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Efficacy of Metformin in Weight Management and Glycemic Control in Type 2 Diabetes: An Updated Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic condition where obesity plays a key role. Metformin is commonly used to manage T2DM, with benefits in both glycemic control and weight management. This systematic review and meta-analysis update the evidence on metformin's impact on weight loss and glycemic control in T2DM patients.
Objective: To assess metformin's efficacy in reducing body weight and improving glycemic control in T2DM patients by synthesizing recent studies.
Methods: Following PRISMA guidelines, relevant studies were identified in PubMed, EMBASE, and clinicaltrials.gov. Fourteen randomized controlled trials and cohort studies, involving 11,686 T2DM patients, were analyzed using RevMan 5.4 software.
Results: Metformin led to a modest but significant reduction in body weight (Mean difference = 0.16; 95% CI: 0.69 to 1.02, p<0.00001) and significantly lowered glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG) levels. Despite some study heterogeneity, the risk of bias was minimal.
Conclusions: Metformin is effective in modest weight reduction and significant glycemic control in T2DM patients, supporting its use as first-line therapy, especially for those who are overweight or obese.

Keywords: Type 2 diabetes; metformin; weight loss; glycemic control; systematic review.

1. INTRODUCTION

The global burden of type 2 diabetes mellitus (T2DM) has reached epidemic proportions, with an estimated 463 million adults living with T2DM in the year 2019, and this number is expected to climb up to about 700 million by the year 2045 [1,2]. The management of obesity is one of the more critical challenges around T2DM since the majority of patients with T2D are overweight or else obese. Obesity worsens insulin resistance, impairs glycemic control, and elevates the risk of cardiovascular complications [3]. Thus, knowledge about effective weight management strategies has become very important in the overall care of a patient with T2DM.

Since its introduction in the 1950s, metformin has been one of the mainstays for treating T2DM. Metformin is a biguanide-class drug. It works mainly by lowering hepatic glucose production and increasing insulin sensitivity. In addition to glucose lowering, metformin has generated considerable interest in its ability to reduce weight in T2DM [4,5]. Various studies have proposed that, apart from the antihyperglycemic activity, metformin could result in modest weight loss, which would be an additional advantage in metabolic control in T2DM.

The intertwining of metformin and weight loss goes deep. This includes direct effects on appetite regulation and fat metabolism as well as indirect effects through improved insulin sensitivity and glycemic control [6,7]. Indeed, metformin-induced weight loss will also be investigated to determine the extent and consistency of this phenomenon across various populations and different clinical frameworks.

Therefore, this updated systematic review and meta-analysis aims to critically appraise our available evidence on metformin as a weight-reduction strategy in people with T2DM. This review aims to collate the evidence from recent randomized controlled trials (RCTs) and observational studies to provide an up-to-date overview of metformin's efficacy in weight management for T2DM patients. The results of this review will apply to clinical practice, especially in forming treatment strategies for glycemic control and obesity among persons with T2DM.

2. MATERIALS AND METHODS

2.1 Study Design

The "Reporting Items for Systematic Review and Meta-Analysis (PRISMA)" guidelines were adhered to in a recent study [8]. Since the latest study was predicated on a systematic review and meta-analysis of previously published RCT trials, no extra ethical review was necessary.

2.2 Selection Criteria

PRISMA criteria were followed in selecting and screening research publications [9]. The screening of research articles was aided by the predetermined selection criteria.

2.3 Inclusion Criteria

Only those articles were included in the recent meta-analysis and systematic review that met the following criteria: 1). Discussing obese or non-obese populations having type 2 diabetes (DM2) 2). Discussing the efficacy or impact of metformin drugs for weight loss and glycemic control 3). Studies based on randomized controlled trials and cohort studies, 4). Studies with full text and published in English.

2.4 Exclusion Criteria

Only the following studies were not included: 1. Talking about people who don't have diabetes or those with different kinds of diabetes 2. talking about the other anti-diabetic medication for glycemic control, cardiovascular risks, and weight loss 3. Systematic reviews, meta-analyses, scoping reviews, literature reviews, conferences, and case studies that have already been published 4. Studies with duplicate publications or non-full-text papers were published in languages other than English.

2.5 Search Strategy

The study aims of "Impact of metformin on weight loss in patients with type 2 diabetes" were addressed in research articles that were retrieved from several databases using the PRISMA criteria [2]. A recent systematic review and meta-analysis employed three electronic databases: clinicaltrails.gov, EMBASE, and PubMed. These MeSH terms were combined in the literature search. "Type 2 diabetes" OR "DM2" OR "obese diabetic patients" AND "metformin" OR "MET") AND "placebo" OR "sulfonylurea" OR "rosiglitazone" OR "miglitol" OR "Dapagliflozin") AND "weight loss" OR "BMI" OR "Glycosylated hemoglobin (A1C)" OR "Fasting plasma glucose FPG" were the MeSH keywords used for data extraction. The study timeline was extended to January 2024.

2.6 Study Question

Among patients undergoing strabismus surgeries, what are the impacts of metformin on weight loss among type 2 diabetes patients? The recent study used the Population Intervention Control Outcome (PICO) framework to guide the search (Table 1).

2.7 Data Extraction

Following the selection and screening of research articles, we extracted the demographic data pertaining to authors, study year, country, study population, sample size, study design, Intervention period, type of corticosteroid, and primary outcomes like body weight reduction and glycemic control from selected articles, as Table 2.

2.8 Study Outcomes

The primary outcomes of the recent study were related to the effectiveness of metformin in reducing body weight and glycemic control for type 2 diabetes mellitus patients. These outcomes were a reduction in body weight and glycemic control.

2.8.1 Quality assessment

The critical appraisal skills program checklist (CASP) was used to perform a quality assessment, and it designed the overall judgment of the included studies. The Critical Appraisal Skills Programme introduced the CASP checklist for assessing the methodological quality of non-RCTs (prospective cohort study & Retrospective cohort study) [10]. Four included studies were entered into the quality assessment procedure by CASP to ensure the use of criteria uniformly.

Table 1. PICO framework for research question of recent study

PICO	Description	Search Terms
Population	Patients diagnosed with Type 2 Diabetes	"type 2 diabetes" OR "DM2" OR "obese diabetic patients"
Intervention Control/ comparison	Metformin in monotherapy Placebo and combination therapy	"metformin" OR “MET” "placebo" OR “sulfonylurea” OR “rosiglitazone” OR “miglitol”
Outcome	Loss in body weight (BMI), Decrease in Glycosylated hemoglobin (A1C), and Fasting plasma Glucose FPG (mmol/l)	"weight loss" OR "BMI" OR "Glycosylated hemoglobin (A1C)” OR “Fasting plasma Glucose FPG"

2.8.2 Risk of bias assessment

The risk bias of the included RCTs was evaluated using the Cochrane risk of bias method [11]. Seven areas were used to assess the risk bias of included studies: allocation concealment, participant blinding, selection bias, blinding of outcome assessment, selective reporting, and additional bias. Each included study's score or level was divided into three categories: low risk, unclear risk, and high risk.

2.8.3 Statistical analysis

In a recent meta-analysis, the pooled analysis was conducted by using RevMan (Review Manager) software version 5.4. the Mantel-Haenszel (M-H) random effect model was applied [11] for evaluation of the mean difference of expected outcomes after metformin in comparison to placebo and other drugs in combination therapy for weight loss among type 2 diabetes patients was evaluated by pooled analysis. Furthermore, the I2 statistics was used to measure the heterogeneity. A significant difference was considered if the p-value > 0.05. If the I2 value was >50%, heterogeneity was considered significant.

3. RESULTS

3.1 Included Studies

The PRISMA standards in a recent meta-analysis were followed in selecting and screening research papers relevant to the study's objectives, "Impact of Metformin on Weight Loss in Patients with Type 2 Diabetes." In total, 1175 research articles were extracted from three electronic databases using the aforementioned search approach. Just 562 papers were examined using the PRISMA procedures, while 613 articles were disqualified before screening. Only 8 of those papers were evaluated for eligibility, and 14 research articles remained after exclusion criteria were applied. As shown in Fig. 1, only 14 papers were included in the most recent meta-analysis since they satisfied the inclusion criteria.

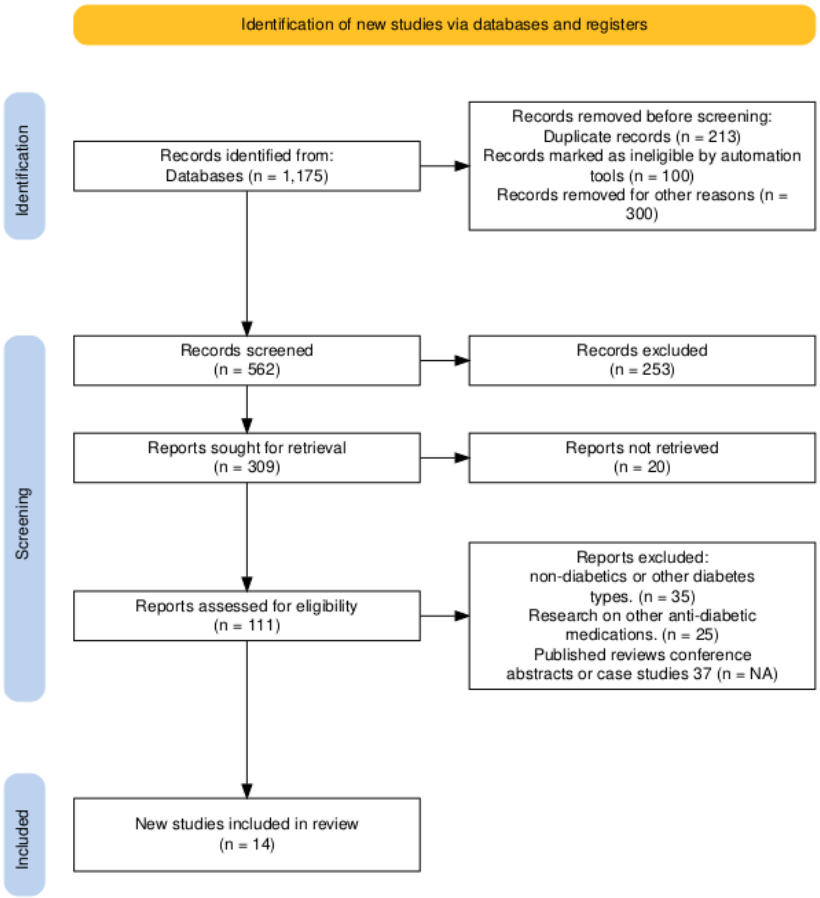

Fig. 1. PRISMA Flowchart for screening and selection of included studies

3.2 Risk of Bias & Quality Assessment

The Cochrane risk of bias tool was used to assess the studies, and the findings are presented in Figs. 2 and 3. All our studies were considered to have minimal risk of bias, indicating a high level of reliability. The quality assessment of eleven studies was performed using the CASP checklist, which recognized 11 standards or questions for quality assessment. The scores of included studies were recorded in response to each standard; the study having a score of less than 5 was considered weak, a score of 5-7 was moderate, and more than 6 scores were a strong study. Among included studies, 2 studies [12,13] were strong, 1 study [14] was moderate and 2 study [15] was weak, as shown in Table 2.

3.3 Characteristics of Included Studies

In a recent meta-analysis, studies involving metformin drugs for weight loss among type 2 diabetes mellitus were included to evaluate its effectiveness. To produce heterogeneity, 10 RCT's and 4 non RCT's involving 11686 type 2 diabetes mellitus patients were taken from 10 different countries such as 4 from USA [16,17,15,18], 3 from Sweden [19,20,21], 1 from Denmark [12], 1 from Netherland [8,15], 1 from Canada [22], 1 from Australia [13], 1 from Israel [23], 1 from China [14] and 1 from Japan [24].

Table 2. The quality assessment of included studies by using CASP Checklist [3]

Standards of CASP checklist	Myette et al., [9]	Ji et al., [16]	Abbasi et al., [10]	Ong et al., [17]
Focused issue	Y	Y	Y	Y
Appropriate methodology related to aim	Y	Y	Y	N
Data resources linked authenticity	N	Y	Y	N
selection of control group	Y	N	Y	N
Negligence to Bias	Y	N	N	Y
Considering confounding factors	Y	Y	Y	N
Clarity of results	Y	Y	N	N
Result Accuracy	Y	Y	Y	Y
Model validation	N	Y	Y	Y
Applicability Of study	Y	N	Y	N
Fitness of results	Y	Y	Y	N
Total score	9	8	9	4

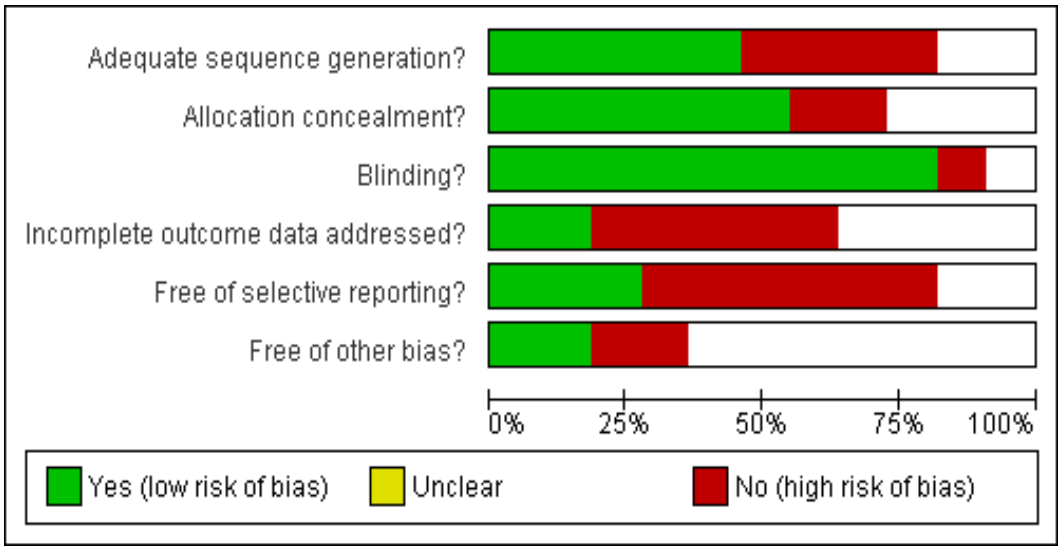

Fig. 2. Graph of Risk bias of included studies

Table 3. Characteristics of included studies in recent systematic review and meta-analysis

Author, Year	Country	Study Population	Sample size	Study design	Type of Intervention (dose up to 1000mg)	Study follow up	Glycosated hemoglobin (A1C)	Fasting plasma Glucose FPG (mmol/l)	Decrease in BMI (kg/m2)
Gram et al., 2011 [12]	Denmark	371 Type 2 diabetes patients (30–70 years old)	37 in metformin & 40 in placebo	Randomized controlled trial	Metformin	2 years	T: −0.60 ± 0.10 C: −0.41 ± 0.10	T: 1.9 ± 5.7 C: 6.7 ± 9.9	T: 2.8 ± 0.6 C: - 1.6 ± 0.6
Chukir et al., 2021 [18]	USA	222 type 2 diabetes patients	103 in treatment 119 in placebo	Retrospective cohort study	Metformin monotherapy	12 months			T: 6.5 [6.0%] C: 7.4 [6.2%]
Jones et al., 2002 [17]	California, USA	481 type 2 diabetes (8–16 years)	42 in treatment 40 in placebo	Randomized controlled trial	Metformin monotherapy	16 weeks	T: 7.5 C: 8.6	T: −2.4 C: +1.2	T: −0.5 C: −0.4
Kooy et al., 2009 [25]	Netherlan d	390 patients (30-80 years)	196 in treatment 194 in placebo	Randomized controlled trial	Metformin	4 years	T: −0.55 C: −0.25	T: 2.1 C: 2.6	T: −1.37 C: −0.81
Myette et al., 2016 [22]	Canada	10 DM2 patients (40-70 years old)		Pilot study	Metformin	6 years	T: 6.6±0.6%	T: -1.1 C: 0.3	T: -2.9. C: 1.2
Abbasi et al., 2004 [15]	CA, USA	31 DM2 patients	16 in metformin & 15 in combination therapy	Prospective study	Metformin plus sulfonylurea (combination therapy)	12 weeks	T: 2.91 ± 0.47 C: 3.52 ± 0.85	T: 0.43 ± 0.09 C: 0.34 ± 0.07	
Fonseca et al., 2000 [16]	Louisiana, USA	348 DM2 (40-80 years)	116 in metformin & 119 in combination therapy	Randomized, double-blind, placebo-controlled trial	Metformin plus rosiglitazone	26 weeks	T: 1.0 C: 1.2	T: 2.2 mmol/L C: 2.9 mmol/L	
Bolinder et al., 2012 [19]	Sweden	314 DM2 patients	91 in metformin & 89 in combination therapy	Randomized controlled trial	Metformin plus Dapagliflozin	24 week	T: - 0.10 C: -0.39	T: 2.4 (0.13) C:-14.7 (-0.82)	T: -2.22 C: -0.74
Erikson et al., 2006 [20]	Sweden	21 DM2 patients	16 in metformin 5 in placebo	Randomized controlled trial	Metformin	4 weeks	T: 0.7 C: -0.12	T: 2.04 C; 1.06	
Ong et al., 2006 [13]	Australia	8,304 individuals	394 in metformin & 250 in combination therapy	Prospective study	Metformin versus Sulfonylurea	5 years	T: -1.3 C: -0.97		T: -16.07 C: -2.3

Author, Year	Country	Study Population	Sample size	Study design	Type of Intervention (dose up to 1000mg)	Study follow up	Glycosated hemoglobin (A1C)	Fasting plasma Glucose FPG (mmol/l)	Decrease in BMI (kg/m2)
Rachmani et al., 2002 [23]	Israel	393 patients (40–75 years)	195 in metformin & 198 in placebo	Randomized controlled trial	Metformin	2 weeks	T: 5.8 C: 2.3		T: 4.2 C: 1.3
Chiasson et al., 2001 [26]	France	324 DM 2 patients (40 to 60 years)	83 in metformin, 76 in combination therapy	Randomized controlled trial	Metformin plus miglitol	8 week	T: -0.85 ± 0.12 C: -1.39 ±0.11	T: -17.4 ± 4.7 C; -12.4 ±3.8	T: -0.79 ±0.33 C; -1.87 ±0.33
Hermann et al., 2001 [21]	Sweden	37 DM2 patients	16 in metformin & 16 in placebo	Randomized controlled trial	Metformin	12 months	T: −1.1 ± 0.7% C; 0.3 ± 0.8%	T: −1.4 ± 2.1 C: 0.6 ± 2.2	
Ji et al., 2013 [14]	China	371 DM2 patients with obesity	233 in metformin 112 in placebo	Prospective open label trial	Metformin	16 weeks	T: –1.78 (–1.67) C: –1.84 (–1.73)	T: –2.14 (2.03) C: –1.98 (1.79)	T: –1.04 (1.11) C: –0.54 (0.84)
Kawai et al., 2008 [24]	Japan	69 Japanese type 2 diabetic patients	35 in metformin & 28 in placebo	Randomized controlled trial	Metformin plus Pioglitazone	24 weeks	T: 0.6% ± 0.1 C;	T: -18.5 C: - 3.5	T: 0.2± 3.4 C: 0.1±1.2

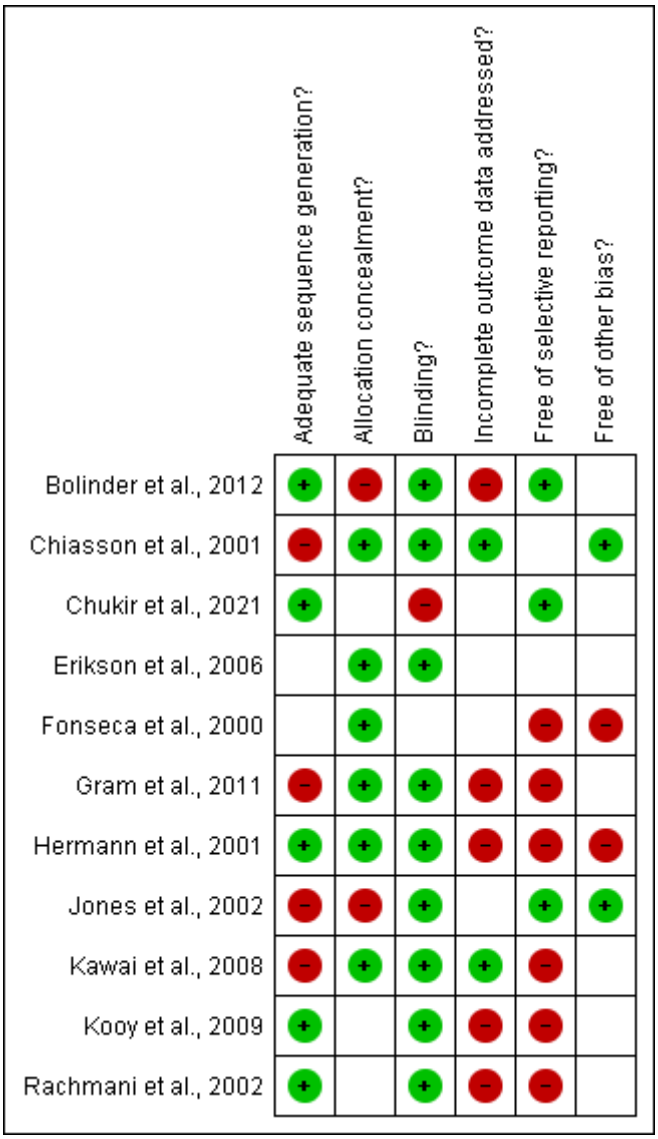

Fig. 3. Graph of risk bias summary of included studies

3.4 Primary Outcome

3.4.1 Glycosylated hemoglobin (A1C)

Among 14 included studies, the outcome of glycosylated hemoglobin (A1C) was discussed among 7 research articles on metformin versus placebo [12,17-19] and 6 research articles on metformin versus other antibiotic drugs [20-25]. There was a significant difference in glycosylated hemoglobin (A1C) levels among metformin and placebo groups (Mean difference = 0.69;- 0.93 to 2.23 CI: 95%, p< 0.00001). However, there was a slight difference in glycosylated hemoglobin (A1C) (Mean difference= 0.36; -0.08 to 0.34, CI; 95, p,0.00001) among groups receiving metformin and another antidiabetic drug such as miglitol, rosiglitazone, and heterogeneity was found (df = 13; I2 = 99%), as shown in Figs 4 and 5. The mean difference values of the pooled analysis showed that metformin drugs have not reduced A1C levels among type 2 diabetes patients.

3.4.2 Fasting plasma glucose FPG

Among 14 included studies, the outcome of Fasting plasma Glucose FPG was discussed among 7 research articles of metformin versus placebo [12,15-19] and 5 research articles of metformin versus other antibiotic drugs [20, 22-24]. There was a significant difference in fasting plasma glucose levels among metformin and placebo groups (Mean difference = -1.38; -

2.78 to 2.23 CI: 95%, p< 0.00001). However, there was a significant difference in FPG (Mean difference -6.49; -9.943 to 3.34, CI; 95, p,0.00001) among groups receiving metformin and other antidiabetic drug such as miglitol, rosiglitazone, and heterogeneity was found (df = 1; I2 =33.1%), as shown in Figs 6 and 7.

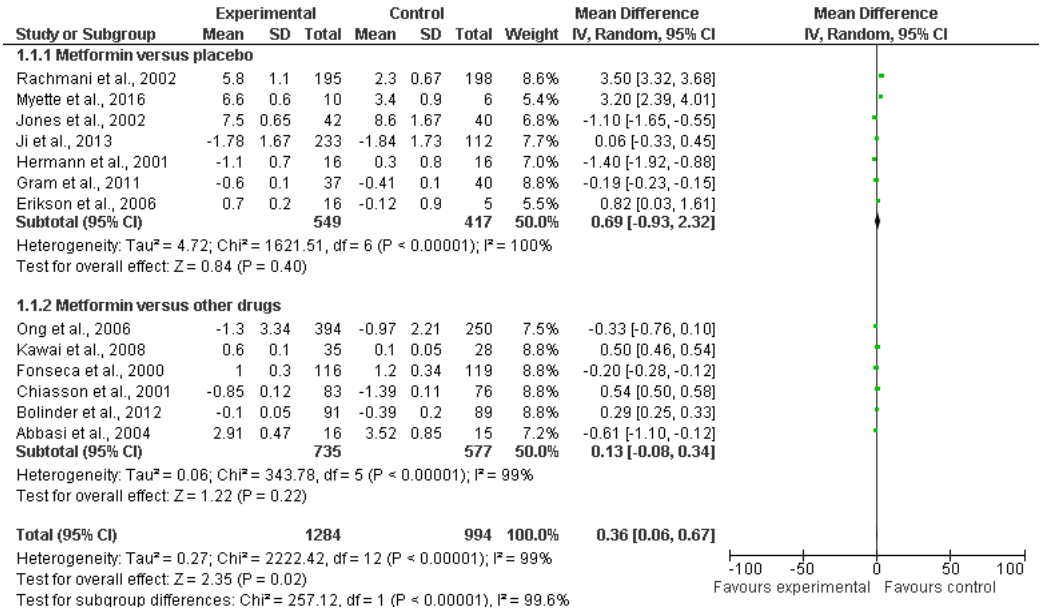

Fig. 4. Forest plot of mean difference of A1C levels among metformin and placebo or other antibiotic drug [12, 24]

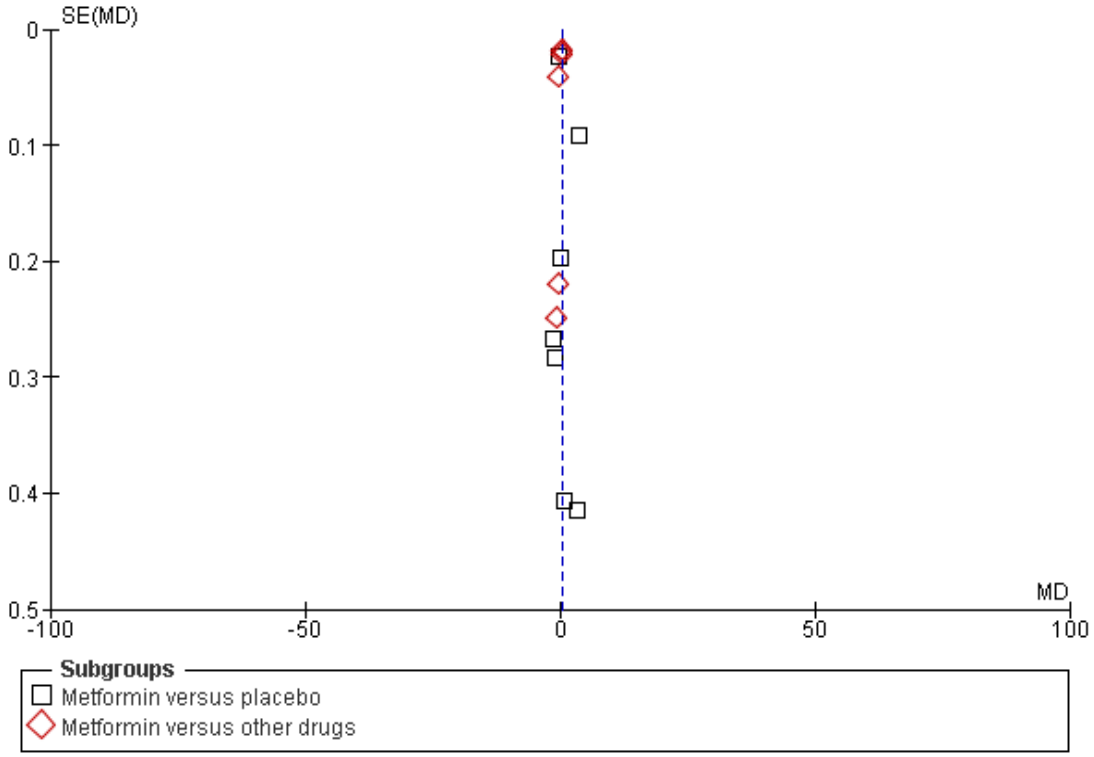

Fig. 5. Funnel plot of mean difference of A1C levels among metformin and placebo or other antibiotic drug

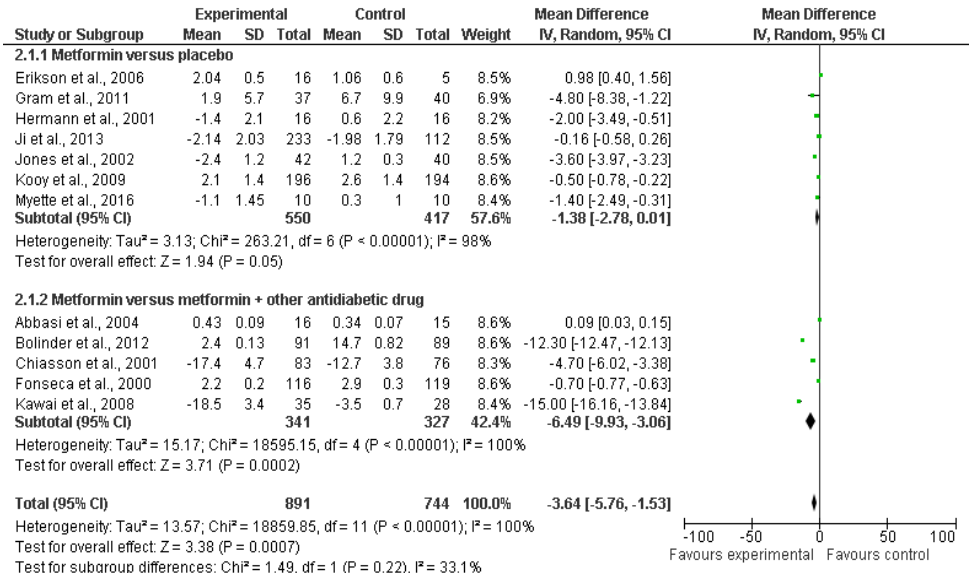

Fig. 6. Forest plot of mean difference of FPG levels among metformin and placebo or other antibiotic drug [12-24]

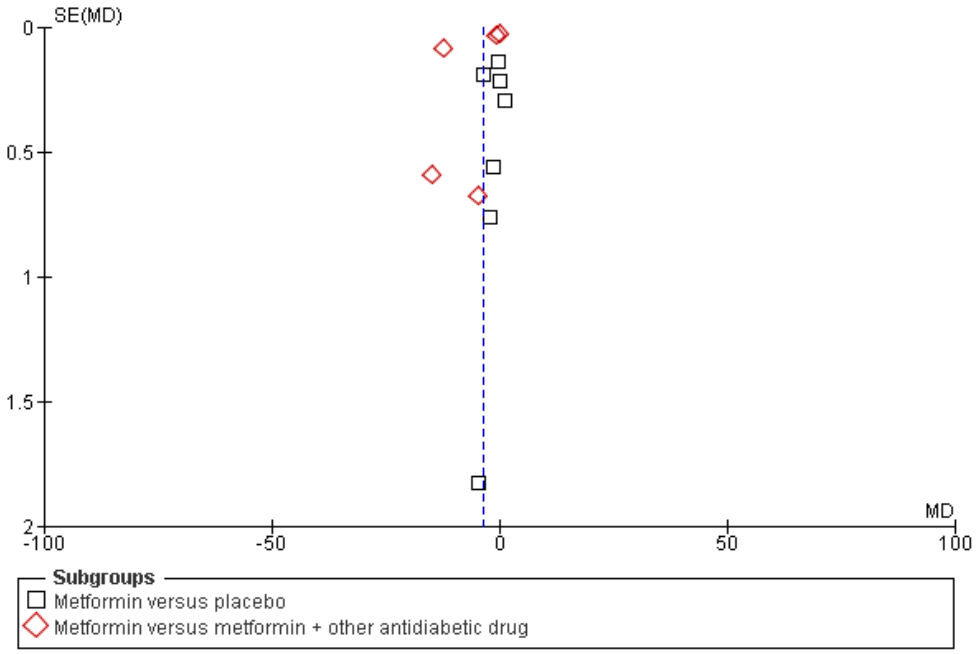

Fig. 7. Funnel plot of mean difference of FPG levels among metformin and placebo or other antibiotic drug

3.4.3 Weight loss

Among 14 included studies, the outcome of body weight or BMI was discussed among 7 research articles of metformin versus placebo [12, 14-19] and 4 research articles of metformin versus other antibiotic drugs [20, 22-23, 25]. There was a slight difference in body weight loss among metformin and placebo groups (Mean difference = 0.16; 0.69 to 1.02 Cl: 95%, p< 0.00001). However, there was a significant difference in FPG (Mean difference -3.67; -11.58 to 4.34, Cl; 95, p,0.00001) among groups receiving metformin and other antidiabetic drug such as miglitol, rosiglitazone, and heterogeneity was found (df = 9; I2 =100%), as shown in Figs 8 and 9.

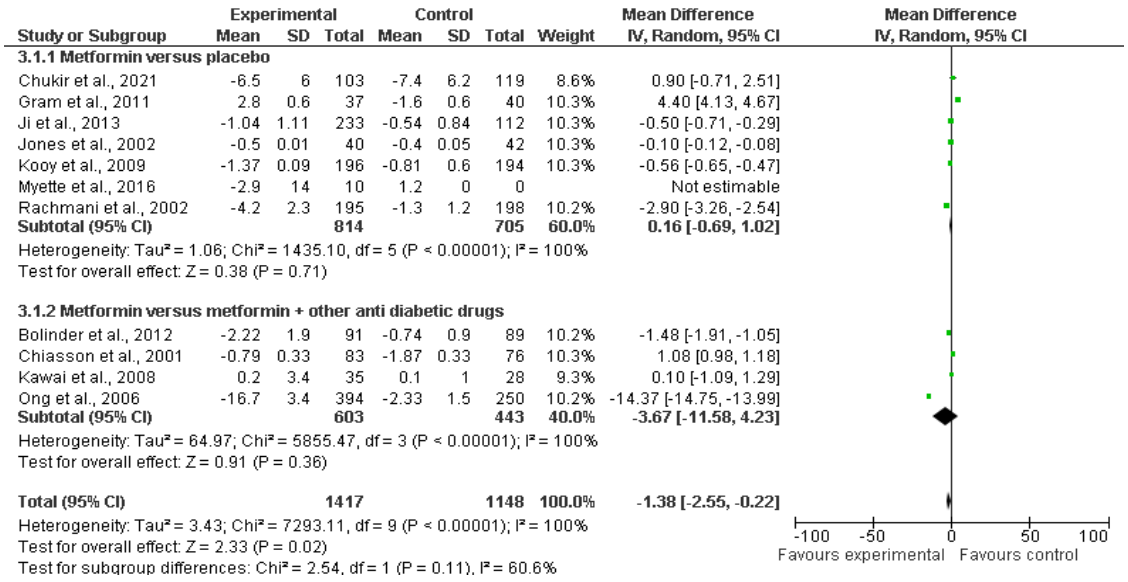

Fig. 8. Forest plot of mean difference of Metformin versus placebo and Metformin versus metformin, other anti diabetic drugs [12-16, 19-26]

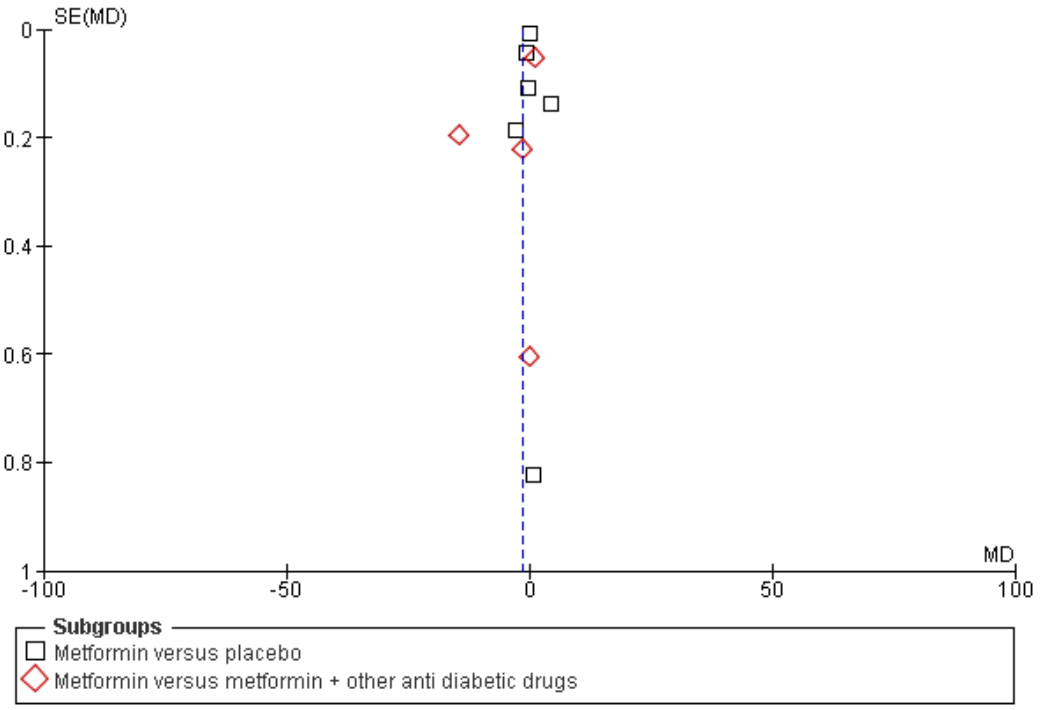

Fig. 9. Placebo effect of metformin with other anti-diabetic drugs

4. DISCUSSION

The present updated meta-analysis provides an overview of the weight loss effects associated with metformin in patients diagnosed with T2DM. Findings show that metformin induces minor weight and hemoglobin A1c levels reductions but is more effective than other antidiabetic agents.

This analysis indicates that metformin reduces body weight slightly among T2DM patients. This was consistent with prior literature, which has shown metformin to be weight-neutral or even cause a small degree of weight loss when taken by overweight/obese diabetic patients. The average difference of a few kilograms in weight loss between metformin and placebo groups is

not great but clinically meaningful. An essential point is that obesity can exacerbate insulin resistance and further complicate diabetes management. This is crucial as weight loss reduces cardiovascular risks and improves overall metabolic health compared to other antidiabetic medications that may have the potential to increase body weight. [27,28].

The pooled data support the effectiveness of metformin in decreasing glycosylated hemoglobin (A1C) levels. The metformin groups had significantly lower A1C, an important marker of long-term glycemic control compared with placebo. This further confirms that metformin improves insulin sensitivity and decreases intrahepatic glucose production. The pronounced lowering of Fasting Plasma Glucose (FPG) seen here also underscores the concept that metformin is optimal for treating patients with their initial hyperglycemia and defines its role as first-line therapy in T2DM [29].

Metformin is much better than other antidiabetic agents like sulfonylureas, rosiglitazone, and miglitol in terms of weight management. Although some of these drugs have been linked with weight gain, metformin either has a neutral effect on body weight or causes modest weight loss. Horizontal gene transfer is especially good; one of the big problems with many antidiabetic drugs is that they cause weight gain, which can exacerbate insulin resistance and other metabolic ills. So, the glycemic control and weight reduction effects of metformin both confer individual advantages in T2DM cohorts [30, 31]
The high degrees of heterogeneity identified in the selected studies emphasize variance between study designs, populations, and intervention durations. In light of that, the risk of bias was generally low, and most studies were of high quality. This increases the robustness of our conclusions but also points towards the impact of patient-specific characteristics (age, baseline BMI, DT2 duration) on outcomes. To counter any risk of bias, reviewed articles were formally assessed using the CASP checklist and Cochrane risk of bias tool for randomized controlled trials to ensure that they met rigorous standards with regard to methodological quality [32,33].

5. CONCLUSION

In conclusion, this updated systematic review and meta-analysis confirm that metformin results in a small weight reduction among T2DM patients concurrent with its well-accepted advantage relating to glycemic control. The beneficial effect on body weight, in addition to the safety and cost-effectiveness of metformin, reinforces its use as a first-line therapy alongside regular exercise for the management of T2DM. Their results endorse metformin as a first-line treatment, especially for overweight or obese type 2 diabetic individuals, and emphasize the importance of continued research to enhance this therapeutic utility.

6. CLINICAL IMPLICATIONS

The implications of these findings are monumental for clinical practice. As metformin is a drug inducing weight loss with relatively modest effects compared to its primary glucose-lowering effect, it confirms the importance of using this agent in overweight or obese patients. Metformin has been shown to have this dual benefit, so there is evidence amongst others for still using metformin as a first-line therapy. Clinicians should be mindful of prescribing metformin in light of these findings not only for the glucose-lowering properties but also due to its possible assistance with weight management, a clinically relevant agent that is critical within T2DM development.

7. LIMITATIONS AND FUTURE RESEARCH

Although the meta-analysis provides essential information, there are limitations that future studies might possibly be able to address. The marked heterogeneity in metabolic benefits undoubtedly emerged, and consequently, more granular segregation by readily available patient characteristics such as age, gender, or baseline metabolism might possibly be subjected to further stratified analyses. Further, long-term studies are warranted to appraise the durability of metformin-induced weight loss and glycemic control processes. Consequently, future research should seek to further elucidate the pathways by which metformin accomplishes weight loss to enable an optimal individualization of diabetes treatment and different therapeutic regimens.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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