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Effect of metformin treatment on inflammatory markers in type 2 diabetes mellitus—A systematic review and meta-analysis

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ABSTRACT

Background: Inflammatory markers have a crucial role in the development and pathogenesis of type 2 diabetes mellitus (T2DM). Therefore, an ideal treatment for T2DM should exert multidimensional beneficial effects for the management of diabetes. Metformin, being a first-line therapy for T2DM, has proved to have an excellent hypoglycemic effect, but the conclusion of its effect on inflammation is inconsistent. This study aims to evaluate the pooled effect of metformin on inflammatory markers in T2DM.
Methods: PubMed, CINHAL, and Scopus were searched systematically, and the references were further explored for eligible articles. 28 articles were extracted from 2,514 studies after eligibility screening based on the selection criteria. The data of inflammatory markers were then analyzed for meta-analysis in RevMan software.
Results: The result of the subgroup meta-analysis shows that C-reactive protein (CRP) and high sensitivity C-reactive protein proved to be statistically significant for metformin in the placebo compared group. However, interleukin-6 and adiponectin proved to be beneficial for the comparator group.
Conclusion: It is important to understand the validated effect of metformin on inflammatory markers in T2DM, which is possible by following an appropriate and universal assessment method with a uniform time and dose of metformin.
Systematic Review Registration: The protocol for this systematic review is registered with PROSPERO (CRD42020180403).

INTRODUCTION

Type 2 diabetes mellitus (T2DM), a metabolic disorder, is characterized by high blood sugar (Zubair and Ahmad, 2019), which arises due to insulin insufficiency and pancreatic cell destruction (Engelmann *et al*., 2016; Padilha *et al*., 2016). T2DM is a complex disease that poses a critical health problem worldwide (Chaudhury *et al*., 2017; Xie and Du, 2011; Zheng *et al*., 2018). Impaired insulin secretion due to pancreatic beta-cell destruction and insulin resistance are the main factors in the development and pathogenesis of type 2 diabetes (Pradhan and Ridker, 2002).

The research has been conducted to indicate that inflammation is a pathogenic element in the occurrence of hyperglycemia in T2DM (Sjöholm and Nyström, 2006). The association of inflammation in diabetes is characterized by the presence of an increased level of circulatory cytokines, chemokines, and acute phase proteins (Greevenbroek *et al*., 2013; Herder *et al*., 2009; Spranger *et al*., 2003). Even though the magnitude of these inflammatory markers in different peripheral tissue is unclear, it is known that an increased level of these markers will activate the innate immunity in T2DM due to the overproduction of free fatty acids (Eguchi and Nagai, 2017). Various factors have been associated with an inflammatory process in diabetes which may

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be common or tissue-specific. The action of these inflammatory mediators that induces insulin resistance in different tissue involves many metabolic signaling pathways like IkB kinase-b and c-jun N-terminal kinase. These pathways are involved in the pathogenesis of diabetes (Shoelson, 2006) and activate nuclear factor-kB, inducing the production of cytokines like tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and acute-phase proteins in tissues like liver and adipose and provoking insulin resistance in these tissues (Arkan *et al*., 2005). Cytokines such as TNF-α, IL-1β, and IL-6 play an important role in the development of T2DM. Inflammation is mainly induced by the accumulation of fatty acids in islets of the pancreas, leading to the activation of the IL system and the production of these cytokines and chemokines. Thus, it is critical to recognize the function of inflammation in the development and pathogenesis of T2DM to find a way for causative treatment. The advancement in the development of the new drug for many other diseases associated with inflammation provides a unique opportunity in the field of research that led to the expressive and fast performance of clinical trials (Coughlan *et al*., 2014; Donath, 2014; Dunmore and Brown, 2013; Esser *et al*., 2014; Tilg and Moschen, 2008). The primary purpose of diabetes treatment is to improve the quality of life and lifespan in comparison with healthy individuals, and the necessity for achieving this goal is to prevent the progression of diabetic complications (Knowler, 2005). Metformin is the first-line medication for T2DM, which controls hyperglycemia by decreasing glucose secretion from the liver and boosting insulin sensitivity (Foretz *et al*., 2019). Metformin activity is believed to intercede through the enactment of AMPK (Adenosine Monophosphate-activated protein kinase), a key controller of cell vitality homeostasis known to apply both antioxidant and anti-inflammatory impact (Pollack *et al*., 2016). The lone effect of metformin proved to have good management in control of inflammation, but it is essential to know the pooled effect of metformin on markers of inflammation in type 2 diabetes. Meta-analysis is an important technique for evaluating the comparative efficacy of different treatments. Therefore, an attempt is made to review the effect of metformin on inflammatory markers to examine the primary research and summarize the overall findings objectively. This review provides an updated view of the status of inflammatory markers in metformin-treated alone or with combination in T2DM patients. This study's approach may validate the future implementation of drugs targeting multiple effects that immensely improve the quality of life in type 2 diabetes patients.

METHODS

We directed this meta-analysis utilizing the preferred reporting items of systematic review and meta-analysis (PRISMA) guidelines.

Search strategy

Eligible studies were searched in electronic databases such as Medline, Scopus, Web of Science, and CINAHL complete from 2000. The search terms "Metformin" AND "Inflammatory markers" OR "Inflammatory biomarkers" OR "Markers of inflammation" AND "Type 2 Diabetes Mellitus" were included to identify relevant studies. The search screening was also done using separate terms instead of inflammatory markers such as "IL-6," "TNF-α," and "CRP" to extract more studies. No limitations were made in the study language, and also the references of included studies were checked to prevent missing publications.

Inclusion and exclusion criteria

The inclusion criteria include all the studies that evaluated metformin's effects on inflammatory markers in T2DM patients. The studies with Metformin and control or placebo or any other treatment or with combination treatment group were evaluated. Full-length publication studies reported with at least one biomarker outcome and published in the English language were included. The result should be reported as mean or median for inflammatory markers at pretreatment and posttreatment in both experimental and control groups. The intervention period of more than 4 weeks was only considered.

Studies were excluded if they had no comparison group, no intervention given, type 1 diabetes, and if experimental models were animals.

Data extraction and quality assessment

Data were extracted by three authors independently, and the findings were compiled. The fourth author reviewed the extracted data. Any disagreement regarding the extracted data was settled by the viewpoint of a fourth author if required. The method of data extraction was done using standard data extraction form, which included the title, name of author, publication year, study design, study duration, country, sample size, details of the intervention, any co-interventions, and outcome measure.

The quality assessment of the included studies was evaluated using the Cochrane collaboration modified tool. This tool is assessed based on randomization and allocation concealment, blinding of the participants and researchers, attrition bias, selective reporting, and other biases.

Outcome measures and data analysis

Metformin and placebo were the key groups studied to determine the precise effectiveness of metformin on inflammatory markers. The effectiveness of metformin was also compared to that of other comparator groups to see if there was a difference. Metformin's efficacy was also tested in conjunction with other comparators to determine its efficacy both alone and in combination. The outcome measures include C-reactive protein (CRP), high sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), adiponectin, and intercellular adhesion molecule (ICAM-1). The pre- and post-treatment changes in the experimental and control/comparator groups were pooled to evaluate each outcome's effects. The outcome measure was calculated as mean and standard deviation. The random-effect model was used to find the total effect which detects the variation between the studies. I^2 statistics was used to determine the study heterogeneity. Subgroup analyses were conducted to find the effect of different treatment modalities. The quantitative analysis of the data was done using the software Review Manager 5.2 (https://review-manager.software.informer.com/5.2/).

FINDINGS AND DISCUSSION

A total of 237 articles were obtained after the title and abstract screening from 1,510 articles filtered after duplicate

removal. Subsequently, after the full-text screening of articles, 28 studies were found to be eligible for meta-analysis. The detailed procedure of study choice and screening is displayed in Figure 1. The baseline characteristic of included studies is depicted in Table 1.

Study characteristics

The research studies included in the review were published between 2000 and 2020. The study duration ranged from 4 to 52 weeks. Totally 2,975 subjects were involved in this study. The mean age in three studies (Carter *et al*., 2005; Chakraborty *et al*., 2011; Zhang *et al*., 2018) was not reported, in few studies, the average mean age was mentioned (Eriksson *et al*., 2007; Lund *et al*., 2008; Ragonesi *et al*., 2012; Schiapaccassa *et al*., 2019), and rest all the studies reported mean age in both groups. The eligible criteria for glycated hemoglobin are >6.5 (Eriksson *et al*., 2007; Hanefeld *et al*., 2011; Lund *et al*., 2008; Natali *et al*., 2004; Ragonesi *et al*., 2012; Zhang *et al*., 2018), >7.0 (Abdulkadir, 2012; Chakraborty *et al*., 2011; Derosa *et al*., 2008; Erem *et al*., 2014; Esteghamati *et al*., 2013; Jager *et al*., 2005, 2014; Mo *et al*., 2019; Pradhan and Ridker, 2002; Schiapaccassa *et al*., 2019; Tousoulis *et al*., 2011), >7.5 (Derosa *et al*., 2013) and >8.0 (Chu *et al*., 2002; Derosa *et al*., 2012; Li and Shen, 2019). The study population comprised T2DM patients with participants having several other criteria's including overweight or obesity (Carter *et al*., 2005; Derosa *et al*., 2008, 2013; Schiapaccassa *et al*., 2019), with coronary artery disease (Derosa *et al*., 2012; Jager *et al*., 2005; Lund *et al*., 2008), newly diagnosed type 2 diabetes (Abdulkadir, 2012; Erem *et al*., 2014; Esteghamati *et al*., 2013; Li and Shen, 2019; Mo *et al*., 2019; Tousoulis *et al*., 2011; Zhang *et al*., 2018), hypertension (Chu *et al*., 2002; Jager *et al*., 2014; Natali *et al*., 2004; Ragonesi *et al*., 2012), female participants only(Mo *et al*., 2019; Schiapaccassa *et al*., 2019), and elderly patients above the age of 50 (Derosa *et al*., 2008; Kadoglou *et al*., 2010).

Study interventions

The different groups of interventions were used in the comparator group in different studies. The intervention groups in one study (Derosa *et al*., 2013) were assigned to receive metformin (dosage of 2,500 ± 500 mg) for 8 ± 2 months and then were randomly assigned, in addition to the previously determined metformin dose, 100 mg of sitagliptin in the comparator group. In contrast, the metformin group continued the predetermined dosage. The subjects in another study (Jager *et al*., 2005) were randomly assigned to receive either metformin or placebo in addition to the existing insulin therapy. In some of the studies (Derosa *et al*., 2008, 2012, 2013; Forst *et al*., 2012; Kadoglou *et al*., 2010; Tousoulis, 2019), the comparator group had a combination therapy of another drug along with metformin. In one study (Abdulkadir, 2012), the process and the dosage of interventions were not mentioned.

Risk of bias assessment

Figure 2 shows the Cochrane risk of bias in these randomized clinical trial studies. We assessed the overall quality of 28 studies. Two of the included studies did not state the random sequence generation, and four studies did not mention group allocation concealment. The performance and detection criteria had a high risk of bias for most of the studies, as clarity for blinding of participants in seventeen studies and blinding of outcome assessment in 20 studies is not clear. Twenty-six studies described the clear outcome and reporting data. Four articles were evaluated as high risk due to the poor quality of study design.

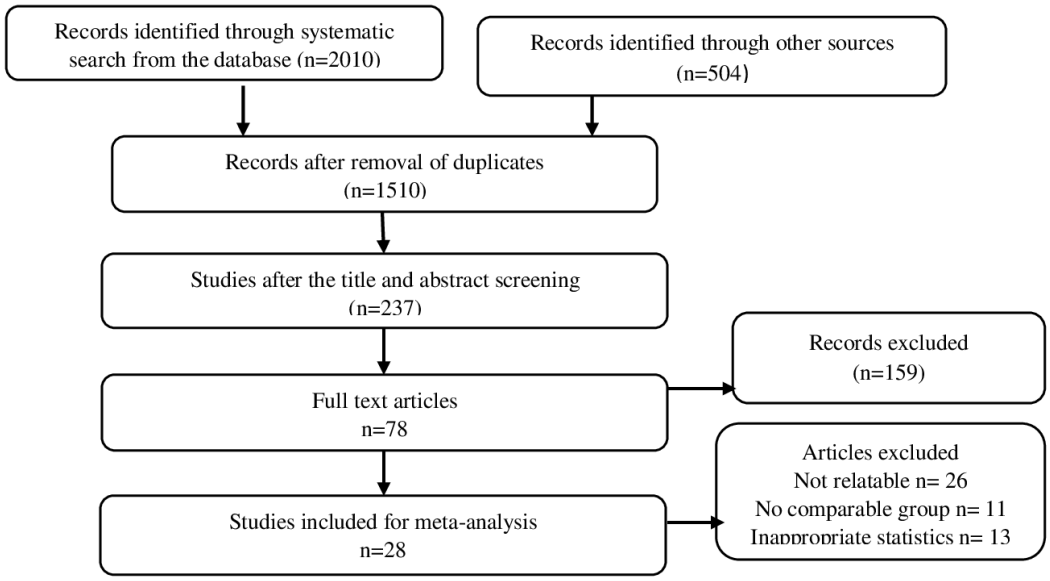

Figure 1. PRISMA stream chart for study choice.

Table 1. Baseline qualities of eligible studies.

Author	Publication year	Design	Control	Sample size	Intervention dose	Outcome	Duration	Age (mean)	Country
Chakraborty *et al*., 2011	2011	R/DB/P	Placebo	208	850 mg/day of metformin titrated up to 2,000 mg/day	CRP	24 weeks	NR	India
Bulcao *et al*., 2007	2007	R/OL	Simvastatin	41	Metformin—850 mg/day, simvastatin—20 mg/day	CRP, IL-6	16-week	M: 48.6 ± 9.1 C: 50.7 ± 8.2	Brazil
Kim *et al*., 2007	2007	RCT	Rosiglitazone	113	Metformin—1,000 mg once daily, Rosiglitazone—4 mg once daily	CRP, TNF-α, IL-6, adiponectin	12 weeks	M: 57·6 ± 9·4 C: 56·5 ± 10·1	Korea
Jager *et al*., 2005	2005	R/P	Placebo	313	850 mg metformin—1-3 tablet/day	CRP, ICAM-1	16 weeks	M: 63.2 ± 9.8 C: 58.9 ± 11.1	Netherlands
Lund *et al*., 2008	2008	R/DM	Repaglinide	165	1 g metformin twice daily, 2 mg repaglinide thrice daily	TNF-α,	4 months	61.4 ± 9.3	Denmark
Esteghamati *et al*., 2013	2013	R/OL	Lifestyle modification	99	1,000 mg metformin daily	hs-CRP	3 months	M: 49.74 ± 8.23 C: 52.38 ± 8.38	Iran
Derosa *et al*., 2012	2012	R/DB/P	Placebo	171	Metformin titrated 2,500 ± 500 mg/day, exenatide 5–10 µg twice a day	hs-CRP, Adiponectin	12 months	57.0 ± 7.5	Italy
Mo *et al*., 2019	2019	RS	Acarbose	70	500 titrated up to 1,500 mg of metformin once daily, 50 mg titrated to 300 mg of Acarbose once daily	TNF-α, IL-6	12 months	M: 51.31 ± 9.02 C: 51.38 ± 9.61	China
Tousoulis *et al*., 2011	2011	RS	Atorvastatin + metformin	35	Metformin 850 mg/day, atorvastatin 10 mg/day	TNF-α	12 weeks	M: 53.88 ± 11.06 C: 52.53 + 9.57	Greece
Derosa *et al*., 2013	2013	R/DB/P	Metformin + sitagliptin	178	Metformin gradually titrated to a mean dose of 2,500 ± 500 mg/day, 100 mg of sitagliptin	TNF-α	12 months	M: 55.9 ± 8.8, C: 54.8 ± 7.9	Italy
Schiapaccassa *et al*., 2019	2019	RCT	Vildagliptin	38	1,700 mg/day of metformin and 100 mg/day of vildagliptin	CRP, TNF-α, Adiponectin	30 days	39.4 ± 6.5	Brazil
Ragonesi *et al*., 2012	2012	R/DB/P	Vildagliptin + metformin	160	Metformin gradually titrated until a mean dosage of 2,500 ± 500 mg/day, vildagliptin 50 mg twice a day	TNF-α, Adiponectin	12 months	M: 53.2 ± 7.8 C: 53.7 ± 7.9	Italy
Derosa *et al*., 2008	2008	R/SB	Rosiglitazone + metformin	117	Metformin 2,500 ± 500 mg/day, Rosiglitazone (8 mg/day) + metformin (mean dosage 1,500 ± 500 mg/day)	TNF-α, Adiponectin	6 months	M: 54 ± 3 C: 55 ± 4	Italy
Eriksson *et al*., 2007	2007	R/SB	Placebo	20	500 mg once daily and was increased to 500 mg twice daily after 1 week treatment and to 1,000 mg twice daily after 2 weeks	Adiponectin	28 days	64 ± 6	Sweden

Continued

Author	Publication year	Design	Control	Sample size	Intervention dose	Outcome	Duration	Age (mean)	Country
Abdulkadir, 2012	2012	CS	Glibenclamide	103	NR	hs-CRP	8 weeks	M: 51.27 ± 9.07 C: 49.40 ± 7.81	United Arab Emirates
Everett *et al*., 2009	2009	R/OL	Placebo	244	500-mg metformin 1 pill at dinner with weekly titration by 1 pill to a maximum of 4 pills per day.	hs-CRP	14 weeks	M: 53.8 ± 11.5 C: 54.0 ± 10.9	United States
Zhang *et al*., 2018	2018	RCT	Liraglutide	60	Metformin 1–2 g/day, 0.6 mg/day for increased up to 1.2 mg/day	hs-CRP	8 weeks	NR	China
Erem *et al*., 2014	2014	R/OL	Gliclazide	38	30–60 mg/day in gliclazide group; 2,000 mg/day in metformin group	TNF-α, IL-6	12 months	M: 52.2 ± 10.5 C: 55 ± 8.7	Turkey
Chu *et al*., 2002	2002	CS	Troglitazone	22	Metformin—850 mg once daily and increased to thrice daily. Troglitazone—200 mg once daily	CRP	4 months	M: 56 ± 2 C: 56 ± 2	United States
Jager *et al*., 2014	2014	RCT	Placebo	290	Metformin 850 mg one to three times daily	CRP, ICAM-1	52 months	M: 64 ± 10 C: 59 ± 11	Netherlands
Carter *et al*., 2005	2004	R/DB	Placebo	42	Metformin 1,500 mg/day	CRP	24 weeks	NR	UK
Caballero *et al*., 2004	2004	R/DB	Placebo	55	Metformin 1,000 mg twice a day	ICAM -1	16 weeks	M: 47.7 ± 9.8 C: 49.3 ± 9.6	Mexico
Kadoglou *et al*., 2010	2010	CS	Metformin + rosiglitazone	97	Metformin gradual titrated from 850 to 2,550 mg/day, comparator group-metformin 850 mg/day plus rosiglitazone 8 mg/day	hs-CRP	14 weeks	M: 62.7 ± 6.8 C: 62 ± 8.3	Greece
Hanefeld *et al*., 2011	2011	R/DB/P	Pioglitazone	76	Metformin (2 × 850 mg daily) Pioglitazone (2 × 15 mg daily)	hs-CRP	6 months	M: 64.2 ± 7.3 C: 61.5 ± 7.1	Germany
Natali *et al*., 2004	2004	R/DB	Rosiglitazone	74	Rosiglitazone (8 mg/day), Metformin (1,500 mg/day)	TNF-α, hs-CRP, IL-6	16 weeks	M: 58 ± 10 C: 59 ± 9	Italy
Li and Shen, 2019	2019	CS	Rosiglitazone	79	Not known	TNF-α, hs-CRP, IL-6	48 weeks	M: 42.13 ± 9.54 C:40.36 ± 10.02	China
Kiyici *et al*., 2009	2009	R/OL	Rosiglitazone	35	Metformin 850 mg/day, rosiglitazone 4 mg/day	MCP-1	52 weeks	M: 52.4 ± 8.3 C: 50.7 ± 6.4	Turkey
Forst *et al*., 2012	2012	R/OL	Liraglutide + metformin	40	Liraglutide was initiated with 0.6 mg/day increased to 1.8 mg after 6 weeks.	MCP-1	12 weeks	M: 57.9 ± 5.9 C: 55.1 ± 6.2	Germany

R = Randomized, DB = double blind, SB = single blind, P = placebo, OL = open label, RCT = Randomized controlled trial, CS = clinical study, RS = randomized study, NR = not reported, M = Metformin, C = Control.

Meta-analysis

The meta-analysis of sub-group based on intervention was conducted to determine the disparities in the studies.

C-reactive protein

A total of eight studies were analyzed for CRP as shown in Figure 3. There was no significant effect overall (SMD = −0.20, 95% CI = −0.72 to 0.31, p = 0.44, n = 1,167) but the four studies for the effect of metformin on CRP in metformin and placebo group proved to be significant (SMD = −0.73, 95% CI = −1.43 to −0.04, p = 0.04, n = 953), whereas the other four studies in metformin in comparison to the other comparator group did not show any significance (SMD = 0.40, 95% CI = −0.05 to 0.86, p = 0.08, n = 214).

High sensitivity C-reactive protein

Figure 4 depicts meta-analysis of hs-CRP. Four studies in comparison of metformin with placebo reported significance effect (SMD = −0.31, 95% CI = −0.60 to −0.01, p = 0.04, n = 560), and also hs-CRP showed significant effect (SMD = 0.27, 95% CI = 0.00 to 0.54, p = 0.05, n = 467) in metformin and comparator group in six studies. The overall effect showed to be non-significant (SMD = −0.03, 95% CI = −0.24 to 0.30, p = 0.84, n = 1,027).

Tumor necrosis factor-α

A total of 11 studies were analyzed to study the effect of metformin intervention on TNF-α in Figure 5, and the pooled effect proved to be non-significant (SMD = −0.01, 95% CI = −0.41 to 0.39, p = 0.96, n = 1,045). No significant effect was achieved in metformin and comparator group (SMD = −0.16, 95% CI = −0.55 to 0.22, p = 0.40, n = 590) for eight studies as well as in metformin and combination therapy group (SMD = 0.42, 95% CI = −0.61 to 1.45, p = 0.42, n = 455) for three studies.

Interleukin-6

A significant difference was observed among six studies for IL-6 in metformin and comparator group (SMD = 0.37, 95%

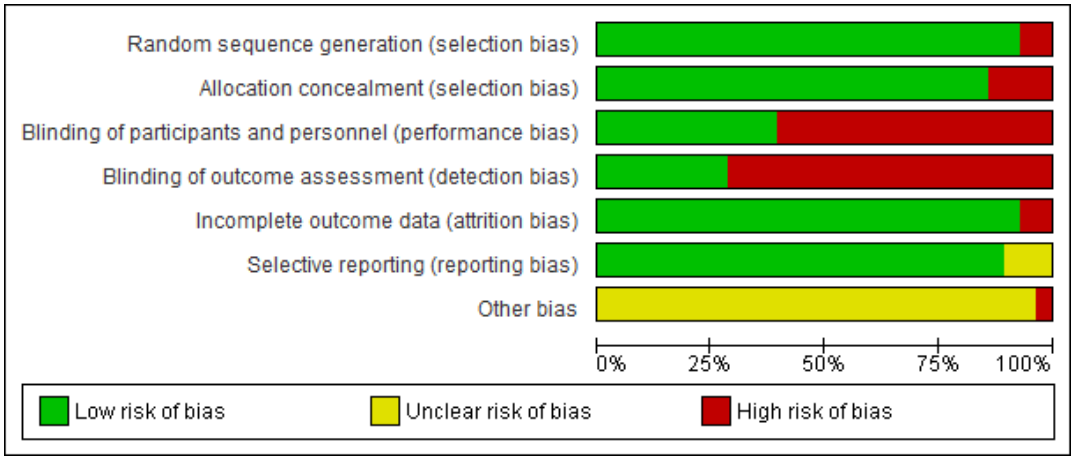

Figure 2. Quality evaluation of the studies contained in the meta-analysis. Risk of bias graph for the studies (above) and lanes (below).

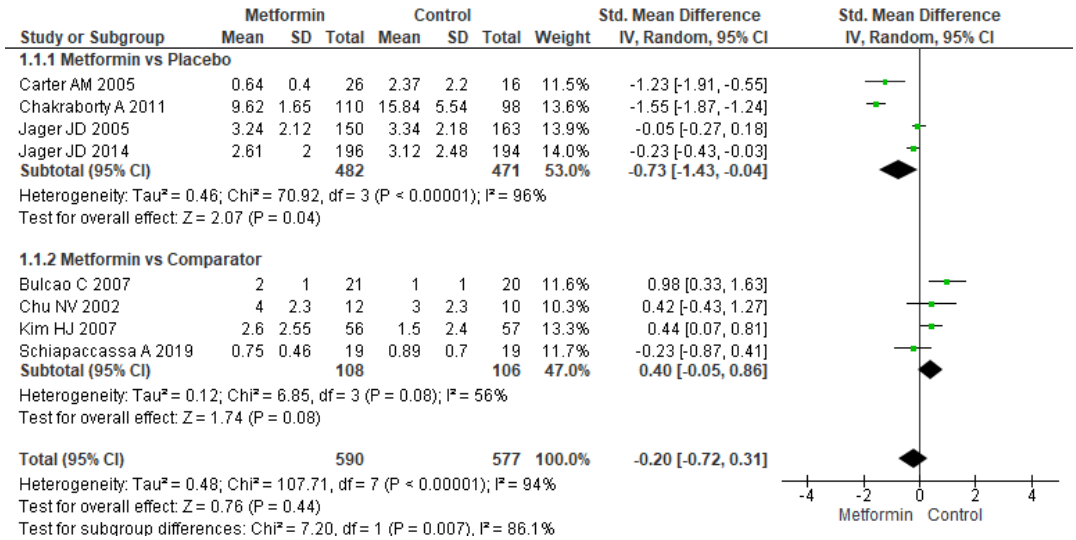

Figure 3. Forest plots for CRP level in comparison with metformin and control group in T2DM.

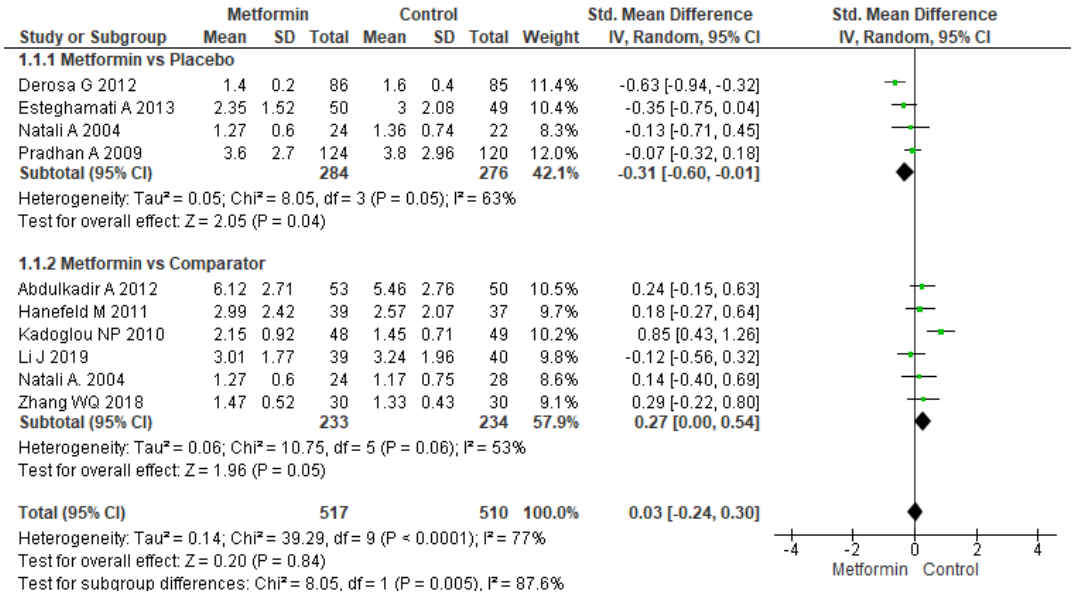

Figure 4. Forest plots for hs-CRP level in comparison with metformin and control group in T2DM.

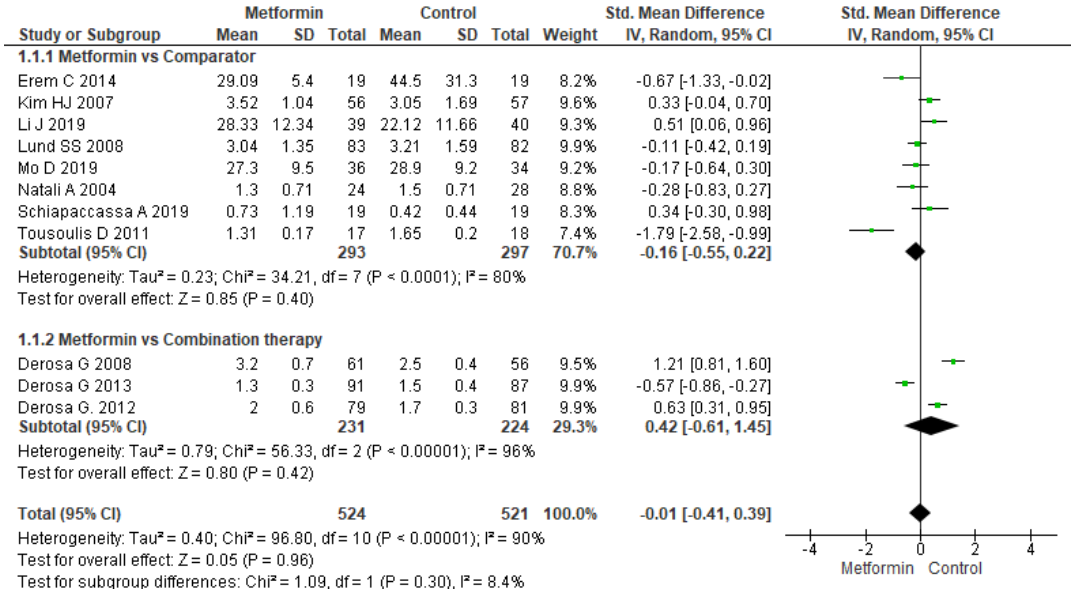

Figure 5. Forest plots for TNF-α level in metformin and control group.

CI = 0.17 to 0.57, p = 0.0004, n = 393) as shown in Figure 6 favoring comparator group.

Monocyte chemoattractant protein-1

Only two studies were eligible for meta-analysis of MCP-1 which showed to be non-significant (SMD = −0.44, 95% CI = −0.90 to 0.02, p = 0.06, n = 75) in metformin and combination treatment group as shown in Figure 7.

Intercellular adhesion molecule-1

The forest plot in Figure 8 for three studies in metformin and placebo group did not provide any significant effect (SMD = −0.12, 95% CI = −0.29 to 0.04, p = 0.14, n = 758).

Adiponectin

Six studies were analyzed to assess the effect of metformin treatment on adiponectin as shown in Figure 9 and the overall effect mentioned as statistically significant (SMD = −0.40, 95% CI = −0.56 to −0.24, p < 0.001, n = 622). The beneficial effect was found towards comparator group in three studies (SMD = −0.41, 95% CI = −0.72 to −0.11, p = 0.008, n = 174) that analyzed for metformin and comparator group, the same beneficial effect was found for combination therapy (SMD = −0.40, 95% CI = −0.59 to −0.21, p < 0.001, n = 448) when compared to metformin in another group of three studies.

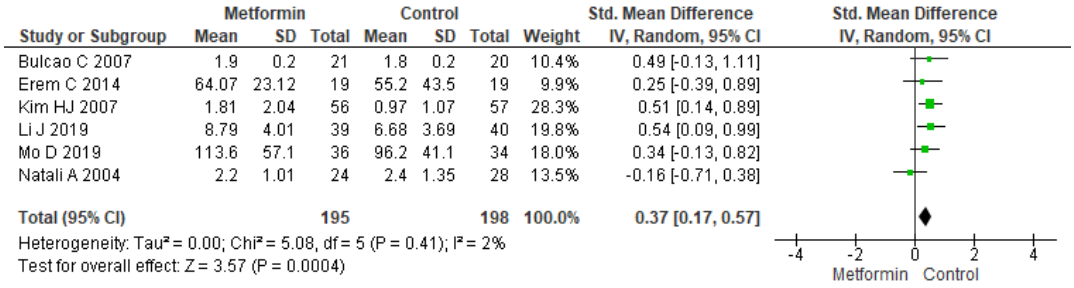

Figure 6. Forest plots for IL-6 level in metformin and comparator group.

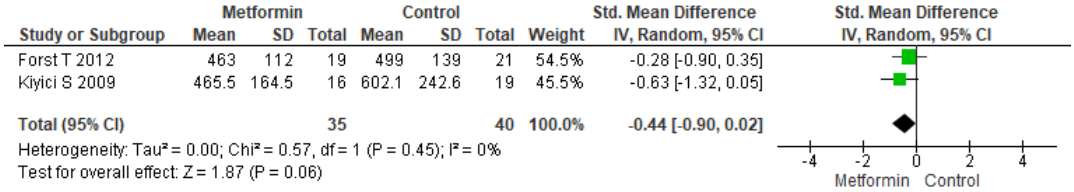

Figure 7. Forest plots for MCP-1 level in metformin versus combination treatment group.

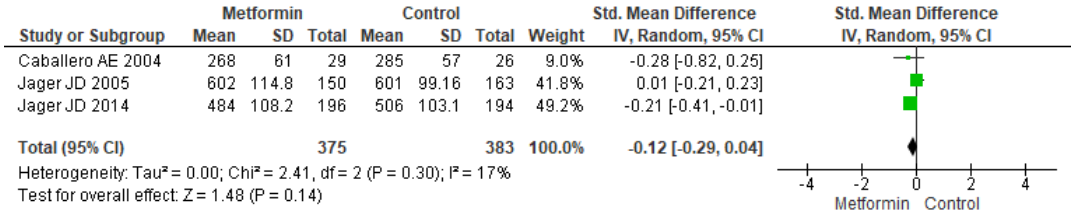

Figure 8. Forest plots for ICAM-1 level in metformin and control group.

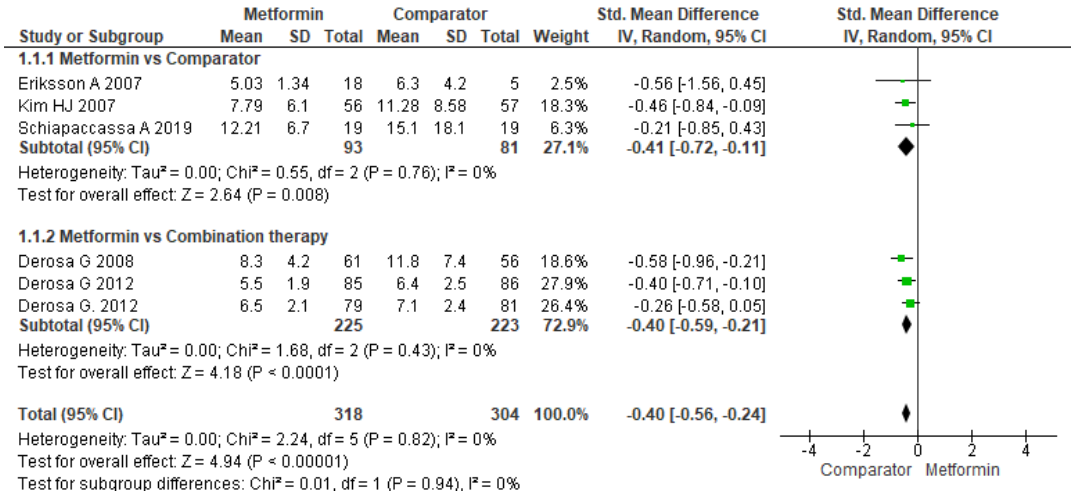

Figure 9. Forest plots for Adiponectin level in comparison with comparator and metformin group.

Publication bias

The publication bias for this meta-analysis was assessed by performing a funnel plot for hs-CRP as a representative index for inflammatory markers. Based on the plots, there was an indication that there had been minimum publication bias in metformin effect on type 2 diabetes for hs-CRP. This was authenticated by performing Egger's linear regression in EZR (hs-CRP: intercept: 0.18; standard error: 1.41; 95% CI: −1.30, 1.68; t = 2.75, z = −0.26, p = 0.78) (Fig. 10) (https://www.R-project.org/).

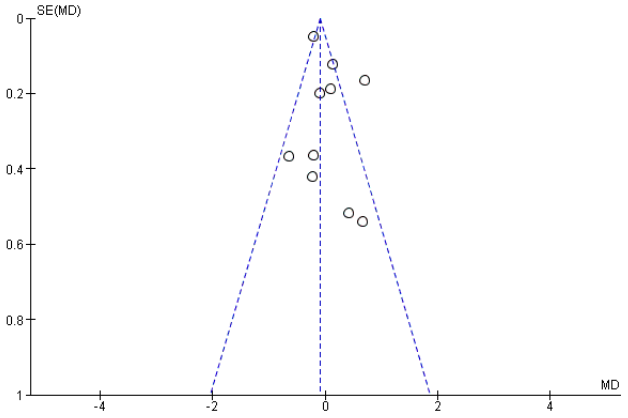

Figure 10. Funnel plot of included articles in the meta-analysis for hs-CRP. SE: standard error, MD: mean difference.

CONCLUSION

The sub-group analysis of CRP and hs-CRP in the metformin and placebo groups showed a favorable effect for metformin. CRP in the metformin and comparator group did not show any significance whereas hs-CRP did. IL-6 and adiponectin in metformin and comparator group mentioned to be favoring comparator group and also the adiponectin levels seem to be improved in combination therapy when compared to metformin alone proving better efficacy in inflammation control. TNF-α, MCP-1, and ICAM-1 showed no improvement in the metformin group. The combination of metformin with other drugs is effective in controlling inflammation in type 2 diabetes. In this way, metformin has an advantage and can be used in tandem with other drugs in treating and management of diabetes. In the compromised studies, the span of the treatment period ranged from 4 weeks to 12 months and the metformin dose from 0.5 to 3.0 g/day. Because of the low number of the included studies, the ideal dose and the length of treatment were hard to determine.

The relation between inflammation, hyperglycemia, and complications of diabetes is well manifested now. Since low-grade inflammation is a predictor in the progression of diabetes and its complications, an increased level of CRP may be the significant risk marker in the pathogenesis of T2DM (Duncan *et al*., 2003). The evidence says that some metabolic factors such as hyperglycemia and free fatty acid may provoke CRP production by macrophages and endothelial cells (Mugabo *et al*., 2010), and increased production of CRP may be also due to increased IL-6 and TNF-α production that trigger inflammation in different tissues (Dehghan *et al*., 2007). Additionally, CRP has a role in impairing nitric oxide production, which leads to endothelial dysfunction (Stehouwer, 1987). IL-6 is associated with T2DM as well as impaired glucose tolerance specifying its role in the development of T2DM (Saxena *et al*., 2013). IL-6 has its contribution to the pathology and physiology of diabetes by its association with β-cell function and insulin-signaling pathways (Fève and Bastard, 2009), and also IL-6 triggers the CRP production (Pickup, 2004). TNF-α is a cytokine that is mainly delivered by monocytes and macrophages and has an action on insulin resistance in peripheral tissue (Ruan *et al*., 2002) as well as insulin secretion (Hotamisligil, 1999). Adiponectin inhibits the production and action of TNF- α, which may influence IL-6 and CRP production. Therefore, adiponectin may affect CRP levels in plasma and adipose tissue by modulating the inflammatory cascades. TNF-α development and action are inhibited by adiponectin, which can affect the production of IL-6 and CRP. As a result of inflammatory pathway modulation, adiponectin can also affect CRP levels and other inflammatory markers in plasma and adipose tissue (Schulze *et al*., 2004).

These inflammatory markers play a direct role in impairing insulin signaling pathways which contribute to insulin resistance in diabetes. However, the anti-inflammatory action of various medications is partial and conflicting, most likely because of deficient normalization of metabolic dysregulation or because diabetes-related aggravation is multifactorial but is not restricted to hyperglycemia. Improved diabetes prevention and treatment modalities could benefit from a greater understanding of the inflammatory basis for diabetes, which could involve innovative targeted therapies in addition to existing pharmacologic and lifestyle strategies. In this meta-analysis, metformin therapy did not show a true effect on inflammatory markers in T2DM patients. It was difficult to assess the positive effect of metformin which may be due to short treatment duration and different comparator groups. Therefore, further randomized, placebo-controlled clinical trials are required to confirm the metformin effect on inflammatory markers in T2DM patients.

Even though this systematic review gains the knowledge of metformin on inflammatory markers; it has few limitations. First, few of the trials had smaller sample sizes and shorter study duration. Second, wellbeing status, lifestyle, and essential oral anti-diabetic treatment were distinctive among the subjects and might be a significant source of heterogeneity. Third, the control group used in the review were not similar drugs which again accounts for heterogeneity. Fourth, though comprehensive information was separated for statistics investigation, studies included in this meta-analysis contained different ethnic populations and countries.

To find a more sustainable effect of metformin on inflammatory markers, future studies ought to build up a uniform assessment technique of inflammatory markers and explore the ideal dose and duration of metformin therapy along with better combination therapy in diabetes. In light of the prevalence of T2DM among Indians and the fact that metformin is the first-line therapy, it is important to control this disease effectively. This can be done by focusing on different mechanisms of metformin treatment, such as inflammatory markers in T2DM. Since inflammation is an additional risk factor in diabetes, the methodology of treatment towards this field will be gainful and accommodating in the management of T2DM.

LIST OF ABBREVIATIONS

hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; ICAM-1, intercellular adhesion molecule; MCP-1, monocyte chemoattractant protein-1; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-alpha.

AUTHORS CONTRIBUTION

All authors contributed to this review manuscript equally. Data were extracted and compiled with the aid of Renuka Suvarna, Revathi P. Shenoy, and M. Mukhyaprana Prabhu.

Guruprasad Kalthur was able to review the extracted data and any discrepancies in the data extraction were further discussed with all the authors. Basavaraj S. Hadapad and Varashree B. S. collaborated to review the study's methods, as well as the results and discussion of the manuscript. All the included authors of this study presented an equal contribution in data analysis and complete manuscript review.

CONFLICT OF INTEREST

The authors proclaim no conflict of interest.

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