**Effect of Metformin on Lipid Profiles of Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials**

Syed Wasif Gillani¹, Nahal Ghayedi², Pardis Roosta², Parvin Seddigh², Omaimah Nasiri²

¹Department of Pharmacy Practice, College of Pharmacy, Gulf Medical University, Ajman, UAE, ²College of Pharmacy, Gulf Medical University, Ajman, UAE

**Objective:** The study aimed to perform a meta-analysis on randomised controlled trials to investigate the effect of metformin on lipid profiles among type 2 diabetes mellitus patients. **Material and Methods:** All published, randomised controlled trials with double blind assessment of outcome were included in the review. **Clinical trials were identified by searching:** PubMed, SCOPUS, TRIP, Clinical Trial registry and Cochrane. We included all RCT with no language restriction, published from January 2010 to January 2020. Two primary authors of this study were served as independent reviewers to assess the quality and bias risk assessment of each study by using Cochrane instrument. Pooled analysis was performed to determine the efficacy of metformin versus placebo on the body weight, total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides. **Results:** Overall 6 were used for Meta-analysis. All of the studies reported that groups were similar at baseline, patients were blinded to the study, the study dropout rate was described and acceptable, and studies had reports free of suggestions. The pool analysis showed significant effect of metformin on the reduction of mean bodyweight over time compared to placebo -1.66 (95%CI -1.88 to -1.44) p<0.000. No heterogeneity and effect of publication bias found with outcome variable. The data was extracted from all the six studies to analyze the overall effect. The overall effect is z = 5.40, with no heterogeneity and reported publication bias effect on outcome variable. The pooled effect showed significant reduction of mean triglyceride among patients with metformin as compared to placebo -0.24 (95%CI -0.33, -0.15) p<0.0001). **Conclusion:** This meta-analysis concluded that Metformin has significant reduction effect on body weight, Total Cholesterol, LDL and triglycerides in patients with type 2 diabetes mellitus.

**Keywords:** Evidence-based practice, meta-analysis, metformin, systematic review, type 2 diabetes mellitus

**INTRODUCTION**

Diabetes mellitus, abbreviated as DM, is referred to a series of metabolic disorders with characteristic features such as an elevated blood glucose level, along with altered fat and/or protein metabolism, which results from impaired insulin secretion or insulin sensitivity or both.[1] These complications may further lead to chronic complications, which include microvascular, macrovascular, and even neuropathic disorders.[1] Diabetes type 2 is considered a very serious and common chronic disease, which possesses a major worldwide public health problem, affecting all populations alike, with a high rate of diabetes-related morbidity and mortality.[2] Type 2 diabetes mellitus

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T2DM results from a rather complex inheritance–environment interaction along with other risk factors such as obesity and sedentary lifestyle. Patients with T2DM are more susceptible to different forms of both short- and long-term complications, which include macrovascular diseases (hypertension, hyperlipidemia, heart attacks, coronary artery disease, strokes, cerebral vascular disease, and peripheral vascular disease), microvascular diseases (retinopathy, nephropathy, and neuropathy), and cancers. The treatment of T2DM may include a dynamic range of attempting to achieve a near normoglycemia. An optimal management of the patient with DM can surely prevent and reduce its complications and furthermore decrease morbidity and mortality, and improve quality of life.

The first-line therapy for DM is biguanide, as it is one of the major classes of antidiabetic drugs, among which metformin is the most common drug used.

Glucose control alone is not sufficient, and along with pharmacological interventions as with oral antidiabetic agents, patients have to be counseled about the lifestyle changes they need to make. The primary goal of management would be to reduce the risks of both microvascular and macrovascular disease complications, improve symptoms, and reduce mortality. A general approach would be to set goals for hyperglycemia, blood pressure, and blood cholesterol; monitoring for complications; making appropriate food choices and maintaining a healthy weight; engaging in regular physical activity; selecting and using medications wisely; and performing self-monitoring of blood glucose (SMBG) with periodic laboratory assessment of the aforementioned parameters.

The management of T2DM is very often backed up with maintaining a healthy weight and blood cholesterol. A study suggested that metformin counters insulin resistance and offers benefits against many features of the insulin-resistance syndrome (Syndrome X) by preventing body weight gain, reducing hyperinsulinemia, and improving the lipid profile. It was suggested that the drug metformin can also be used to improve lipid profile in addition to its glucose-lowering properties; however, metformin has cardiovascular protective effects, independent of glucose-lowering effects, as the risk factors of cardiovascular disease include both dyslipidemia and obesity.

This meta-analysis aimed to evaluate the impact of metformin in controlling and/or delaying the development and progression of hyperlipidemia among patients with type 2 diabetes, by amalgamating the trials whose methods are of the highest quality so that meta-analysis and systematic review can produce valid results.

**Materials and Methods**

**Types of study**

All published, randomized controlled trials (RCTs) with double-blind assessment of outcome were included in the review. Open-label trials and observational studies were excluded. RCTs, including published and unpublished trials that tested the effectiveness of metformin as an agent, which can affect lipid profile, were eligible. The required studies were to include human participants and were to present original data.

**Search methods for identification of studies**

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocols.

Meta-analysis was performed using Population Intervention Comparison & Outcome (PICO) format: whether administration of metformin compared to placebo has any effect on body weight (primary outcome), total cholesterol, LDL, HDL, and triglyceride levels (secondary outcomes) in patients with age between 25-60 years.

**Data sources**

Clinical trials were identified by searching in PubMed, Scopus, TRIP, Clinical Trial Registry, and Cochrane. We included all RCTs with no language restriction, published from January 2010 to January 2020.

**Keywords**

Keywords used were “type 2 diabetes,” “diabetes mellitus,” “macrophascular,” “hyperlipidemia,” “obesity,” “microvascular,” “lipid profile,” “hyperlipidemic agents,” “immediate-release metformin,” “randomised controlled trials,” “extended-release metformin.” We restricted our searches to randomized clinical trials, systematic reviews, and also meta-analyses.

**Study selection**

We included RCTs, which used metformin as an agent for treatment of type 2 diabetes and/or hyperlipidemia in patients aged 25–60 years. A wide age range was included, as type 2 diabetes may develop at any age. In this research, we studied the effect of metformin medication in patients with type 2 diabetes, and how it can affect the lipid profile to reduce or avoid hyperlipidemia. We also looked at the references of selected full-text articles.

**Inclusion criteria**

Inclusion criteria consisted of RCTs that used metformin as an agent for treatment of type 2 diabetes...
and/or hyperlipidemia in patients aged 25–60 years with no systemic or inflammatory disease, which were published between 2000 and 2020.

**Exclusion criteria**

Exclusion criteria included patients who were pregnant, under screening of lactation, fertile females who were not using anticonception, patients with major cardiovascular illness, a history of heart failure, and diabetic complications, which include serious brain, kidney, lung, liver, or heart complications.

**Bias risk measure and data extraction**

The titles and abstracts were reviewed according to the inclusion and exclusion criteria and PICO. In the second step of screening, duplicates were removed to avoid inappropriate studies and studies that were not in the aforementioned eligibility criteria. The articles were assessed based on the literature, publication year, study design, patient population, and type of diabetes considered, for example, literature focused on gestational diabetes and type 1 diabetes were excluded.

Two primary authors of this study served as independent reviewers to assess the quality and bias risk assessment of each study by using Cochrane instrument.[11,12] The criteria for evaluations included random sequence generation, double-blinding, which included blinding of the investigators and the participants, detection bias, incomplete outcome data, and baseline clinical characteristics. Studies with three or more bias risks were considered ineligible for data synthesis and analysis.[13] A standardized data extraction form was used to evaluate the quality of identified studies. Any form of disagreement on findings between reviewers was resolved by discussion.

Data retrieved from studies included the first author name, year, country of origin, number of patients, therapy period, intervention method, baseline data, and postintervention outcomes. Some raw data was not available online, efforts were applied to obtain the data via emails from the corresponding authors for associated conference proceedings and articles cited in this study.

**Data synthesis, primary, and secondary variables**

Pooled analysis was performed to determine the efficacy of metformin versus placebo on the body weight, total cholesterol, LDLs, HDLs, and triglycerides.

**Data analysis**

Review Manager (Cochrane, USA, RevMan 5.0) was used to perform statistical analysis. The weighted mean difference and the 95% confidence interval (CI) were calculated for each outcome. The standard deviation, including the sample size, was taken into consideration to calculate the weight given to each study. The standard deviations not mentioned were obtained from the Cochrane Handbook or were calculated. Forest plot was used for reporting of adverse events. Heterogeneity was evaluated using $F$ statistics, and a $P$ value of less than 0.05 was considered statistically significant. The Egger test and inverted funnel plots were applied to evaluate publication bias.

**RESULTS**

**General data**

A total of 459 articles fit the criteria we were looking for; however, many of them were excluded as they did not meet the requirement of being an RCT or they were conducted before January 2020. A total of 173 studies were screened, assessing for the eligibility of these titles and abstracts resulted in 11 publications that met our inclusion criteria for use in this systematic review and meta-analysis. The rest were excluded because they did not contain adequate data on the primary outcome. Overall nine studies of the 11 were used for qualitative synthesis, and six[14-19] were used for meta-analysis and the rest three studies were excluded because the studies did not have the same trial timing for all groups. Figure 1 shows the selection of studies.

**Quality features of articles included for review**

Figure 2 displays quality assessment features of the six controlled clinical trials. All of the studies were randomized. Only one of the studies did not report allocation concealment.[14] All of the studies reported that groups were similar at baseline, patients were blinded to the study, the study dropout rate was described and acceptable, and studies had reports free of suggestions. Seven of the studies were caregiver blinded. Four studies were outcome assessor blinded, four of them were co-interventions avoided or similar, and three utilized intention to treat. All the studies had compliance acceptable in all groups except one specific study.[17] Two of the studies did not have the same trial timing as all groups.

**Effect on mean body weight**

Body weight was a parameter, which was measured and noted in almost all of the six studies [Figure 3]. The pool analysis showed significant effect of metformin on the reduction of mean body weight over time compared to placebo ($-1.66, 95\%\ CI: \(-1.88\) to \(-1.44\); $P < 0.000$). No heterogeneity and effect of publication bias were found with outcome variable.

**Effect on mean total cholesterol**

All the six studies were included for the analysis. The pooled data analysis showed significant reduction effect on mean total cholesterol with metformin compared to placebo ($-0.24, 95\%\ CI: \(-0.33\), \(-0.16\); $P < 0.0001$). No
Records identified through database searching (n = 615)

Additional records identified through other sources (n = 227)

Records after duplicates removed (n = 459)

Records excluded (n = 163)

Records screened (n = 173)

Full-text articles excluded after duplication (n = 383)

Full-text articles assessed for eligibility (n = 11)

Full-text articles excluded, with reasons (n = 2)

Studies included in qualitative synthesis (n = 9)

Studies included in quantitative synthesis (meta-analysis) (n = 6)

Figure 1: PRISMA study selection process

Figure 2: Quality assessment diagram
heterogeneity was shown with overall effect ($z = 5.46$) [Figure 4].

**Effect on mean low-density lipoproteins**
The findings and evidences showed significant reduction of LDL with metformin compared to placebo among patients' with T2DM ($-0.38$, $95\%$ CI: $-0.47$, $-0.30$; $P < 0.0001$). Overall effect, $z$, is 8.51 with no heterogeneity in reported data [Figure 5].

**Effect on mean high-density lipoprotein**
As evidenced in Figure 6, it showed inconclusive findings. There was no reported heterogeneity and publication bias effect on the outcome variable. However, the findings showed no effect of metformin on mean HDL increase or decrease compared to placebo ($-0.01$, $95\%$ CI: $-0.10$, $0.08$; $P = 0.82$).

**Effect on triglycerides**
The data were extracted from all the six studies to analyze the overall effect. The overall effect is $z = 5.40$, with no heterogeneity and reported publication bias effect on outcome variable. The pooled effect showed significant reduction of mean triglyceride among patients with metformin as compared to placebo ($-0.24$, $95\%$ CI: $-0.33$, $-0.15$; $P < 0.0001$) [Figure 7].

**Discussion**
Meta-analysis of six studies found that treatment with metformin resulted in no significant change in body weight or other lipid profile criteria. This systematic review and meta-analysis showed discrepant results about the influence of metformin on lipid profile as a whole. Some studies are in agreement with metformin...
reducing lipid profile, and have reported a reduction, whereas the others have had contradictory values and results. Similar to the findings of Hadigan et al.,[13] we did not observe any significant changes in lipid profile in different studies that this systematic review focused on and reviewed.

In nearly all of the studies, body weight was measured at baseline and also toward the end of the research. The only study that did not provide enough information about body weight was one which was conducted by Gillani et al.[14] Our meta-analysis revealed a raw difference of −1.38 kg body weight change. A study conducted by Preiss et al.[15] showed the highest difference in the body weight change. The decrease in weight was not significant, contrary to the results from a study by Kooy et al.,[16] which suggested that metformin treatment prevented weight gain; however, they also suggested that a better outcome would be with metformin added to insulin in patients with T2DM. The difference in clinical outcomes in various studies can be a consequence of the different doses of metformin in each study or the initial values of LDL and other lipid profile values.

Similar to other measurements obtained by researchers, the total cholesterol also was measured before and after the research. A total cholesterol reduction by using metformin was observed in almost all the studies. The only study that showed an increment in the cholesterol level was the study conducted by Gillani et al.[14] The highest difference was shown in the study conducted by Kooy et al.[16] with the difference of −2.91 mmol/L. So this systematic review as a whole shows that metformin can be helpful in the reduction of total cholesterol level in the patient with diabetes.

As per all the studies checked, we have no enough strong evidence that metformin causes LDL reduction in patients with type 2 diabetes. Some of the studies showed some reduction in LDL level. The greatest reduction observed was in the study of Kooy et al.[16] which was −3.25 mmol/L. However, some studies also revealed that metformin caused an increment in the LDL level, an average of +3.01 mmol/L increase in LDL.[17] Overall, more studies need to be conducted on the effect of metformin on the LDL level, as we need stronger evidence to know if it causes any reduction or not.[18-22]

Most of the studies represented an elevation in the HDL level by using metformin as treatment for patients with DM. The findings showed effect on HDL levels but remained inconclusive due to lack of clinical evidence. One of the studies involved in meta-analysis reported significant increment in HDL level of serum (1.1 ± 0.1 to 1.4 ± 0.1 mMol/L, \( P < 0.005 \)).[18,23,24] This has been proven in other studies conducted by Kooy et al.[16] which says the overall treatment with metformin results in increasing HDL level, but this elevation is not significant. However, most studies prove that metformin increases HDL level, there is not enough evidence to
prove if metformin has a major or minor increment effect on HDL level, so it needs further analysis.

Most of the studies showed a decrease in plasma triglyceride level in patients who had type 2 diabetes and were treated with metformin. This was also in confined in a study conducted by Grant,[20] that there was a fall in triglyceride ($P < 0.05$) with a high dose of metformin.[19] In another study by Kooy et al.,[16] it was suggested that the change in plasma triglycerides was only statistically significant when metformin was given in higher doses.

**Conclusion**

The study concluded the significant effect of metformin on decrease in body weight, total cholesterol, LDL, and triglycerides in patients with T2DM. Some studies suggested a slight change in HDL; however, data were limited and these changes were not expected to result in a major reduction. A further investigation is required for the dose-dependent effect of metformin on liver and renal profiles among patients with T2DM.

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**Conflicts of interest**

There are no conflicts of interest.

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