (I^2 = 91%; P<0.00001) for the 8 RCTs pooled for low density lipoprotein cholesterol. For

triglyceride and high density lipoprotein cholesterol, the effect estimates were non-significant as shown in Figure 4. Publication bias was assessed by visual inspection of the funnel plot for the pooled studies for each of the lipid profile outcome and no publication bias was noticed.

Medication adherence

Four out of the six RCTs that reported medication adherence were pooled in this study with an Odds Ratio (OR) of 3.07 [95% CI: 1.32, 7.15; P = 0.009], in favor of usual care group. The heterogeneity was significantly high (I^2 = 76%; P = 0.005). No publication bias was observed. The quality of evidence of the four RCTs was very low due to risk of bias inconsistency and imprecision (Table 3)

Quality of life

Standard mean difference for the three pooled RCTs was in favor of the usual care group 0.27 [95% CI: -0.12, 0.67, P = 0.17] without significant difference from the PC intervention group. The quality of evidence for the three RCTs was very low (Table 3) and no publication bias was detected.

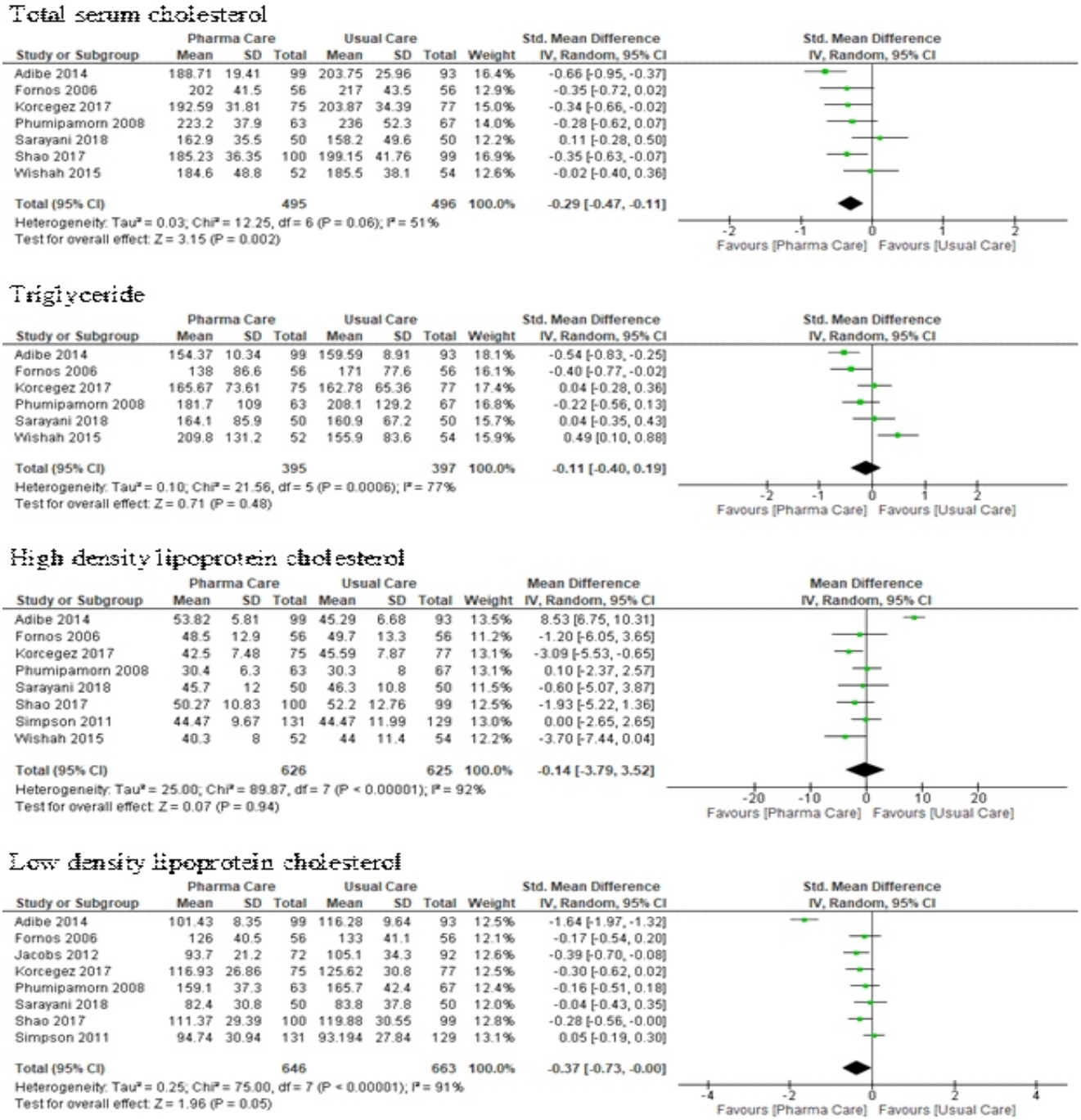

Figure 4: Forest plot for total cholesterol, triglyceride, high density lipoprotein cholesterol and low density lipoprotein cholesterol

Diabetes disease knowledge

The mean disease knowledge in the PC intervention group was 2.72 standard deviations higher (95% CI; -0.33, 5.78; P = 0.08) with significant heterogeneity (I^2 = 97%; P < 0.00001) than the usual care group. The quality of evidence for the two randomized controlled trials pooled for this outcome was very low due to risk of bias, inconsistency and imprecision (Table 3). No publication bias was detected.

Sensitivity and subgroup analyses

Fixed and random effect models were compared for each of the outcomes in the study for sensitivity analysis. A change from random effect to fixed effect model showed marked reductions in the standard mean differences of HbA1c, FBG, SBP, DBP, LDLc, medication adherence, quality of life and disease knowledge without a corresponding change in the heterogeneity. The model change resulted in increase in the SMD of TC, TG, and HDLc. Omission of selected studies; Adibe, et al[18]; Sarayani et al[51] and Wishah et al[16] resulted in low heterogeneity in the effect estimates for HDLc, LDLc and TC as observed in Table 4. Omission of Oparah et al[2] and Ramanath et al[36] from the pooled studies for medication adherence and quality of life outcomes respectively resulted in low heterogeneity for the effect estimates for these outcomes (Medication adherence SMD 1.95, (95% CI: 1.33, 2.86); I^2=0% and quality of life SMD 0.11 (95% CI: -0.05, 0.27); I^2=0%.

The subgroup analyses on the basis of country of study, length of study, and sample size of patients showed that length of study had appreciable effect on the SMD and heterogeneity of TC, TG, HDLc and LDLc (Table 4). Studies from developed countries had lower or no heterogeneity compared with studies from developing countries for outcomes such as TC, HDL and LDLc (Table 4); likewise studies with sample population less than ≤ 150 participants.

Table 4: Table of sensitivity and subgroup analyses

Outcomes (Ref)	TC	TG	HDLc	LDLc
	N; SMD (95% CI, P); I^2 (P)	N; SMD (95% CI, P); I^2 (P)	N; SMD (95% CI, P); I^2 (P)	N; SMD (95% CI, P); I^2 (P)
Model effect				
Random effect model	7; -0.29 [-0.47, -0.11]; I^2=51%	6; -0.11 [-0.40, 0.19]; I^2=77%	8; -0.14 [-3.79, 3.52]; I^2=92%	8; -0.37 [-0.73, -0.00]; I^2=91%
Fixed effect model	7, -0.31 [-0.44, -0.19]; I^2=51%	6; -0.14 [-0.28, -0.00]; I^2=77%	8; 1.60 [0.63, 2.58]; I^2=92%	8; -0.34 [-0.45, -0.23]; I^2=92%
Study omission				
Adibe 2014[18]	6; -0.23 [-0.38, -0.08]; I^2=12%	5; -0.01 [-0.29, 0.27]; I^2=67%	7; -1.40 [-2.58, -0.23]; I^2=0%	7; -0.18 [-0.30, -0.05]; I^2=11%
Oparah 2009[2]	N/A	N/A	N/A	N/A
Ramanath 2011[36]	N/A	N/A	N/A	N/A
Sarayani 2018[51]	6; -0.35 [-0.51, -0.19], I^2=31%	5; -0.13 [-0.48, 0.21]; I^2=81%	7; -0.08 [-4.09, 3.93]; I^2=93%	7; -0.41 [-0.82, -0.01]; I^2=92%
Wishah 2015[16]	6; -0.33 [-0.52, -0.14]; I^2=48%	5; -0.22 [-0.46, 0.01]; I^2=59%	7; 0.36 [-3.55, 4.27]; I^2=93%	N/A
Country of study				
Developed countries	3; -0.35 [-0.53, -0.16]; I^2=0%	2; -0.17 [-0.60, 0.26], I^2=68%	4; -1.68 [-3.18, -0.18]; I^2 = 0%	5; -0.20 [-0.37, -0.04]; I^2 = 36%
Developing countries	4; -0.23 [-0.58, 0.12]; I^2=75%	4; -0.07 [-0.50, 0.36]; I^2=84%	4; 1.23 [-4.85, 7.30]; I^2 = 95%	3; -0.62 [-1.66, 0.42]; I^2 = 96%
Length of study				
Study period ≤ 6 months	4; -0.35 [-0.60, -0.10]; I^2 = 59%	3; -0.10 [-0.68, 0.48]; I^2 = 89%	3; -1.49 [-3.67, 0.69]; I^2 = 32%	2; -0.24 [-0.45, -0.02]; I^2 = 0%
Study period > 6 months	3; -0.21 [-0.49, 0.08]; I^2 = 46%	3; -0.10 [-0.38, 0.18]; I^2 = 46%	5; 0.83 [-4.54, 6.21]; I^2 = 94%	6; -0.41 [-0.92, 0.09]; I^2 = 93%
Sample size				
Patients N≤ 150	5; -0.19 [-0.37, -0.02]; I^2 = 16%	5; -0.01 [-0.29, 0.27]; I^2 = 67%	5; -1.72 [-3.29, -0.15]; I^2 = 14%	5; -0.23 [-0.39, -0.08]; I^2 = 0%
Patients N> 150	2; -0.50 [-0.80, -0.21]; I^2 = 54%	N/A	3; 2.29 [-4.64, 9.22]; I^2 = 96%	2; -0.11 [-0.44, 0.22]; I^2 = 68%

TC = Total cholesterol, TG = Triglyceride, HDLc = High density lipoprotein cholesterol, LDLc = Low density lipoprotein cholesterol.

Diet Adherence

In the study by Oparah *et al*[2], pharmacists' interventions optimized patients' awareness of the role of diet. Diet adherence when compared with control (22, 45%) was found to be higher in the intervention group (45, 90%; P<0.0001). The instrument used to determine the level of adherence was however not mentioned. Korcegez et al[48] on the other hand used the Morisky Green test and showed that patients in the intervention group achieved significant improvements in their total diet score (+0.51 day/week; P < 0.001).

Test Adherence

Oparah *et al*[2] showed that generally in both the intervention and control groups, all the patients were aware of their involvement in the management of their diseases especially as far as test adherence is concerned.

Exercise adherence

Using the Summary of the Diabetes Self-Care Activities (SDSCA), Korcegez *et al*[48] showed that exercise adherence was not significantly different in the control and PC intervention groups before the study. At the end of the study, though, there was an increase in the score (number of days in which at least thirty minutes of exercise was carried out in the last one week) for the intervention group (1.56±2.49 days to 2.34±2.33 days) compared with the slight reduction (1.66±2.30 days to 1.57±1.79 days) for the control group.

Clinic Attendance Adherence

There was significant difference in clinic attendance adherence between the group that had the usual care (34, 69%) when compared with the group that went through PC intervention (47, 94%) (p < 0.0001) with a clinical pharmacist as shown by Oparah et al[2].

Self-Care

To evaluate effects of pharmaceutical care intervention on diabetes mellitus patients, the ability of the patient to actuate self-care measures were also evaluated. There were different scales used for measurement of the parameters by the different studies reviewed.

Jarab et al[34], Korcegez *et al*[48], Schapansky *et al*[37] all used the SDSCA to evaluate the effect of the intervention on self-care among diabetes patients. Jarab et al[34] showed that except for foot care (3.0 days to 3.5 days; p=0.172) and smoking (54.1% to 53.2%; p=0.331), the PC intervention group patients reported significantly better self-care activities at the end of the study: diet (4-2 days to 4.7 days; *P*=0.041), exercise (2.3 days to 3.7 days; *P*=0.025), and SMBG (4.5 days to 5.3 days; *P*=0.007) compared with the usual care group at 6 months follow-up. Korcegez et al[48] showed a change of 2.93±1.11 to 3.44±0.85 days for diet score, 1.56± 2.49 to 2.34±2.33 days for total exercise score, 0.22±0.83 to 1.82±1.05 days for foot care and 12 to 8 days for smoking among the intervention group at the end of the study.

Self-care activity was measured using Diabetes Self-care Activity Measurement Scale (DSAMS) questionnaire by Jahangard-Rafsanjani et al[50]. There was improvement with the PC intervention group with general diet score which increased from 0 to 5.0 days, specific diet score decreased from 2.5 to 2.0 days, exercise score and foot care increased from 1.5 to 2.5 days, and 1.5 to 3.5 days, respectively.

DISCUSSION

Most systematic reviews of the impact of pharmaceutical care intervention on the management of diabetes mellitus focused on glycosylated hemoglobin (HbA1c). However, this study improved greatly on reports of other available systematic reviews and meta-analysis by considering other clinical and humanistic outcomes such as systolic blood pressure, diastolic blood pressure, lipid profile, adherence and quality of life, some of which are important modifiable risk factors that can slow down or mitigate against the development of microvascular or macrovascular complications. Also, in this review, unpublished reports such as thesis were included with the eligible published articles, thus reducing the possibility of publication bias, which was also not detected in this study.

Pharmaceutical care service model is a model of care frequently and mostly used by pharmacists to improve pharmacotherapeutic outcomes since an important relationship exists between drug use and morbidity/mortality.[54] Pharmaceutical care not only seeks to improve pharmacotherapy outcomes but also to improve patients' quality of life and better cost of disease management. Ample studies have shown the benefit of PC in the management of chronic diseases like hypertension,[55] heart failure,[56] chronic kidney disease.[57] kidney transplant,[58] chronic obstructive pulmonary disease,[59] hyperlipidemia,[60] asthma,[61] and diabetes.[6, 17] In rendering optimal pharmaceutical care services, the pharmacist must recognize potential and actual drug related problem (DTP), provide care plan to resolve identified DTPs, and forestall future occurrence of similar DTPs. Thus, pharmaceutical care is mutually beneficial to both the pharmacists and patient. In this concept, the patient bequests authority to the

pharmacist as a provider and the pharmacist acknowledges this authority. Here, the pharmacists is considered a provider in that there is an extension of his duty from dispensing of drugs to rendering specialized services.[54] It is this specialized services that are brought to play when pharmaceutical interventions are employed in the management of chronic diseases such as diabetes where patients are at risk of developing macrovascular and microvascular complications with poor glycemic control and comorbid diseases.

Several studies have evaluated the benefit of the provision of PC interventions on glycemic control in diabetes in comparison with usual care received at outpatient and inpatient departments and community pharmacy settings.[19, 32, 48, 49] In this review, the lowering of HbA1c and fasting blood glucose were in favour of PC intervention which is comparable to reports from other reviews[11, 12, 62] As reported by Stratton et al,[4] the United Kingdom Prospective Diabetes Study showed that 1% reduction in the level of HbA1c reduced the risk of diabetes mortality, myocardial infarction, and microvascular complications by > 10%. This evidently suggests that PC intervention provided by pharmacists which led to significant reduction in HbA1c level would eventually lead to reduction in clinical complication in diabetes. Though, it is not very clear which aspect of the multi-faceted pharmaceutical care actually contributed significantly to the reduction in HbA1c, it is possible that the improvement in self-care, recognition and resolution of drug therapy problems and frequent counselling, medication review and regular contact with the patient could have imparted on the outcome. Though, for type 1 and type 2 diabetes patients with severe insulin deficiency, HbA1c only is not sufficient to determine glycemic control. In these classes of patients, FBG should also be considered.[18] It is noteworthy that source of heterogeneity for the effect estimate of HbA1c could not be traced as sensitivity and subgroup analysis considered in this review and meta-analysis did not alter the heterogeneity. It is possible that the heterogeneity might have been as a result of the non-standardized mode of PC intervention. This may be further looked into by evaluating the effects of standardized PC intervention approach.

Reduction in systolic and diastolic blood pressure was clearly significantly in favour of PC intervention, though the observed difference is relatively low. Several individual studies reported appreciable lowering of blood pressure in the PC intervention group.[3, 31, 52] These studies suggested that the reason for this might be the prompt resolution of drug therapy problems and the improvement in quality of life of the patients. Diabetes and hypertension may be co-morbid in patients with diabetes, and both increase the risk of cardiovascular diseases. An intervention that would considerably reduce the incidence of long term complications of these diseases could be employed to curb increasing prevalence of cardiovascular diseases and other complications.

Of the four lipid profile parameters, PC intervention participants had significantly lower total cholesterol and low density lipoprotein cholesterol. Since these are secondary outcomes which may take some time for the effects to be seen, a longer period of study might have given a more definite picture of the effects of PC on lipid profile. There may be a need for further studies to evaluate the effects of standardized PC intervention for a longer period of study.

Quality of life, disease knowledge and medication adherence favored usual care. This is not surprising as the instrument used in evaluating these outcomes varied from one study to another, while the level and direction of measurement differed. A definite statement about the effect of PC on these can therefore not be made.

Despite the strengths of this review as highlighted above, there are few limitations to the study. Not all eligible articles were included in the meta-analysis, as some did not have the end-point data as mean (±SD). This might have affected the outcome of the meta-analysis. Though, other reviews and meta-analysis used a lesser number of articles than was used in this study, most of the studies included were poorly designed randomized controlled trials, as the risks of bias were not adequately reported. Most importantly, the pharmaceutical care interventions provided by the pharmacists were not standardized across the eligible studies and thus, no definite statement could be made about the aspect of the pharmaceutical care intervention that could be responsible for the outcomes.

CONCLUSION

Pharmaceutical care intervention notably improved clinical outcomes such as glycosylated hemoglobin, blood pressure, lipid profile, and adherence (medical tests, diet, clinic attendance and exercise) and humanistic outcomes such as self-care. The intervention however failed to improve medication adherence and quality of life. The non-standardized nature of the components of the pharmaceutical care offered by the pharmacists in each study did not permit

a causal relationship to be established with the improved outcomes. Thus, it becomes pertinent that future pharmaceutical care interventions in diabetes mellitus and possibly other chronic diseases be standardized, and data endpoints measured similarly across studies to facilitate robust meta-analysis which may guide the implementation of pharmaceutical care services.

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