Glycemic control through pharmaceutical care: A meta-analysis of Randomized controlled trials

Zaheer Ud-Din Babar, Rozina Kousar, Syed Shahzad Hasan, Shane Scahill, Louise Elizabeth Curley

1. Prof Zaheer Ud-Din Babar
Department of Pharmacy
University of Huddersfield
Queensgate, HD1 3DH, United Kingdom
Email: z.babar@hud.ac.uk

2. Rozina Kousar
Department of Pharmacy
COMSATS Information Technology Center – CITC
Abbottabad, Pakistan
Email: rozinakousar168@hotmail.com

3. Dr Syed Shahzad Hasan*
Department of Pharmacy
University of Huddersfield
Queensgate, HD1 3DH, United Kingdom
Email: s.hasan@hud.ac.uk

4. Dr Shane Scahill
School of Management
Massey University (Albany Campus)
Private Bag 11 222
Palmerston North, 4442, New Zealand
Email: S.Scahill@massey.ac.nz

5. Dr Louise Elizabeth Curley
School of Pharmacy
University of Auckland
85 PARK RD, GRAFTON
AUCKLAND 1023, New Zealand
Email: l.curley@auckland.ac.nz

Abstract

Objectives To evaluate the effect of pharmaceutical care (PC) on glycemic control in patients with type 2 diabetes mellitus.

Methods A systematic search of literature was conducted to identify randomized controlled trials (RCTs) in patients with type 2 diabetes mellitus. RCTs published in English between January 2011 and November 2015 were identified using nine electronic databases: MEDLINE, International Pharmaceutical Abstracts (IPA), EMBASE, Scopus, Science Direct, Cochrane Library, Web of Science, Springer Link, and Google Scholar. Studies were included if they outlined a pharmaceutical care intervention conducted by pharmacists alone or in collaboration with other health care professional(s). The studies were identified and data was extracted independently by two reviewers. The meta-analysis was conducted by using RevMan version 5.3. A random-effects model was used to calculate the standard mean difference (SMD) with a 95% confidence interval in glycosylated hemoglobin ($HbA1_C$) levels.

Key findings Thirteen RCTs outlining PC interventions in type 2 diabetes mellitus patients (n=1828) were included. The interventions included care plan development, medication reviews, patient education and counselling of patients with follow-up. All RCTs reported statistically significant reductions in HbA1c in the intervention group (SMD = -0.97; 95% CI -1.21 to -0.73; p=0.00001) as compared to the control group. Significant heterogeneity in SMD (χ^2= 68.96) was observed.

Conclusions The findings suggest that PC interventions are effective (at least in short-term follow-up in hospital setting) in reducing HbA1c levels in patients with type 2 diabetes mellitus. Pharmacists, working alone or in collaboration with other health professionals have significant impact on improving the health status of patients with type 2 diabetes mellitus.

Keywords Glycemic control, meta-analysis, pharmaceutical care, randomized controlled trial

Introduction

Diabetes mellitus is a major public health concern. It was identified by world leaders in the 2011 Political Declaration on the Prevention and Control of Non-communicable diseases as the one of the four major priority health conditions. It is a long-term condition associated with an higher incidence of morbidity and mortality; it has been reported that patients with diabetes mellitus have an 11 times greater morbidity than the non-diabetic population.[1] In addition, the prevalence of the condition is increasing worldwide. In 2010 global estimates reported the proportion of people with diabetes mellitus between the ages 20 to 79 years was 6.4%,[2] and in a World Health Organisation report on diabetes, it has been estimated that the number of patients with diabetes mellitus has doubled between 1980 and 2014.

Diabetes can be controlled by modification of lifestyle and/or through adherence to antidiabetic medicine regimens. It has been well established that poor glycemic control leads to hospitalization, long-term complications, disease progression, premature disability and greater mortality.[3,4] A study conducted by Statton et al. found that for every 1% decrease in glycosylated hemoglobin ($HbA1_C$) there was a 37% reduction in the risk of microvascular complications, 14% for myocardial infarction and 21% in diabetes related risk of death.[5]

The role of the pharmacist has shifted over-time, from product-oriented practice, to a role that has a strong involvement in patient-centred care. The provision of pharmaceutical care (PC) has been one means by which this is being achieved. PC is the responsible provision of drug therapy to patients in-order to achieve defined outcomes and to improve patient quality of life.[6] Clinical pharmacists in collaboration with patients and other health professionals design, implement and monitor pharmaceutical care plans which are intended to identify and resolve actual drug-related problems (DRP) as well as preventing potential DRPs.[7]

Studies have reported significant positive effects associated with PC as it relates to the control of $HbA1_C$ in type 2 diabetes patients.[8,9] There have been published systematic reviews and meta-analyses on patient adherence to anti-diabetic medications (10, 11). Meta-analyses have also been conducted on randomized controlled trials (RCTs) published up until 2010,[12,13] and another included RCTs through to 2011,[14] albeit the database search was limited.

The present meta-analysis was conducted to investigate an up-to-date evaluation of the effectiveness of PC on glycemic control. The objective was to report the main components of PC interventions and their impact on patient health outcomes in addition to providing an evaluation of the effect of PC on glycemic control of type 2 diabetes patients.

Methods

Search strategy

A systematic search of literature was conducted to identify RCTs published in English between January 2011 and November 2015 by using the following electronic databases: MEDLINE (Ovid SP), International Pharmaceutical Abstracts (IPA), EMBASE, Scopus, Science Direct, Cochrane Library, Web of Science, Springer Link, and Google Scholar. Two authors (RK and ZUB) searched following keywords 'pharmaceutical care' or 'medicine management' or 'medicine therapy assessment' or 'pharmacy services' or 'patient centered care' or 'pharmacist' or 'community pharmacist' or 'hospital pharmacist' or 'diabetes' or 'diabetes mellitus'. The search was restricted to randomized controlled trial only.

Inclusion/exclusion process

Two of the authors (RK and ZB) reviewed the titles and abstracts of all selected articles for relevance. In case of any doubt regarding inclusion each full text article was reviewed for relevance. Non-randomized and secondary studies including literature reviews, systematic reviews and meta-analyses were excluded.

Data extraction and quality assessment

The following characteristics were documented for each study included in this review: authors, country, sample size, study design, study population, follow up period, study setting, study outline (intervention provided) outcome measure and the effect of the intervention. Two reviewers (RK & ZB) extracted the data and rated the studies for quality and outcome measures. The quality of studies were evaluated according to a hierarchy of study designs reported by the Scottish Intercollegiate Guidelines Network (SIGN).[15]

Quantitative Data Synthesis

In this meta-analysis, the authors included all those studies that reported appropriate data. The majority of studies only reported the means and standard deviations (SD) of HbA1c at baseline and at the final point, for both intervention and control groups without calculation of means and SD changes in HbA1c from baseline to the final recording. For these studies,

means and SD changes from baseline to final point were calculated using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2.[16] In this manner, the change in mean of HbA1c in each group was calculated by subtraction of the final mean value from the baseline mean value. The missing SD change in HbA1c level was substituted by an imputed value. For example, the SD change in HbA1c in intervention group was calculated using the following formula:

$$SD(C) = \sqrt{SD\ (B)^2 + SD(E)^2 - (2 \times R \times SD(B) \times SD(E)}$$

Where, SD(C) was the SD change of HbA1c level in the intervention group, SD(B) was the SD of baseline HbA1c level in the intervention group, SD(E) was the final SD of HbA1C level in the intervention group and R was the correlation coefficient.

The value of correlation coefficient (R) was calculated from one study reporting the complete data and hence was substituted into the calculation of the overall change of SD. Assuming that one study (RCT_x), included in the present meta-analysis reported the values of means and SD of HbA1C level for change and for baseline and final point and then the formula could be presented as:

$$R = \frac{SD_x\ (B)^2 + SD_x(E)^2 - SD_x(C)^2}{2 \times SD_x\ (B) \times SD_x(E)}$$

Where, SD_x(B) was the baseline SD ofHbA1C level of the intervention group in RCT_x, SD_x(E) was the final SD of HbA1C level of the intervention group in RCT_x, and SD_x(C) was the SD change of HbA1C level of the intervention group in RCT_x. The SD change of HbA1C level in control groups was also be calculated by using the above formulas.

In the present meta-analysis, the outcome of interest was the mean reduction in HbA1c level of the intervention and control groups over the follow-up period of the study. For the meta-analysis of continuous data, standard mean difference (SMD) the estimated

confidence intervals (CIs) for SMD were 95%. The Chi square (χ^2) test was used to evaluate the heterogeneity between the included studies. A p value $\leq$ 0.1 was considered as statistically significant. In the presence of heterogeneity (p value $\leq$0.1), the outcomes were combined by using a random-effect model whereas in the absence of heterogeneity (p value $\geq$0.1), outcomes were combined by using the fixed-effect model. Visual inspection of funnel plot of SMD against standard error (SE) was used to identify the publication bias. Asymmetry of funnel plot was tested by Egger's test (p value $\leq$0.05 was statistical significant). Statistical analysis was performed by using Review Manager (version 5.3).

Results

Selection and characteristics of studies

The literature search identified 1989 titles/abstracts and those containing key terms were selected (n=291). A total of 205 studies were found after removing duplicates. Thirteen randomized controlled trials (RCTs) fulfilled the inclusion and exclusion criteria of study and were included in this meta-analysis.

The studies were conducted in USA,[17] UK,[18] Belgium,[19] Brazil,[20] Jordan,[21] Taiwan,[22] Iraq,[23] Iran,[24] India,[25] China,[26,27] and Malaysia.[28,29] **Figure 1** depicts the study selection conducted according to the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) Statement.

From the thirteen trials, eleven RCTs were conducted at a single centre (hospitals or clinic) while two were multicentre studies (community pharmacies). Seven RCTs included follow-up period of ≤ 6 months, the remainder being greater than 6 months. The total patient sample across all the studies was 1828 patients. All 13 RCTs included type 2 diabetes mellitus patients. Eleven of the 13 RCTs reported the age of patients and only included adults. The basic characteristics of the studies included are summarized in **Table 1**.

Methodological quality of included studies

The methodological quality of the included RCTs was variable. Allocation concealment from the patients was not feasible; therefore, RCTs have not properly described how they address the allocation concealment. Due to the nature of pharmaceutical care interventions, the majority of the RCTs were not completely blinded. Two RCTs were assigned 1++, six RCTs as 1+ and five RCTs were assigned 1-. These scores are listed in **Table 1**.

Types of interventions included

The basic components of the interventions are summarized in **Table 2**. Eleven studies included interventions provided by clinical pharmacists in the hospital setting and two studies involved service provision via community pharmacists. Four RCTs described the training pharmacists received including an 8-hour diabetes training program, ambulatory care training, training session on pathophysiology of T2DM and pharmacological and non-

pharmacological management and certified diabetes education. The basic components of interventions included: care plan development, medication review, patient education and counselling regarding diabetes, its complications, medications, life-style modification, exercise and self-monitoring. In some studies, patients received verbal as well as written information. Almost all RCTs included patient- pharmacist's face-to-face interviews however, some studies also included follow-up telephone calls along with patient visits to the study site.

Impact of pharmacists' interventions on change in HbA1c level

Ten RCTs reported change in $HbA1_c$ level as the primary clinical outcome and in three RCTs it was the secondary clinical outcome. Two RCTs reported mean and SD changes of HbA1c level from baseline to final point for both groups. Eleven RCTs included the means (and SD) of $HbA1_c$ levels for both groups at baseline and final point. For these studies the mean (and SD) changes of HbA1c levels were calculated for both groups by using an imputed value. Differences in changes of HbA1c between intervention and control groups are summarized for each study in **Table 3**.

All RCTs have shown statistically significant reductions in HbA1c level. This showed that pharmacists' interventions led to an improved glycemic control as compared to control group. There was significant heterogeneity of SMD (χ^2= 68.96: df=12; p=0.00001). Thus, the random effect (RE) model was used to combine the outcomes. The pooled estimate of 13 trials presented a statistically significant reduction in HbA1c for intervention group patients in comparison to control group patients. The SMD and 95% CIs for 13 RCTs analysed are presented as a forest plot in **Figure 2**. The present study reported a statistically significant difference in pooled effect size that favoured the pharmaceutical care group over the control group (SMD = -0.97; 95% CI -1.21 to -0.73; z = 7.87; p=0.00001).

Potential publication bias

Publication bias (also known as reporting bias) was evaluated by creating a Begg-Mazumdar's funnel plot (**Figure 3**). The results did not show any publication bias in the studies.

Discussion

Glycemic control represented by HbA1c, is an important test for the measurement of effective blood glucose control in diabetic patients over time. The aim of the present meta-analysis was to collect and quantitatively analyze HbA1c data from RCTs that implemented a pharmaceutical care intervention that involved a pharmacist. The results of this analysis would therefore provide evidence as to whether pharmaceutical care interventions were effective in reducing HbA1c levels in patients with diabetes type 2 and what these interventions were. The findings of this meta-analysis report a statistically significant reduction in the HbA1c level i.e. ≥0.50% in the pharmaceutical care intervention group as compared to controls. These results are consistent with the findings of an earlier meta-analysis demonstrating significant improvements in diabetic patients receiving pharmaceutical care.[12,30] It would appear that the effects of the pharmaceutical care model have been sustainable over time.

The components of pharmaceutical care which were most commonly implemented included: care plan development, medication review, patient education (via verbal and written information) and counselling regarding diabetes, its complications, medications, life-style modification, exercise and self-monitoring. RCTs with patient education relating to self-monitoring and self-management of diabetes reported statistically significant improvements in glycosylated hemoglobin levels. These findings provided the evidence for the effective role of pharmacists in patient education and counselling. Our findings are supported by a previous meta-analysis (that included studies published prior to 1999), that reported effective patient education led to statistically significant improvement in glycemic control.[31]

Four RCTs included interventions conducted by well-trained pharmacists reporting statistically significant decreases in HbA1c levels in the intervention group compared with the control group. These findings highlight the importance of well-trained pharmacists for successful implementation of PC and for improving the patient outcomes. The present study findings are in line with a previous systematic review showing the improved outcomes resulted from the interventions conducted by well-trained interventionists (pharmacists).[32]

The emergence of clinical pharmacy services is at early stages of development in some developing countries. In the present meta-analysis, except for three RCTs (US, UK, Belgium) all the others were conducted in developing countries (Brazil, China, Jordan, India, Iran, Iraq, Malaysia and Taiwan). Type 2 diabetes has become a major health problem in developing countries; therefore, strategies are required for treatment as well as prevention of this condition. The findings from a recent systematic review and meta-analysis provided the evidence for the effectiveness of different strategies in type 2 diabetes mellitus prevention.[33]

The present systematic review showed that RCTs with follow-up of greater than 6 months report more significant mean reductions in HbA1c levels than RCTs with shorter follow-up. This suggests that better control is afforded through sustained PC interventions. The present study supports the previous meta-analysis in reporting a high mean reduction in glycosylated hemoglobin level resulting from longer follow-up.[13]

Implications for practice

The main aim of this study was to evaluate the effect of pharmaceutical care on glycemic control in patients with type 2 diabetes mellitus. We have done so by systematically searching and reporting on the outcome of pharmaceutical care in the management of type 2 diabetes, with special attention to the effect of pharmacists' interventions. Our findings suggest that globally, there is great variability in the use of pharmaceutical care for achieving clinical outcomes (e.g. glycemic control). Published RCTs have clearly demonstrated that pharmaceutical care interventions are effective in glycemic control in type 2 diabetes mellitus patients. The literature also shows that pharmacists have specific set of skills, strategies, and practices related to medicines use and this sets apart the work of the pharmacist from other members of the healthcare team. The data also suggest the description of the interventions regarding how to develop and support the patient-centred activities in the management of type 2 diabetes.

Limitations

The present meta-analysis has limitations based on the reporting bias in some of the RCTs that may be due to the reporting of the desired outcome (reduction in HbA1c) as a

secondary outcome measure. Furthermore, there is heterogeneity in the studies including; smaller study sample size, shorter follow-up time period and study setting.

This study quantitatively analyses only RCTs and excludes all other interventional studies including; non-RCTs, cohort and pre-post studies to minimize the selection bias of patients. Additionally, the present study includes only patients diagnosed with type 2 diabetes mellitus to minimize the heterogeneity of the patient population. The results cannot be generalized to community pharmacies as most the clinical trials included were performed in hospitals or clinics. Future research is needed with pharmaceutical care conducted by well-trained pharmacists with longer term follow-up.

Conclusion

Quantitative analysis of the collective literature suggests that pharmaceutical care interventions are effective (at least in short-term follow-up in hospital setting) in reducing HbA1c levels in type 2 diabetes mellitus patients. Pharmacists working alone or in collaboration with other health professionals have a significant impact on improving the health status of patients with type 2 diabetes mellitus.

References

1. Clifford RM *et al*. Effect of a Pharmaceutical Care Program on Vascular Risk Factors in Type 2 Diabetes The Fremantle Diabetes Study. *Diabetes Care* 2005;28(4):771-6.
2. Shaw JE *et al*. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87(1):4-14.
3. Pladevall M *et al*. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care* 2004;27(12):2800-5.
4. Group UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317(7160):703.
5. Stratton IM *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321(7258):405-12.
6. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1990;47(3):533-43.
7. Beney J *et al*. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. The Cochrane Library. 2000.
8. Gold R *et al*. Synchronous provider visit and self-management education improves glycemic control in Hispanic patients with long-standing type 2 diabetes. *Diabetes Educ* 2008;34(6):990-5.
9. Howteerakul N *et al*. Adherence to Regimens and Glycemic Control of Patients with Type 2 Diabetes Attending. *Asia Pac J Public Health* 2007;19(1).
10. Omran D *et al*. Systematic review of pharmacist interventions to improve adherence to oral antidiabetic medications in people with type 2 diabetes. *Can J Diabetes* 2012;36(5):292-9.
11. Antoine S-L *et al*. Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a systematic review of randomized controlled trials. *BMC Endocr Disord* 2014;14(1):53.
12. Li X *et al*. Effect of pharmaceutical care programs on glycemic control in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *J Pharm Technol* 2010;26(5):255-63.
13. Collins C *et al*. Effect of pharmacist intervention on glycemic control in diabetes. *Diabetes Res Clin Pract* 2011;92(2):145-52.
14. Poolsup N *et al*. Effect of Pharmacist's Interventions on Glycemic Control in Diabetic Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Mahidol University Journal of Pharmaceutical Sciences* 2013; 40 (4), 17-30
15. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guidline developer's handbook. 2011.
16. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions 5.0. 2 [updated September 2009]. The Cochrane Collaboration 2009. Available from www cochrane-handbook org. 2008.
17. Jacobs M *et al*. Pharmacist Assisted Medication Program Enhancing the Regulation of Diabetes (PAMPERED) study. *J Am Pharm Assoc* 2011;52(5):613-21.
18. Ali M *et al*. Impact of community pharmacy diabetes monitoring and education programme on diabetes management: a randomized controlled study. *Diabetic Med* 2012;29(9):e326-e33.
19. Mehuys E *et al*. Effectiveness of a community pharmacist intervention in diabetes care: a randomized controlled trial. *J Clin Pharm Ther* 2011;36(5):602-13.
20. Cani CG *et al*. Improvement in medication adherence and self-management of diabetes with a clinical pharmacy program: a randomized controlled trial in patients with type 2 diabetes undergoing insulin therapy at a teaching hospital. *Clinics* 2015;70(2):102-6.

21. Wishah RA *et al*. Impact of pharmaceutical care interventions on glycemic control and other health-related clinical outcomes in patients with type 2 diabetes: Randomized controlled trial. *Diabetes Metab Syndr* 2015;9 271-6.
22. Chen J-H *et al*. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. *Int J Clin Pharm* 2015:1-8.
23. Mahwi TO, Obied KA. Role of the Pharmaceutical care in the management of patients with Type 2 Diabetes mellitus. *Int J Pharm Sci Res* 2013;4(4):1363-9.
24. Farsaei S *et al*. Effect of pharmacist-led patient education on glycemic control of type 2 diabetics: a randomized controlled trial. *J Res Med Sci* 2011;16(1):43-9.
25. Sriram S *et al*. Impact of pharmaceutical care on quality of life in patients with type 2 diabetes mellitus. *J Res Med Sc*i 2011;16(Suppl1):S412.
26. Xin C *et al*. effect of pharmaceutical care on medication adherence of patients newly prescribed insulin therapy: a randomized controlled study. *Patient Prefer Adherence* 2015;9:797-802.
27. Chan C-W *et al*. A Pharmacist Care Program Positive Impact on Cardiac Risk in Patients With Type 2 Diabetes. *J Cardiovasc Pharmacol Ther* 2012;17(1):57-64.
28. Butt M *et al*. Impact of a pharmacist led diabetes mellitus intervention on HbA1c, medication adherence and quality of life: A randomised controlled study. *Saudi Pharmaceutical Journal*. 2015:1-9.
29. Chung WW *et al*. Effects of a pharmaceutical care model on medication adherence and glycemic control of people with type 2 diabetes. *Patient Prefer Adherence* 2014;8:1185-94.
30. Machado M *et al*. Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. *Ann Pharmacother* 2007;41(10):1569-82.
31. Norris SL *et al*. Self-Management education for adults with type 2 Diabetes A meta-analysis of the effect on glycemic control. *Diabetes Care* 2002;25(7):1159-71.
32. Sapkota S *et al*. A Systematic Review of Interventions Addressing Adherence to Anti-Diabetic Medications in Patients with Type 2 Diabetes—Components of Interventions. *PloS One* 2015;10(6).
33. Merlotti C *et al*. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. *Diabetes Obes Metab* 2014;16(8):719-27.

Table 1. Basic characteristics of included studies (n=13)

Reference	Country	Sample size (completed follow-up)	Study site	Study design	Randomization method	Study population	Quality grade
Wishah et al. (2015)	Jordan	106 patients (IG= 52 CG=54)	Diabetes clinic Jordan University Hospital	Randomized controlled clinical trial	Coin-toss method	Aged ≥18 years, diagnosed with type 2 diabetes (T2DM), HbA1C ≥6.5% for initial diagnosis and >7% for uncontrolled diabetes	1+
Chen et al. (2015)	Taiwan	100 patients (IG=50 CG=50)	Nantou Hospital	Randomized controlled trial	Random numbers generated by SAS 9.2	Aged ≥65 years, ambulatory patients with T2DM, with HbA1C ≥9.0%	1+
Xin et al. (2015)	China	227 patients (IG=114 CG=113)	Tongde Hospital	Prospective Randomized controlled study	NR	Aged ≥18 years, diagnosed with T2DM, patients had no evidence of filled prescription in insulin therapeutic during previous 18 months	1+
Butt et al. (2015)	Malaysia	66 patients (IG=33 CG=33)	University Medical center	Randomized controlled study	Envelop picking	Diagnosed with poorly controlled T2DM with HbA1C ≥8%	1++
Cani et al. (2015)	Brazil	70 patients (IG=34 CG=36)	Diabetes out-patient clinic of hospital	Randomized controlled trial	Simple randomization	Aged ≥45 years, Diagnosed with T2DM and on insulin	1-

						prescription, HbA1C >8%	
Chung et al. (2014)	Malaysia	241 patients (IG=120 CG=121)	Teaching hospital	Prospective Randomized controlled trial	NR	Aged 21-75 years T2DM, taking at-least one anti-diabetic medication, HbA1C ≥8%	1-
Mahwi et al. (2013)	Iraq	123 patients (IG=62 CG=61)	Diabetes center	Prospective Randomized controlled trial	Simple randomization technique	Aged 30-80 years, T2DM patients	1-
Ali et al. (2012)	England	46 patients (IG=23 CG=23)	2 community pharmacies	Randomized controlled study	Computer generated randomized list	Aged >18 years, T2DM and oral medication, HbA1C ≥7%	1+
Chan et al. (2012)	China	105 patients (IG=51 CG=54)	Diabetes clinic	Randomized controlled study	Computer generated and sealed envelope (pharmacists were blind)	Aged ≥ 18 years, T2DM, with at least 5 drugs (1 hypoglycemic drug) and HbA1C ≥8%	1++
Jacobs et al. (2012)	USA	164 patients (IG=72 CG=92)	Lahey clinic in Burlington	Randomized controlled practice study	Computer randomized sequence of ones and zeros	Aged > 18 years, T2DM, HbA1C >8%	1+
Farsaei et al. (2011)	Iran	172 patients (IG=86 CG=86)	Isfahan Endocrine and Metabolism Research Center	Randomized controlled clinical trial	NR	T2DM patients, HbA1C >7%, with stable therapeutic condition	1-
Mehuys et al. (2011)	Belgium	288 patients (IG=153 CG=135)	66 community pharmacies	Randomized controlled parallel group trial	Randomization was done at pharmacy level by random numbers table generated by using SPSS 14.0 software	Aged 45-75 years, T2DM patients, on oral hypoglycemic medication	1+
Sriram et al. (2011)	India	120 patients (IG=60 CG=60)	Tertiary care teaching hospital	Prospective randomized trial	Random number table	Aged >18 years, T2DM patients	1-

Table 2. Basic components of interventions in RCTs (n=13)

Reference	Follow up period	Interventions provided	Interventionist (team members)	Training of interventionist	Usual care	HbA1C reported outcome measure
Wishah et al. (2015)	6 months	Individual patient care plan was developed and discussed with physician. Pharmacist provided patient education and counselling about disease and medication. Printed leaflets were also given to patients.	Clinical pharmacist, physician	N/A	Usual care provided by medical and nursing staff	Primary outcome
Chen et al. (2015)	6 months	Pharmaceutical care comprised of assessment of adherence to pill box use and insulin injection technique. Diabetes-related care was provided including patient education and recommendation to physician and referral to diabetes care team	Clinical pharmacist	Pharmacist was a certified diabetes educator	Usual care	Primary outcome measured every 3 or 6 months
Xin et al. (2015)	12 months	Pharmaceutical care program was developed for individual patient. Intervention consist of individualized education, educative group activities and telephone counselling	Clinical pharmacist	NR	Usual care with appointments with physician once every month	Secondary outcome
Butt et al. (2015)	6 months	Patients received usual as well as pharmacist care. Patients received counselling about diabetes, complications, medication, adherence, life-style modification and self-monitoring.	Clinical pharmacist	NR	Patient-physician meeting ranging every 4 to 9 months. Patients with poor glycemic control were referred to nurse diabetes educator	Primary outcome
Cani et al. (2015)	6 months	Individualized pharmacotherapy plan was developed. Patients were educated. Pill organizers were given. Written information on acute and chronic complications and importance of life style changes and regular foot inspection etc.	Clinical pharmacist	NR	Standard care. They did not receive advice from clinical pharmacist but were allowed to request information anytime	Primary outcome

Chung et al. (2014)	12 months	Pharmaceutical care. Pharmacist reviewed the medications and tried to resolve any DRPs. Patients received education about disease as well as medication. Received monthly follow-up telephone calls.	Clinical pharmacist	NR	Standard pharmacy services	Primary outcome
Mahwi et al. (2013)	4 months	Pharmaceutical care. Patients were followed for 3 visits with continuous weekly telephone calls	Clinical pharmacist	NR	Standard medical care	Primary outcome
Ali et al. (2012)	12 months	Pharmacists carried out medication review, life style modification counselling. Patients were seen by pharmacists every month for 12 months	Community pharmacist	Pharmacists undertook an 8-hours training program	Usual care received from physicians, practice nurse and community pharmacy	Primary outcome
Chan et al. (2012)	9 months	Patients were interviewed by pharmacist before each physician visit. Complete medication history was recorded and importance of medication adherence was reinforced	Clinical pharmacist	NR	Patients received same medical care without pharmacist	Secondary outcome
Jacobs et al. (2012)	12 months	Comprehensive medication review, education on diabetes and therapies, facilitating self-monitoring of blood glucose and dietary guidelines and exercise	5 Clinical pharmacists	1 pharmacist was trained in ambulatory care and experience in chronic disease patients. Other 4 pharmacists have 10 years' experience in ambulatory care practice	Usual care provided by physicians	Primary outcome
Farsaei et al. (2011)	3 months	Patients participated in two educational sessions. First session was about classification of anti-hyperglycemic agents and the second was education regarding adherence and self-management. Patients were followed by weekly telephone calls	Clinical pharmacist	NR	General education provided by nursing staff	Primary outcome
Mehuys et al. (2011)	6 months	Education about T2DM, hypoglycemic agents, medication adherence, healthy life-style, and reminders about eye and foot examination	Community pharmacists	Training session on pathophysiology of T2DM and pharmacological and non-pharmacological management	Usual care	Primary outcome

Sriram et al. (2011)	8 months	Pharmaceutical care including medication counseling, instructions on diet regulation, exercise and life-style modification. Written information was also provided	Clinical pharmacist	NR	Usual care	No clear description as primary or secondary But I think it is sec

Table 3. Influence of pharmacists' interventions on HbA1c (%)

References	**Intervention group**		**Control group**	
	Average differences in A1c values (Mean ±SD)	**Patient numbers**	**Average differences in A1c values (Mean** ±SD)	**Patient numbers**
Wishah et al. (2015)	-1.7±1.24	52	-0.3±1.12	54
Chen et al. (2015)	-0.83±1.31	50	0.43±1.3	50
Xin et al. (2015)	-2.36±2.14	114	-0.77±1.71	113
Butt et al. (2015)	-1.19±1.35	33	-0.38±1.31	33
Cani et al. (2015)	-0.57±1.26	34	-0.08±1.34	36
Chung et al. (2014)	-1.4±1.1	120	-0.2±1.42	121
Mahwi et al. (2013)	-2.33±1.63	62	-0.47±2.17	61
Ali et al. (2012)	-1.6±1.34	23	-0.6±0.75	23
Chan et al. (2012)	-1.57±1.50	51	-0.40±1.19	54
Jacobs et al. (2012)	-1.8±1.03	72	-0.8±1.24	92
Farsaei et al. (2011)	-1.8±1.4	86	0.1 ±1	86
Mehuys et al. (2011)	-0.6 ±1.30	153	-0.1±0.96	135
Sriram et al. (2011)	-1.71±0.5	60	-0.72±0.39	60

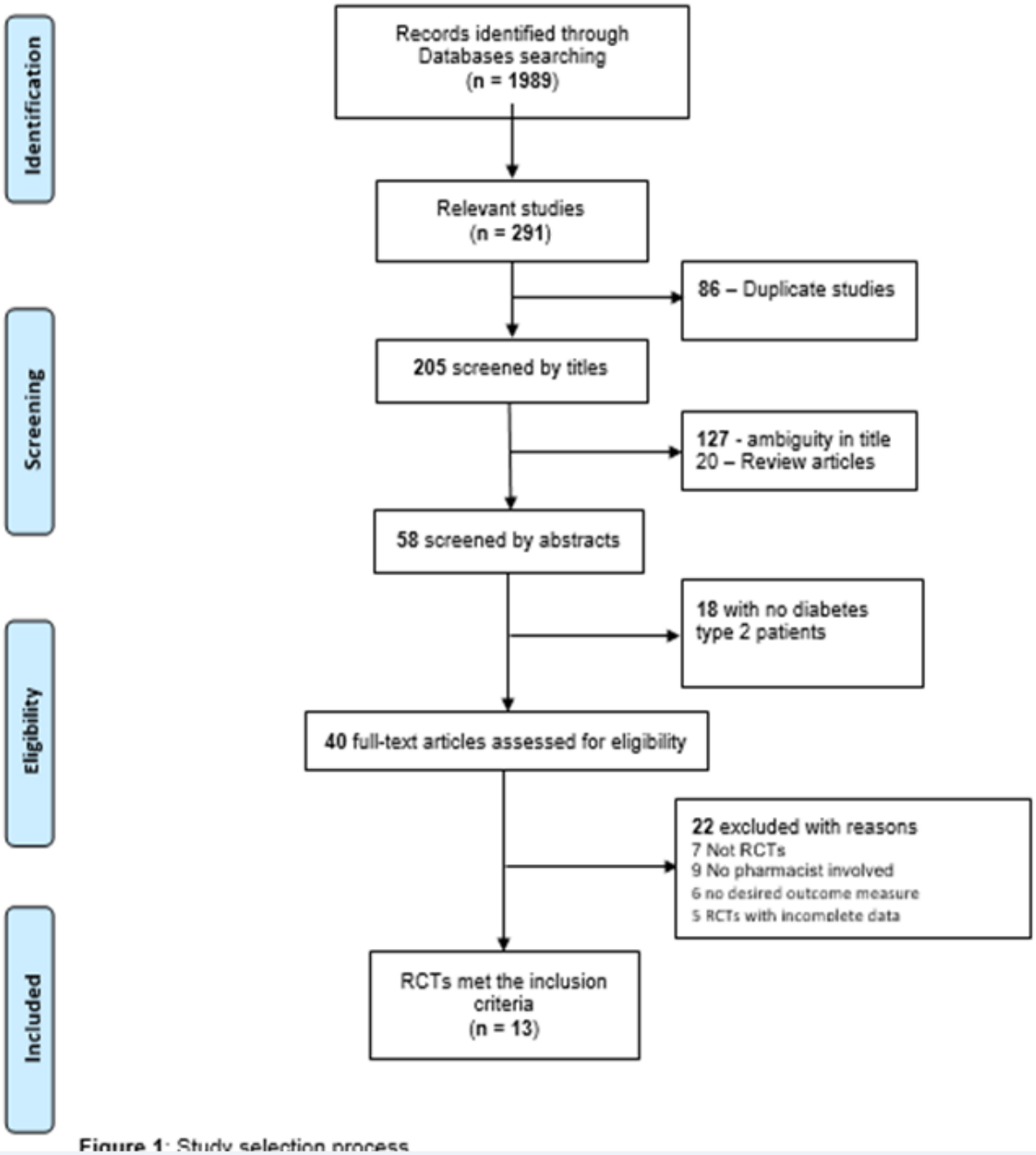

Figure 1: Study selection process

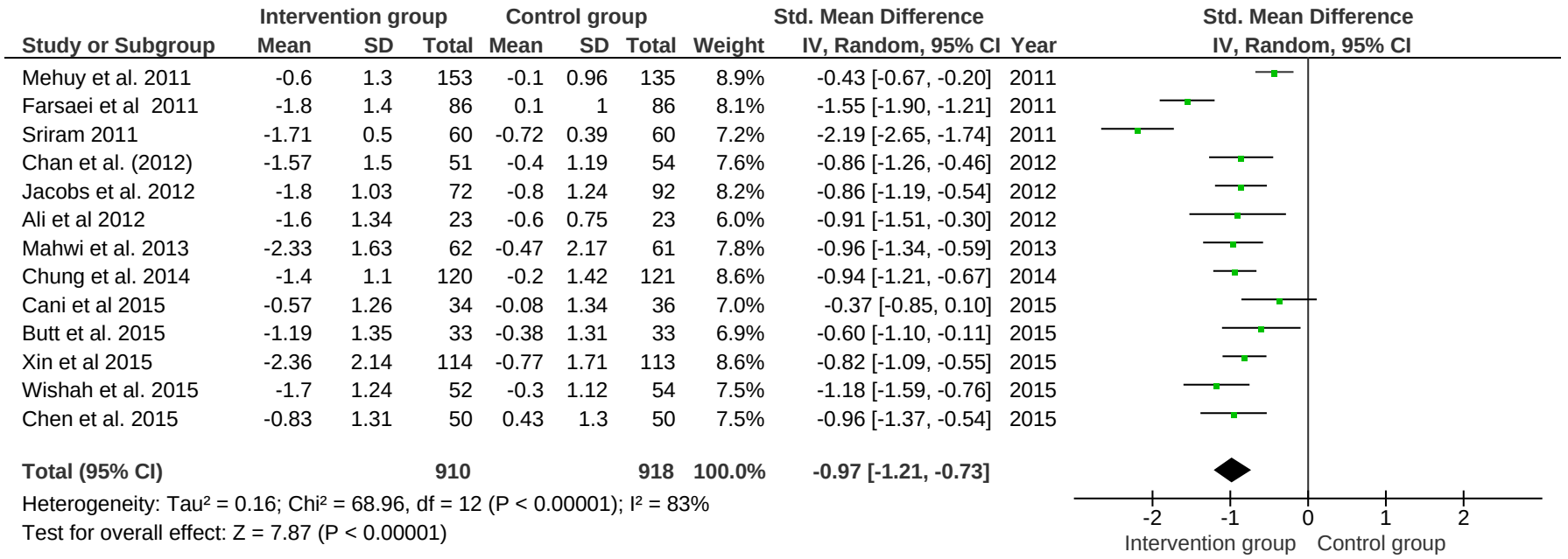

Figure 2. Forest plot of HbA1c change between intervention group and control group (effect size)

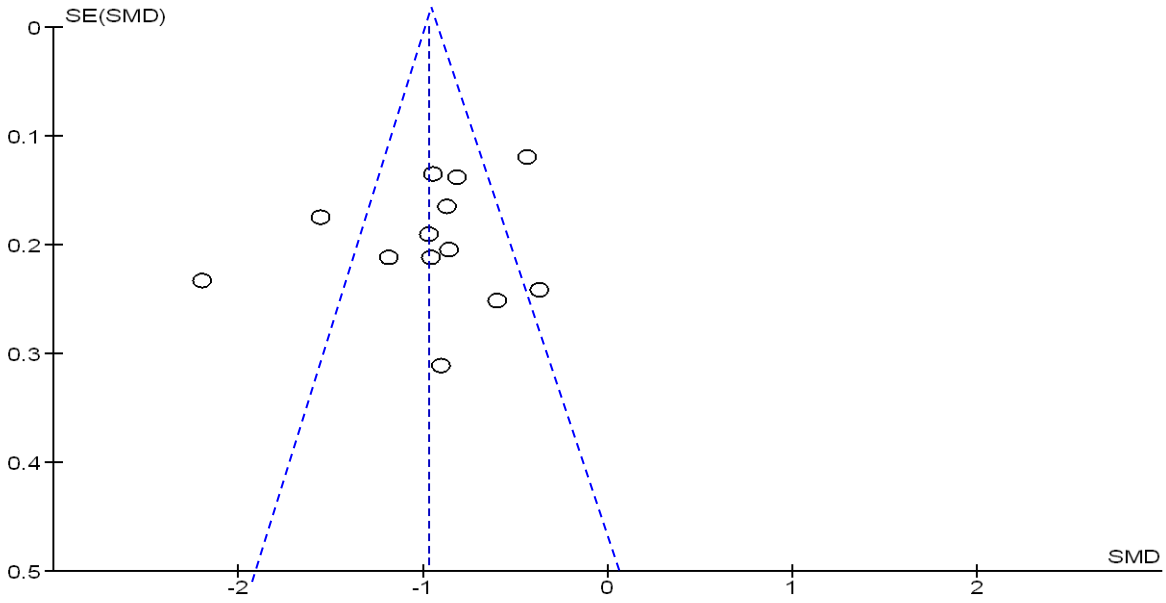

Figure 3. Funnel plot of standard error against standard mean difference (SMD)