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Original Research

Clinical pharmacists´ interventions in the management of type 2 diabetes mellitus: a systematic review

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Abstract

Background: Type 2 diabetes mellitus is a chronic disease that is reaching epidemic proportions worldwide. It is imperative to adopt an integrated strategy, which involves a close collaboration between the patient and a multidisciplinary team of which pharmacists should be integral elements.

Objective: This work aims to identify and summarize the main effects of interventions carried out by clinical pharmacists in the management of patients with type 2 diabetes, considering clinical, humanistic and economic outcomes.

Methods: PubMed and Cochrane Central Register of Controlled Trials were searched for randomized controlled trials assessing the effectiveness of such interventions compared with usual care that took place in hospitals or outpatient facilities.

Results: This review included 39 studies, involving a total of 5,474 participants. Beneficial effects were observed on various clinical outcomes such as glycemia, blood pressure, lipid profile, body mass index and coronary heart disease risk. For the following parameters, the range for the difference in change from baseline to final follow-up between the intervention and control groups was: HbA1c, -0.05% to -2.1%; systolic blood pressure, +3.45 mmHg to -10.6 mmHg; total cholesterol, +10.06 mg/dL to -32.48 mg/dL; body mass index, +0.6 kg/m^2 to -1.94 kg/m^2; and coronary heart disease risk, -3.0% and -12.0% (among the studies that used Framinghan prediction method). The effect on medication adherence and health-related quality of life was also positive. In the studies that performed an economic evaluation, the interventions proved to be economically viable.

Conclusions: These findings support and encourage the integration of clinical pharmacists into multidisciplinary teams, underlining their role in improving the management of type 2 diabetes.

Keywords

Diabetes Mellitus, Type 2; Pharmacists; Pharmacies; Pharmaceutical Services; Blood Glucose; Glycated Hemoglobin A; Quality of Life; Medication Adherence; Cost-Benefit Analysis; Systematic Reviews as Topic

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by several pathophysiologic alterations, including insulin resistance and a progressive decrease in insulin secretion, ultimately leading to increased blood glucose levels.[1,2] This multifactorial disease results from the interaction between genetic, epigenetic and lifestyle factors that act in a specific sociocultural environment.[1] Diabetes-related complications such microvascular and macrovascular alterations, resulting from uncontrolled glycemic levels are responsible for an increased morbidity and mortality, and reduced health-related quality of life.[3,4] The burden of diabetes and diabetic associated complications results in worrisome increased global health expenditure.

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Evidences from the literature suggest that despite tighter control of blood glucose and other cardiovascular risk factors, such as blood pressure and serum lipids as well as the huge number therapies available, recommended targets are hardly achieved among patients with T2DM.[5-7] These unsatisfactory outcomes may result from inadequate intervention strategies by healthcare providers, or patient related problems, such as lack of compliance.[8,9]

To achieve these targets and improves therapeutic outcomes, new healthcare models, based in a collaborative, proactive and integrated team work in which patients play an active role should be implemented.[1,10-12] Some systematic reviews have addressed this topic however they failed in critical review the economic outcomes.[13-17]

The aim of this study is to review and investigate the effect of interventions performed by clinical pharmacists on the management of T2DM, considering clinical, humanistic and economic outcomes, and focusing solely on randomized controlled trials conducted in hospitals or ambulatory healthcare centers.

METHODS

Search strategy and inclusion criteria

Two electronic databases (PubMed and Cochrane Central Register of Controlled Trials) were searched from inception to 13th September 2017 and updated in 30th June 2020.

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The PubMed search strategy served as a template for the search strategy used in the Cochrane Central Register of Controlled Trials database. The search terms included medical subject headings and text terms combined with Boolean operators (Online appendix 1).

Studies were eligible for inclusion if they were in accordance with the following criteria: (1) randomized controlled trials evaluating the effectiveness of interventions provided by pharmacists for patients with T2DM in comparison to usual care were eligible; (2) Studies that took place in hospitals or outpatient centers (e.g. health care centers and clinics) and reported data on one or more of the following outcomes were suitable for this systematic review: glycosylated hemoglobin (HbA1c), blood glucose (fasting or postprandial), blood pressure, lipid profile [total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density (HDL) cholesterol and triglycerides], body mass index, 10-year coronary heart disease (CHD) risk, medication adherence, health-related quality of life (HRQoL) and economic analysis; (3) papers published in English, French, Spanish, or Portuguese; (4) no limitation regarding publication year was imposed.

Study selection

Two reviewers independently screened all titles and abstracts retrieved from the electronic databases using the prespecified inclusion criteria. Then, the full-text of each potentially eligible article was obtained and screened independently by two reviewers to further assess its suitability for inclusion in this review. Preferred reporting items for systematic reviews (PRISMA) standard guidelines were followed when applicable as per recommended practice.[18] Any disagreement was resolved through discussion.

Data extraction and synthesis

A single reviewer extracted data from included studies. Subsequently, another reviewer independently checked the extracted data. The data extracted were summarized in Online appendix 2. The study results for each outcome were presented as change from baseline to final follow-up in both intervention and control groups. When not reported, the difference in change between groups was calculated (change from baseline in intervention group minus change from baseline in control group). To allow comparisons, when necessary, the units of measurement of the clinical results were standardized.

Risk of bias assessment

Two reviewers independently assessed the risk of bias in included studies using the Cochrane risk of bias tool.[19] Due to the allocation concealment methods and cross contamination between participants, the evaluation of bias (blinding) in the included studies was difficult. Given the nature of the interventions under analysis, the criteria concerning blinding of participants and personnel were not considered.

RESULTS

The databases search yielded a total of 748 citations. After screening titles and abstracts, 84 citations potentially met the inclusion criteria. After full-reading, 39 studies met the inclusion criteria and were included in this systematic review (Figure 1).[20-58] Additionally, three study 59-61 reports found among the search results were also obtained and used to extract data as they contained relevant outcome information from some included studies.

Among the included studies, nine were conducted in North America, five in South America, three in Europe, one in Africa, and twenty one in Asia. The settings in which the studies took place included hospitals, primary care health centers and outpatient medical clinics. Pharmacist interventions varied across the studies and were summarized in Online appendix 2. Globally, the included studies involved a total of 6,411 participants. The duration of follow-up ranged from 45 days to 24 months. A detailed description of the characteristics of included studies is presented in Online appendix 2.

Study risk of bias

The risk of bias varied among the 39 studies (Figure 2 and Online appendix 1). In 18 (46.2%) of them, the allocation sequence was sufficiently generated. The allocation sequence was concealed, and outcome assessors were blinded in only a few studies (7.7% and 2.6%, respectively). In most studies (97.5%), there was or might have been a risk of bias due to selective outcome reporting. Only 13 studies (33.3%) reported outcome data completely, and 19 studies (48.7%) were free of other source of bias.

HbA1c and blood glucose

The mean HbA1c value decreased from baseline to follow-up in the intervention group in all studies (Online appendix 3), but this decrease reached statistical significant for only sixteen studies (47%).[23,25,27-29,35,37-39,41,42,45,50,52,56,57] In these studies, the difference showed in HbA1c change from baseline to final follow-up between the intervention group and the control group ranged from -0.05% to -2.1%. Regarding blood glucose, 22 studies reported this parameter as an outcome measure (Online appendix 3). Only six studies (27%) reported a statistically significant decrease in blood glucose (fasting or postprandial).[39,40,42,45,46,56] Overall, the difference in change between both groups, which ranged from -7.74 mg/dL to -76.32 mg/dL.

Blood pressure

Twenty studies evaluated the change in systolic blood pressure (SBP) during the course of the study (Online appendix 3). The difference in change between the two groups ranged from +3.45 mmHg to -10.6 mmHg and was shown to be statistically significant in only seven studies (33.3%).[31,35,39-42,45,50,53,56,57] As for diastolic blood pressure (DBP), 15 studies reported data on this outcome (Online appendix 3). However, only three studies revealed a statistically significant difference in change from baseline to final follow-up between both groups.[39,41,53] The difference in change between the two groups ranged from +1.32 mmHg to -9.1 mmHg.

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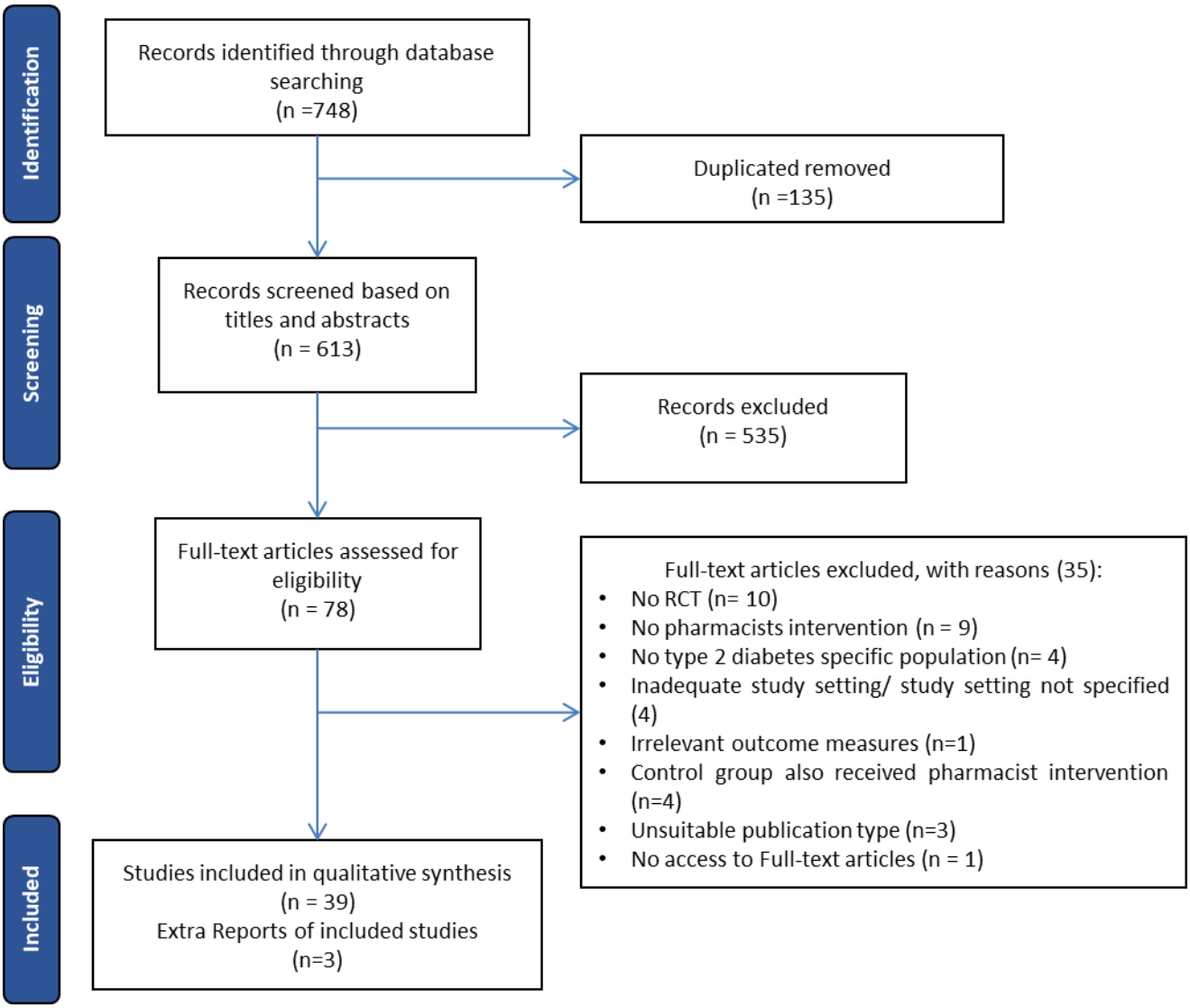

Figure 1. PRISMA flow-chart

Lipid profile

Fifteen studies described total cholesterol as an outcome measure (Online appendix 4). However, only four studies (26.7%) reported as statistically significant in only three studies.[39,41,45] The difference in change between both groups, ranged from +10.06 mg/dL to -32.48 mg/dL. Regarding LDL cholesterol, 21 studies reported data on this outcome (Online appendix 4). For this parameter, the difference in change between both groups ranged from +2.1 mg/dL to -27 mg/dL, and was reported as statistically significant in only seven studies (33.3%).[27,29,35,39,40,45,57]

Among the 15 studies that reported HDL cholesterol as an outcome measure (Online appendix 4), the difference in change between both groups was shown to be statistically significant in only one study (6.7%) 45. The difference in change between the two groups ranged from -5.8 mg/dL to +11 mg/dL. Finally, 16 studies reported data on triglycerides (Online appendix 4) and three studies (18.8%) 39, 40, 45, observed a statistical significance in change between the two groups, ranged from +21.26 mg/dL to -62.0 mg/dL.

Body mass index

Sixteen studies described body mass index (BMI) as an outcome measure (Online appendix 4. Although eleven studies reported a greater reduction in this group in comparison with the control group, Only one study (6.3%) revealed a statistically significant difference in change between both groups.[41] The difference in change between the two groups ranged from +0.6 kg/m^2 to -1.94 kg/m^2.

10-year CHD risk

CHD risk was predicted among study participants in five studies. As observed in Online appendix 4, different methods were used to estimate this outcome. In comparison with the control group, the difference in change between the two groups was reported as statistically significant in only two studies (40%).[27,53] Because the methods used to assess this risk varied among studies, it is not possible to define a range for the difference in change between both groups across all studies. However, among the studies that used the Framingham prediction method, this difference was -3.0% and -12.0%, respectively.

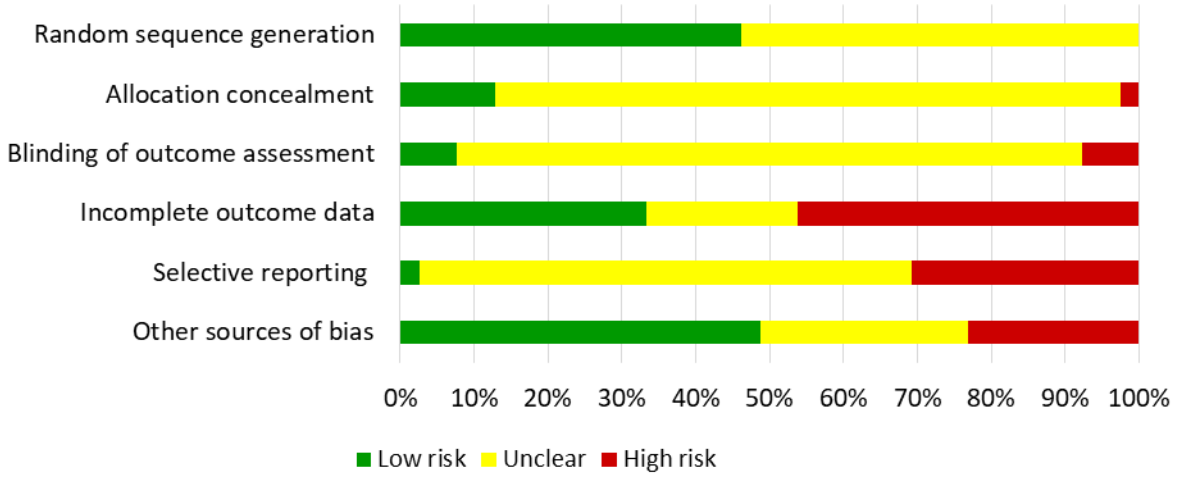

Figure 2. Risk of bias in included studies (percentage across all studies)

Medication adherence and Health-related quality of life

Medication adherence was evaluated, using different methods, in 20 studies. In 12 studies, a greater improvement in medication adherence was observed in the intervention group when compared with the control group, but only four studies reported a statistically significant difference.[23,25,27,35] Regarding HRQoL, despite, the different tools used, only one 25 of the twelve studies that measures this outcome reported a statistically significant difference in change between the two groups (Online appendix 5).

Economic outcomes

Six studies performed an economic analysis, but only 2 provided the p-values, and only one of these was <0.05. Adibe *et al*. conducted a cost-utility analysis of the pharmaceutical care intervention implemented in their study.[59] This analysis was based on the followed resources: the "cost of the intervention," the "cost of drugs," and the "cost of other health care resource use" (including primary care, hospital care, and auxiliary health care). The total cost per patient per year was USD 326 for the control group and USD 394 for the intervention group (p=0.1009). In addition, quality-adjusted life-year (QALY) per patient per year was 0.64 for the control group and 0.76 for the intervention group p<0.0001).[59] Thus, the authors found that the intervention led to an incremental cost of USD 69 and an incremental effect of 0.12 QALY gained, with an associated incremental cost-utility ratio of USD 571 per QALY gained, demonstrating that the intervention was very cost-effective.[59]

Chan *et al*. estimated the cost-effectiveness of the pharmacist care program based on based on projected cost savings anticipated due to CHD risk reduction.[27] The estimated potential saving in costs was USD 5,086.3 per patient.[27]

Simpson *et al*. also conducted a cost-effectiveness analysis.[61] This analysis was based on followed resource costs: the pharmacist intervention, prescription medications, healthcare services provided by physician specialists and other healthcare professionals, emergency department visits and hospitalizations. The authors found that the total cost per patient per year was CAD 190.00 (USD 151.88) lower in the intervention group compared with the control group, and that the intervention group had a 0.26% greater reduction in the annualized risk of cardiovascular event in comparison with the control group.[61] The cost-effectiveness analysis showed that at a societal willingness-to-pay of CAD 4,000.00 (USD 3,196.22) per 1% reduction in annual cardiovascular risk, the probability that the intervention was cost-effective compared with usual care reached 95%.[61]

In the study reported by Chen *et al*., medical expenses were not significantly different between intervention and control groups (p=0.767).[28] However, regarding pharmacist intervention expenditure based on pharmacist's salary, telephone fees and supplies cost, the mean cost per patient was NTD 1,336. 9 (USD 44.10) in the intervention group and NTD 132 (USD 4.35) in the control group, representing an increase of NTD 1,204.9 (USD 39.73) in cost per patient.[28] Since a decrease of 0.83% in HbA1c mean levels was achieved in the intervention group, the incremental cost per 1% reduction in HbA1c mean levels was NTD 1,451.69 (USD 47.87), which could in part be covered by health insurance reimbursement.[28]

Siaw *et al*. also performed an economic evaluation by calculating direct outpatient medical costs, taking into account consultation visits, laboratory tests and procedures, and medications.[52] The mean cost for direct outpatient diabetes-related care was USD 516.77 in the intervention group and USD 607.78 in the control group, which translated into an average cost saving of USD 91.01 per patient.[52]

Wu *et al*. performed an economic evaluation based on the costs of medical visits (only for the intervention arm), medications, hospitalizations, emergency department visits, laboratory testing, procedures, outsource referral or transfer to other facilities and outpatient clinic visits and observed a decreased by 6% for the group visit but increased by 13% for the standard care arm 13 months post-study (p<0.01).[58]

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DISCUSSION

This systematic review analyzed randomized controlled trials that investigated the effects of different interventions performed by clinical pharmacists on various outcomes related to T2DM care. It stands out from previous systematic reviews because besides demonstrating the positive contribution of clinical pharmacists in the metabolic control of patients with T2DM, it also includes economics and humanistic outcomes of pharmacist's interventions.[13-16,62] Considering, that the role of pharmacists remains undervalued in the context of clinical interventions, specifically directed to patients, in contrast to what happens with other healthcare professional with this work, we also intend to underline that pharmacists are highly capacitated professional that are able to integrate multidisciplinary teams for improving practice strategies such patient's educations, drug review and case management with routine follow up. Frequently, pharmacist interventions involved medication management, educational interventions and referrals to other healthcare professionals or services. The diversity of interventions observed may be related to the difference in roles and integration of pharmacists within healthcare systems in different countries, particularly concerning prescribing authority and autonomy to make medication changes. Evidences from the studies included in this review indicate that clinical pharmacists contribute positively to the management of patients with T2DM. For instance, these types of interventions could be even more effective if they were part of the routine follow-up of the patients.[63]

Indeed, an improvement in HbA1c, blood glucose, blood pressure, lipid profile and BMI in the intervention group was reported in almost all studies.

Our findings are consistent with those of other systematic reviews on this topic. In their review on pharmacist interventions in primary care for patients with diabetes, Wubben *et al*. reported an overall improvement in HbA1c mean levels in the intervention group and the difference in change between intervention and control groups ranged from +0.2% to -2.1%.[16] The fact that pharmacist interventions resulted in a reduction in HbA1c and blood glucose is of great importance, since an improvement in glycemic control is linked to a decreased risk of diabetes-related microvascular complications namely a reduced risk of stroke by 12%, a reduced risk of myocardial infarction by 14% and a reduced risk of heart failure by 16%.[64] Inclusion of fasting or non-fasting blood glucose levels as a primary outcome is of far less clinical relevance than that of HbA1c, especially since so few of these studies showed a statistically significant difference.

Regarding blood pressure, lipid profile and BMI, our findings add to the evidence described in other studies.[15-17,62] For instance, in their review assessing the effects of pharmacist care among outpatients with cardiovascular risk factor in diabetes, Santschi *et al*. reported that pharmacist interventions were associated with significant reductions in SBP and DBP, total cholesterol, LDL cholesterol and BMI compared with usual care, but the same was not observed with HDL cholesterol.[15] Wubben *et al*. also found decreases in blood pressure, low-density cholesterol or triglycerides in the intervention group in most studies, although the difference in change between groups was not significant.[16]

There are few studies assessing CHD risk, after pharmacist interventions, however these interventions have been associated with an improvement in CHD risk. Since the tools/formulas used to calculate this risk include some clinical outcomes mentioned above, such as HbA1c, SBP and cholesterol, the decrease in CHD risk can be in part attributable to an improvement in these parameters.[65-67] Pharmacist interventions also had a positive impact on medication adherence in most studies that included this outcome. Although adherence might have been subject to overestimation, since the majority of methods used to assess this outcome were based on self-reported adherence, the existing findings demonstrate that pharmacists have the potential to improve medication adherence among patients with T2DM, which in turn can translate into a beneficial effect on clinical outcomes, as observed in some studies.[68,69]

The fact that pharmacist interventions did not result in a significant increase in HRQoL in the majority of the studies could be explained by the lack of sensitivity of the existing tools in detecting subtle changes on this outcome, since there is no tool specifically designed to determine the effect of pharmaceutical care on patient quality of life.[70]

Although pharmacist interventions have shown to be cost-effective, evidence is limited by the small number of studies that carried out an economic analysis. However, in order to inform and influence the decision of policymakers regarding the widespread involvement of clinical pharmacists in the care of patients with T2DM, economic analyses are essential due to the current resource restraints in healthcare systems. Therefore, pharmacist interventions should be assessed in a comprehensive manner, considering clinical, humanistic and economic outcomes (ECHO approach).[71]

Limitations

This review has some limitations. First, although randomized controlled trials have the most robust study design, the included studies presented some methodological weaknesses, as assessed by the Cochrane risk of bias tool. However, it should be highlighted that some risk of bias criteria, such as random sequence generation, allocation concealment and blinding of outcomes assessment, were rated as "unclear" in a large proportion of studies because the study reports did not provide sufficiently detailed information to enable a more precise evaluation of the risk of bias. Second, because pharmacist interventions were somehow heterogeneous, it is difficult to identify the most effective intervention. In this work, we observed that educational interventions and medication management performed by pharmacists could be a good approach to the management of type 2 diabetes mellitus.

Future prospective

Future studies evaluating the humanistic and economic outcomes of pharmacist interventions must be performed to facilitate policy makers to develop healthcare models, in

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which pharmacists have a proactive role in the improvement of the well-being of the patients.

Moreover, the evaluation of patient related-outcomes such medication adherence should be done using more accurate methods in order to provide more realistic data regarding the effect of pharmacist interventions. Finally and taking into account that the lack of a standard tool to evaluate some outcomes (e.g. medication adherence and HRQoL) limited the direct comparison of the results of different interventions, a well-validated tool to access the most relevant outcomes should be developed in order to identify the best assertive strategy in the management of T2DM.

CONCLUSIONS

The findings from this systematic review strengthen the evidence that pharmacist interventions contribute positively to the control and management of T2D. Patients suffering from this chronic disease often present other comorbidities, such as hypertension and dyslipidemia, and require complex drug regimens. By monitoring drug therapy, educating the patient and promoting medication adherence, pharmacists play an important role on achieving therapeutic outcomes. In fact, the results of the randomized controlled trials analyzed in this review demonstrated that several pharmacist interventions had a beneficial effect on metabolic control, cardiovascular risk factors, medication adherence and HRQoL among patients with T2DM. Therefore, these findings support the idea of considering the clinical pharmacist as an integral element of multidisciplinary health care teams in T2DM care, encouraging the implementation of this approach in health care systems around the world where pharmacists are still not actively involved in the management of this patient population.

CONFLICT OF INTEREST

None to declare.

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