Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Effects of Metformin in Patients with Poorly Controlled, Insulin-Treated Type 2 Diabetes Mellitus

Abid A. Altayari[1], Khalid Faraj Alrehaili[2], Sanad Abdulrahman Alharbi[3], Yahya Ali Kaabi[4], Abdullah Khaled Altamimi[5], Yousra Khudran Alzahrani[6], Sabrin Saleh Albalawi[7], Abdulrahman Soliman Alzeriry[8], Abdullah Abdulrahman Saleh Alruwaythi[9], Althubyani, Mohammed Yahya M[10], Mohammed Al Hassan Al Malki[11], Omar Owaydhah Salem Almotairi[12], Muhannad Naffaa Almatrafi[13]

Abstract

Background: Metformin is an oral anti-diabetic drug widely recognized as the first-line therapy in the treatment of Type 2 Diabetes Mellitus (T2DM). Aim: To assess the impact of metformin on glycemic control, insulin dosage, and side effects in poorly controlled, insulin-treated type 2 diabetes patients. Patients and methods: A comprehensive literature search was conducted using electronic databases such as PubMed, Embase, Cochrane Library, and Web of Science. The search terms included "metformin," "insulin," "type 2 diabetes," "poorly controlled," and "randomized controlled trial." The search was limited to studies published in English up to December 2022. Results: The study analyzed three studies on total cholesterol levels at follow-up, LDL follow-up, HDL at follow-up, and triglycerides at follow-up. A non-significant heterogeneity was detected, resulting in a non-significant difference between groups. A random-effect model was used for analysis, revealing a combined mean difference of -0.11 and 95% CIs of -2.66. The combined results showed no statistically significant difference between groups regarding LDL baseline (Z = 1.73, P = 0.08), HDL at follow-up (Z = 1.87, P = 0.06), and triglycerides (Z = 1.04, P=0.30). A highly significant heterogeneity was detected in the Side Effect (Two studies reported), demonstrating a highly statistically significant difference between groups regarding this effect (Z = 7.01, P <0.001). The results suggest that a combination of factors may influence cholesterol levels and triglycerides at follow-up. Conclusion: Metformin significantly improves diabetes duration, insulin therapy duration, and glycated hemoglobin levels in Type 2 diabetes patients, with moderate side effects risk. Further studies are needed for long-term safety.

Keywords: *T2DM; Metformin; Insulin.*

Introduction

As a chronic metabolic disease with complex pathogenesis, type 2 diabetes mellitus (T2DM) refers to a spectrum of systemic illnesses related to glucose metabolism, lipid metabolism, and amino acid metabolism **(1).**

[1] Senior Pharmacist, Khulais General Hospital

[2] Senior Pharmacist, King Fahad hospital

[3] Pharmacist, King Fahad hospital

[4] Pharmacist, King Fahad hospital

[5] Technical pharmacists, King Fahad hospital

[6] General practitioner, Alqaswa'a PHC

[7] Pediatric specialist, Eastern Jurf PHCC

[8] Pharmacist, Maternity and Children Hospital

[9] Health Assistant Health Security, Badr General Hospital

[10] Technician pharmacist, Mental health hospital in Jeddah

[11] Technician pharmacist, ALTHAGHR HOSPITAL

[12] Technician pharmacist, Rabigh General Hospital

[13] Health security, Rabigh General Hospital

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Yet, there is no cure for T2DM, while its prevalence is largely increasing, with increased risk of complications including diabetic retinopathy, neuropathy, kidney damage, and cardiovascular complications **(2).**

Metformin is an oral anti-diabetic drug accepted as first line therapy in the treatment of T2DM **(3)** It not only improves glycaemic control by enhancing insulin sensitivity in the liver and muscles but also increases insulin receptor tyrosine kinase activity, stimulates glucose transport and glycogen synthesis, and reduces both hepatic gluconeogenesis and glycogenolysis **(4).**

Weight gain is a common adverse effect of some glucose-lowering drugs, especially insulin treatment, while metformin is associated with stable or decreased weight **(5).**

A total of 5 studies were selected for the current analysis, including a total of 988 patients.

This study was aim to assess the impact of metformin on glycemic control, insulin dosage, and side effects in poorly controlled, insulin-treated type 2 diabetes patients.

Patients and methods

A comprehensive literature search was conducted using electronic databases such as PubMed, Embase, Cochrane Library, and Web of Science. The search terms included "metformin," "insulin," "type 2 diabetes," "poorly controlled," and "randomized controlled trial." The search was limited to studies published in English up to December 2022.

Study Selection and Inclusion Criteria:

For this meta-analysis, studies were selected based on the following criteria: Study Design: Randomized controlled trials comparing metformin with placebo in patients with poorly controlled, insulin-treated type 2 diabetes mellitus; Population: Adult patients with type 2 diabetes who were on insulin therapy and had poor glycemic control; Intervention: Metformin as an adjunct to insulin therapy; Comparison: Placebo in addition to insulin therapy; Outcomes: Primary outcomes included changes in HbA1c, fasting plasma glucose, and daily insulin dose, while secondary outcomes included lipid profile and side effects.

Exclusion Criteria: Studies involving patients with type 1 diabetes mellitus or gestational diabetes ,non-randomized studies, observational studies, or studies without a control group and studies with insufficient data for meta-analysis.

Data extraction: Two independent reviewers extracted data from the selected studies using a standardized data extraction form. The extracted data included: Study characteristics: author, year, country, study design, sample size, and study duration. Patient characteristics: age, sex, duration of diabetes, duration of insulin therapy, baseline HbA1c, and baseline insulin dose. Outcome measures: changes in HbA1c, FPG, daily insulin dose, lipid profile, and side effects.

Statistical Analysis

We performed all data analyses using Review Manager version 5.4.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We calculated the odds ratio with 95% confidence interval (CI) for binary outcomes. We calculated mean difference with 95% CI for continuous outcomes. To calculate the overall effect, estimate with 95% CI, we used a fixed-effect model with the method of Mantel-Haenszel when there is no evidence of heterogeneity between studies. Otherwise, a random-effects model with the method of DerSiomonian and Laird was chosen. Heterogeneity between studies was evaluated using the Q statistic and I^2 test which describe the percentage of variability in the effect estimates. A P value of < 0.05 was considered significant.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Results

A total of 5 studies were selected for the current analysis, including a total of 988 patient. The publication year ranged from 1992 to 2016., 1 study was conducted in each of the following: California, America, Netherlands and Italy. Baseline characteristics of included studies are demonstrated in **Table 1**.

Author, year	year	country	Study period		Study design	Sample Size		
			from	to		Metformin	Placebo	total
Larissa Avile´s-Santa. 2016	2016	California			Randomized, controlled trial	21	22	43
MICHIEL G. WULFFELE 2002	2002				Randomized controlled double-blind trial	171	182	353
Alan J. Garber MD 1994	1994	America	1990	1994	Double-blind, dose-response study	73	79	152
Adriaan Kooy 2008	2008	Netherlands			Randomized, controlled trial	196	194	390
D. Giugliano 1992	1992	Italy			Prospective, randomised, trial	27	23	50

Table2. Patient's characteristics

The mean participants' age in studied groups was 51.88 ranging from 35 to 69 years, and gender was reported in 5 studies with 469 male and 519 female as shown in table 2.

Author, year	Age (year)						Sex					
	Metformin			Placebo			Metformin			Placebo		
	mean	SD	total	mean	SD	total	male	female	total	male	female	total
Larissa Avile´s-Santa 2016	53.1	9.4	21	54.6	7.8	22	6	15	21	10	12	22
MICHIEL G. WULFFELE 2002	63.2	9.8	171	58.9	11.1	182	76	95	171	91	91	182
Alan J. Garber MD 1994	57	10	73	55	11	79	45	28	73	44	35	79
Adriaan Kooy 2008	64	10	196	59	11	194	81	115	196	97	97	194
D. Giugliano 1992	60	1	27	60.8	1.1	23	10	17	27	9	14	23

Duration of diabetes (years):

4 studies reported (Duration of diabetes) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 51%, P=0.11). The combined mean difference and 95% CIs was 0.73 (0.15 to 1.30). The combined result demonstrates statistically significant difference between groups regarding (Duration of diabetes) (Z = 2.48, P =0.01).

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

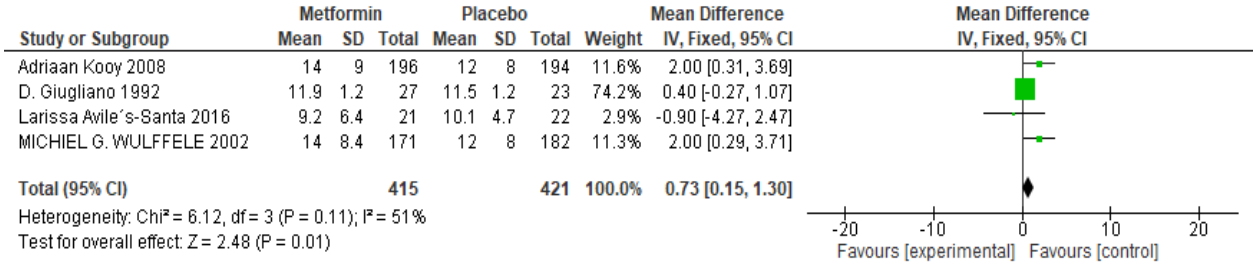


Figure 1. Forest plot of duration of diabetes demonstrates statistically significant difference between Metformin and Placebo groups.

Duration of insulin therapy (years):

3 studies reported (Duration of insulin therapy) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.79). The combined mean difference and 95% CIs was 1.02 (0.08 to 1.95). The combined result demonstrates statistically significant difference between groups regarding (Duration of insulin therapy) (Z = 2.12, P =0.03).

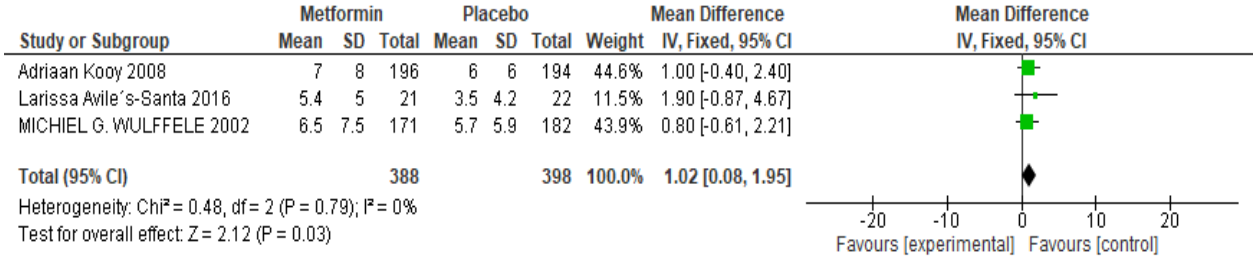


Figure 2. Forest plot of duration of insulin therapy demonstrates statistically significant difference between Metformin and Placebo groups.

GH b (% Hb) Baseline:

3 studies reported (GH b (% Hb) at Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.79). The combined mean difference and 95% CIs was -0.01 (-0.18 to0.16). The combined result demonstrates no statistically significant difference between groups regarding (GH b (% Hb) at Baseline) (Z = 0.15, P =0.88).

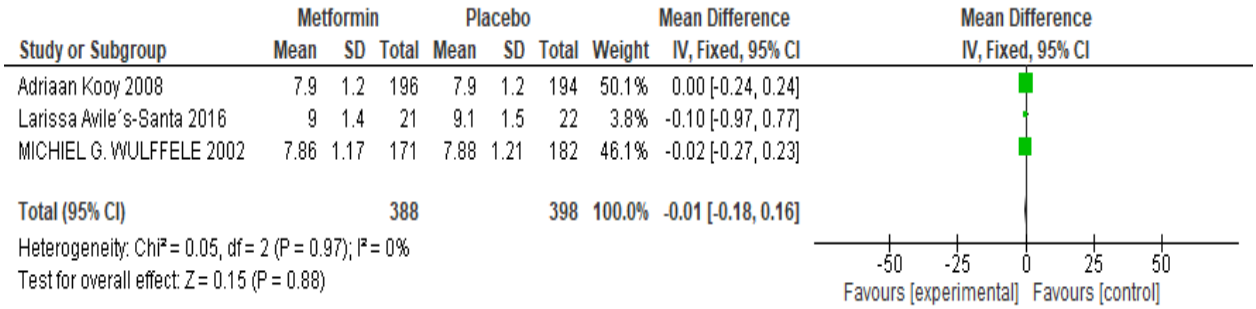


Figure 3. Forest plot of GH b (% Hb) at Baseline demonstrates no statistically significant difference between Metformin and Placebo groups.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

GH b (% Hb) at follow up

3 studies reported (GH b (% Hb) at follow up) and all can be used. A significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P=0.001). The combined mean difference and 95% CIs was -0.37 (-0.56 to -0.18). The combined result demonstrates statistically significant difference between groups regarding (GH b (% Hb) at follow up) (Z = 3.73, P =0.0002).

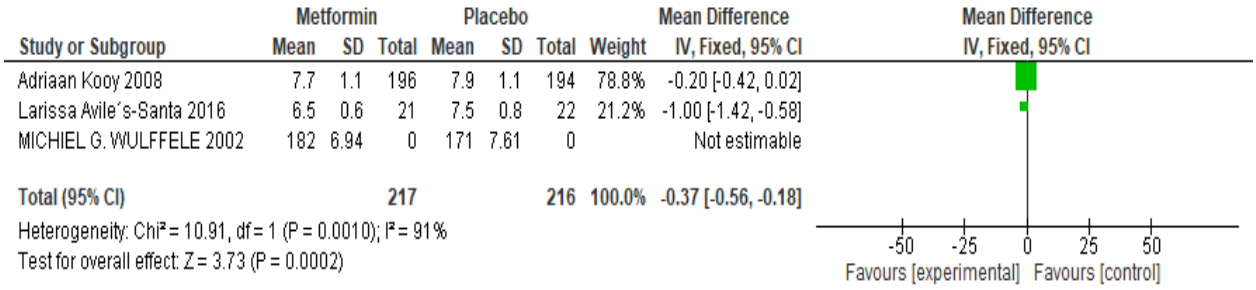


Figure 4. Forest plot of GH b (% Hb) at follow up demonstrates statistically significant difference between Metformin and Placebo groups.

Change in GH b (% Hb):

3 studies reported (Change in GH b (% Hb) and all can be used. A significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 76%, P=0.04). The combined mean difference and 95% CIs was -0.78 (-0.91 to -0.66). The combined result demonstrates statistically significant difference between groups regarding (Change in GH b (% Hb)) (Z = 12.46, P < 0.00001).

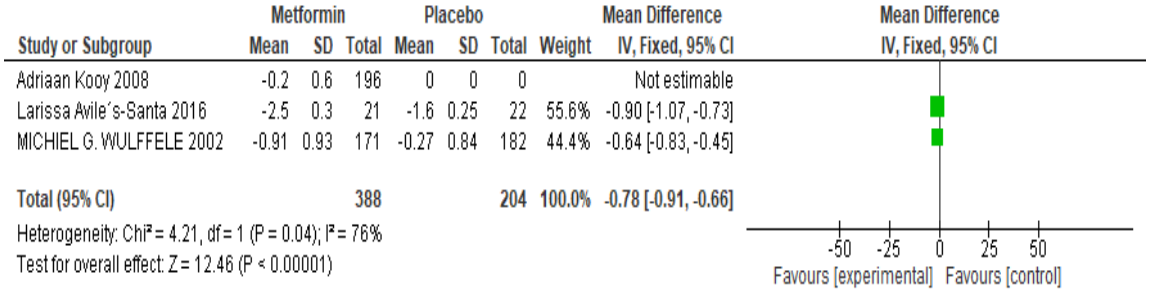
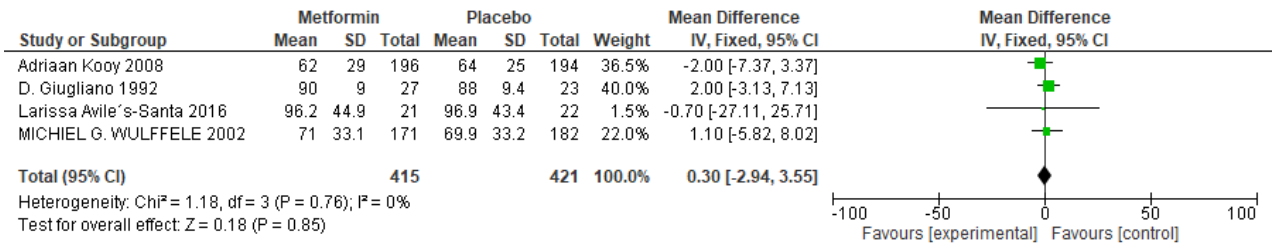


Figure 5. Forest plot of change in GH b (% Hb) demonstrates statistically significant difference between Metformin and Placebo groups.**Daily dose of insulin (IU/day) at baseline**

Four studies reported (Daily dose of insulin (IU/day) at baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.76). The combined mean difference and 95% CIs was 0.30 (-2.94 to 3.55). The combined result demonstrates non-statistically significant difference between groups regarding (Daily dose of insulin (IU/day) at baseline) (Z = 0.18, P =0.85).



Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Figure 6. Forest plot of Daily dose of insulin at baseline demonstrates non-statistically significant difference between Metformin and Placebo groups

Daily dose of insulin (IU/day) at follow up:

Four studies reported (Daily dose of insulin (IU/day) at follow up) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P <0.001). The combined mean difference and 95% CIs was -11.00 (-15.63 to -6.38). The combined result demonstrates highly statistically significant difference between groups regarding (Daily dose of insulin (IU/day) at follow up) (Z = 4.66, P <0.001).

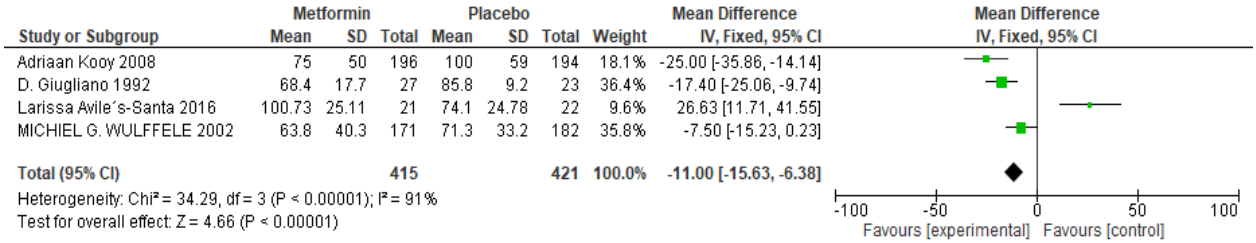


Figure 7. Forest plot of Daily dose of insulin at follow up demonstrates highly statistically significant difference between Metformin and Placebo groups.

Change in Daily dose of insulin (IU/day)

Four studies reported (change in Daily dose of insulin (IU/day)) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 99%, P <0.001). The combined mean difference and 95% CIs was 0.39 (-1.22 to -2.00). The combined result demonstrates non-statistically significant difference between groups regarding (change in Daily dose of insulin (IU/day)) (Z = 0.47, P =0.64).

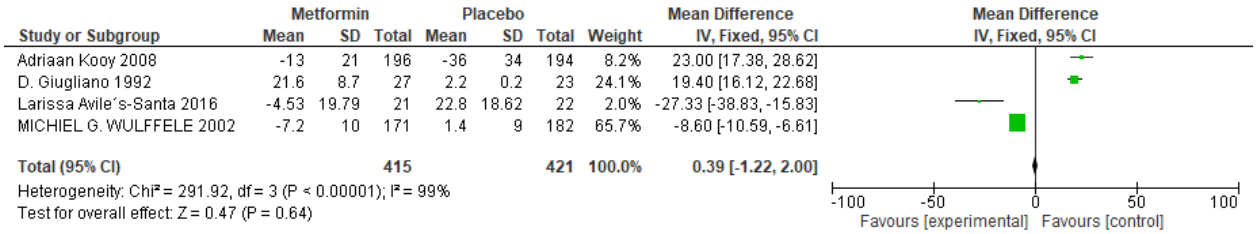


Figure 8. Forest plot of change in Daily dose of insulin demonstrates non-statistically significant difference between Metformin and Placebo groups.

Fasting plasma glucose level, mg/dl at baseline

one study reported (Fasting plasma glucose level at baseline) and all can be used. The combined mean difference and 95% CIs was -21.30 (-64.23 to 21.63). The combined result demonstrates no statistically significant difference between groups regarding (Fasting plasma glucose level at baseline) (Z = 0.97, P =0.33).

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

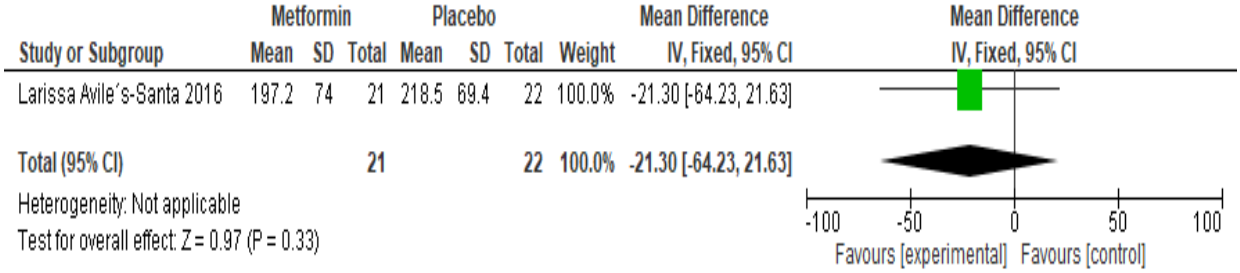


Figure 9. Forest plot of Fasting plasma glucose level at baseline demonstrates no statistically significant difference between Metformin and Placebo groups.

Fasting plasma glucose level, mg/dl at follow up:

One study reported (Fasting plasma glucose level at follow up) and all can be used. The combined mean difference and 95% CIs was -19.70 (-33.53 to -5.87). The combined result demonstrates statistically significant difference between groups regarding (Fasting plasma glucose level at follow up) (Z = 2.79, P =0.005).

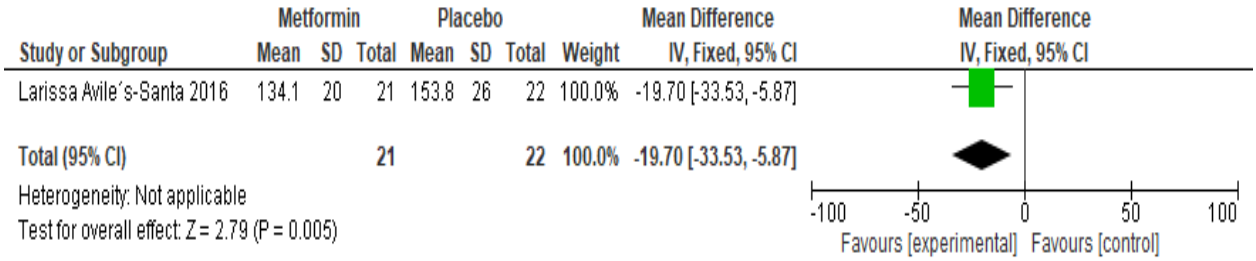


Figure 10. Forest plot of Fasting plasma glucose level at follow up demonstrates statistically significant difference between Metformin and Placebo groups.

Change in Fasting plasma glucose level, mg/dl

One study reported (change in Fasting plasma glucose level) and all can be used. The combined mean difference and 95% CIs was 1.60 (-8.21 to 11.41). The combined result demonstrates no statistically significant difference between groups regarding (change in Fasting plasma glucose level) (Z = 0.32, P =0.75).

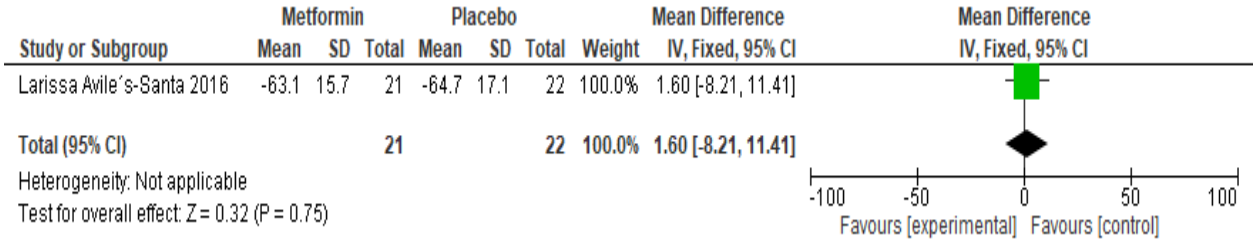


Figure 11. Forest plot of change in Fasting plasma glucose level demonstrates no statistically significant difference between Metformin and Placebo groups.

Total cholesterol level at Baseline

4 studies reported (Total cholesterol level at Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.69). The combined

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

mean difference and 95% CIs was 0.04 (-0.11 to 0.19). The combined result demonstrates no statistically significant difference between groups regarding (Total cholesterol level at Baseline) (Z = 0.51, P =0.61).

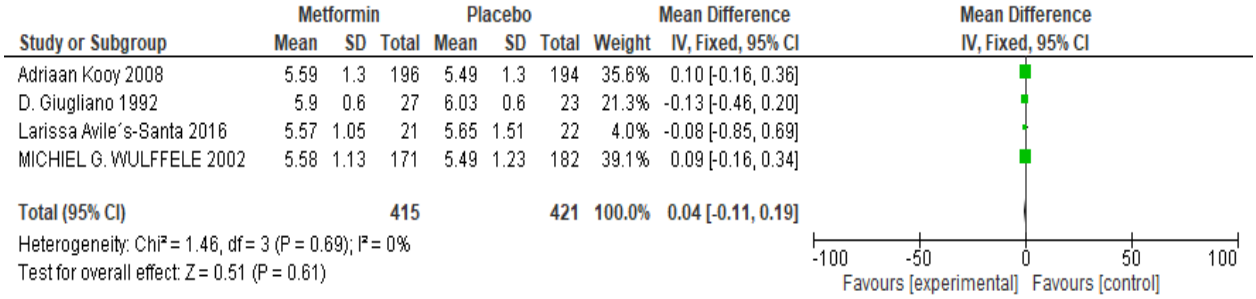


Figure 12. Forest plot of Total cholesterol level at Baseline demonstrates no statistically significant difference between Metformin and Placebo groups

Total cholesterol level at follow-up:

3 studies reported (Total cholesterol level at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 58%, P=0.09). The combined mean difference and 95% CIs was -0.11 (-0.22 to 0.00). The combined result demonstrates statistically significant difference between groups regarding (Total cholesterol level at follow up) (Z = 1.97, P =0.25).

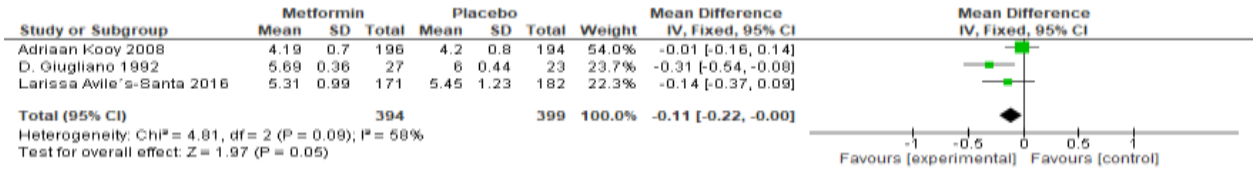


Figure 13. Forest plot of Total cholesterol level at follow up demonstrates statistically significant difference between Metformin and Placebo groups

LDL Baseline

Three studies reported (LDL Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 45%, P =0.16). The combined mean difference and 95% CIs was 4.24 (-2.00 to 10.48). The combined result demonstrates non-statistically significant difference between groups regarding (LDL Baseline) (Z = 1.33, P =0.18).

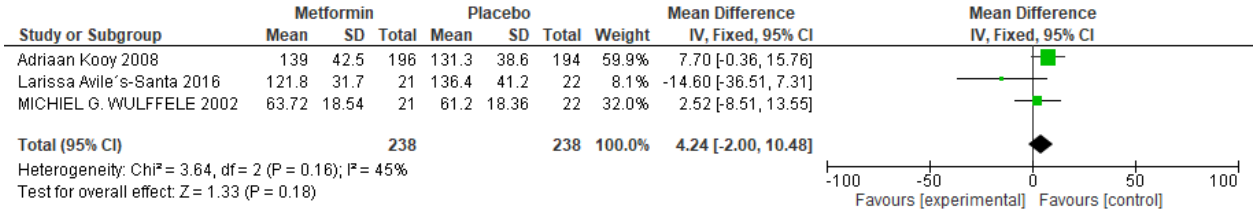


Figure 14. Forest plot of LDL at baseline demonstrates non-statistically significant difference between Metformin and Placebo groups

LDL Follow up

Two studies reported (LDL Follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.52). The combined mean difference

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

and 95% CIs was -2.66 (-5.67 to 0.36). The combined result demonstrates non-statistically significant difference between groups regarding (LDL Baseline) (Z = 1.73, P =0.08).

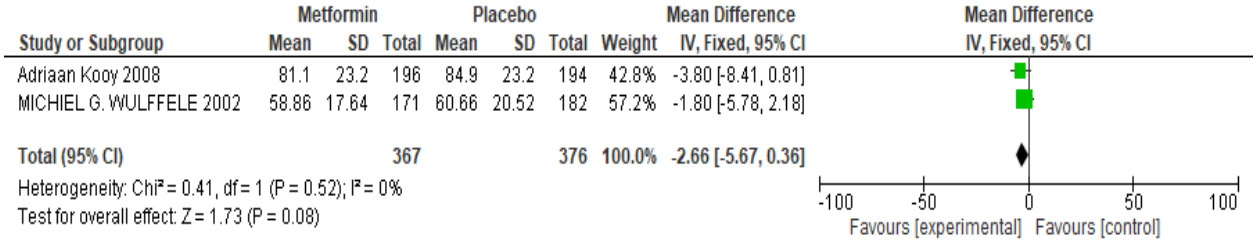


Figure 15. Forest plot of LDL at follow up demonstrates non-statistically significant difference between Metformin and Placebo groups.

HDL at Baseline:

Four studies reported (HDL at baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.59). The combined mean difference and 95% CIs was 0.05 (-0.03 to 0.12). The combined result demonstrates non-statistically significant difference between groups regarding (HDL at Baseline) (Z = 1.22, P =0.22).

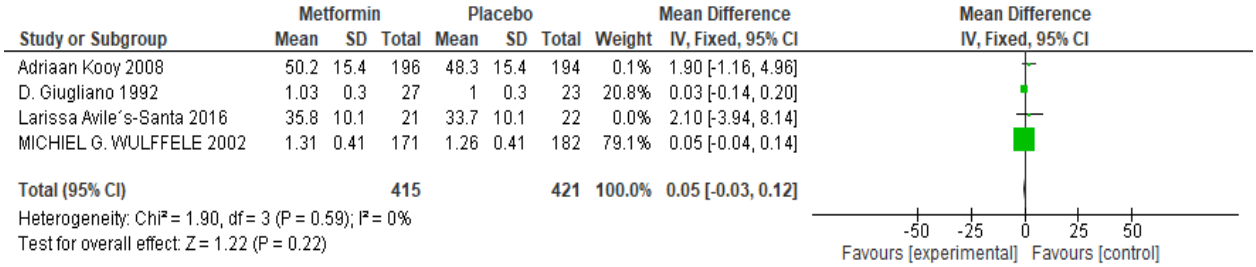


Figure 16. Forest plot of HDL at baseline demonstrates non-statistically significant difference between Metformin and Placebo groups.

HDL follow up:

Three studies reported (HDL at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 18%, P =0.30). The combined mean difference and 95% CIs was 0.07 (-0.00 to 0.14). The combined result demonstrates non-statistically significant difference between groups regarding (HDL at follow up) (Z = 1.87, P =0.06).

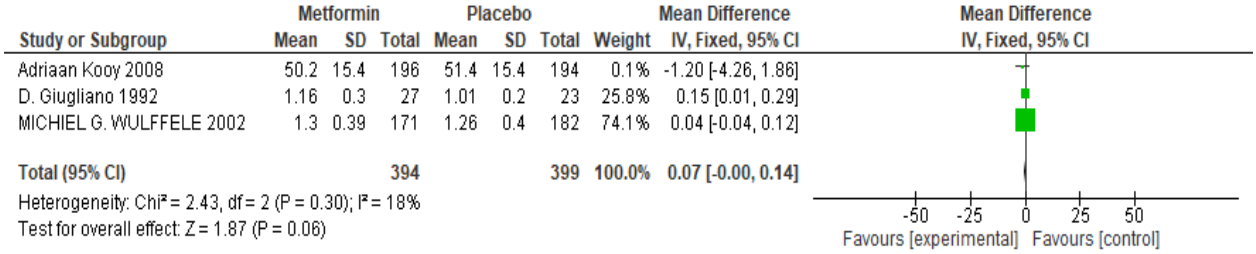


Figure 17. Forest plot of HDL at follow up demonstrates non-statistically significant difference between Metformin and Placebo groups.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Triglycerides at Baseline

Four studies reported (Triglycerides at Baseline) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P < 0.0001). The combined mean difference and 95% CIs was 44.19 (36.30 to 52.08). The combined result demonstrates highly statistically significant difference between groups regarding (Triglycerides at Baseline) (Z = 10.97, P < 0.00001).

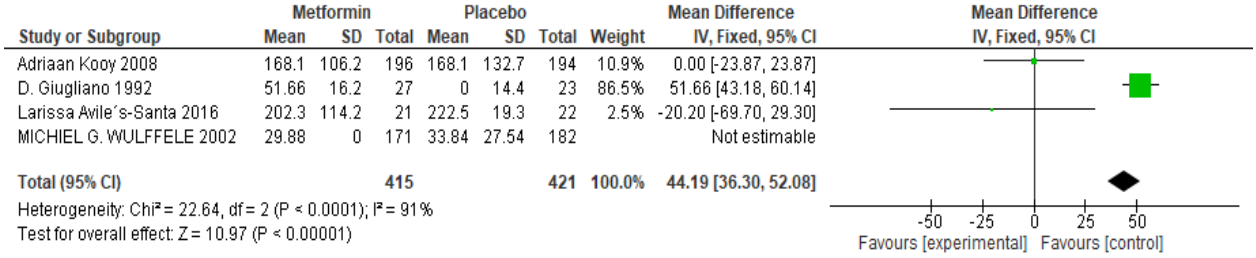


Figure 18. Forest plot of Triglycerides at Baseline demonstrates highly statistically significant difference between Metformin and Placebo groups.

Triglycerides at follow up

Three studies reported (Triglycerides at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.59). The combined mean difference and 95% CIs was -2.88 (-8.29 to 2.53). The combined result demonstrates non-statistically significant difference between groups regarding (Triglycerides at follow up) (Z = 1.04, P=0.30).

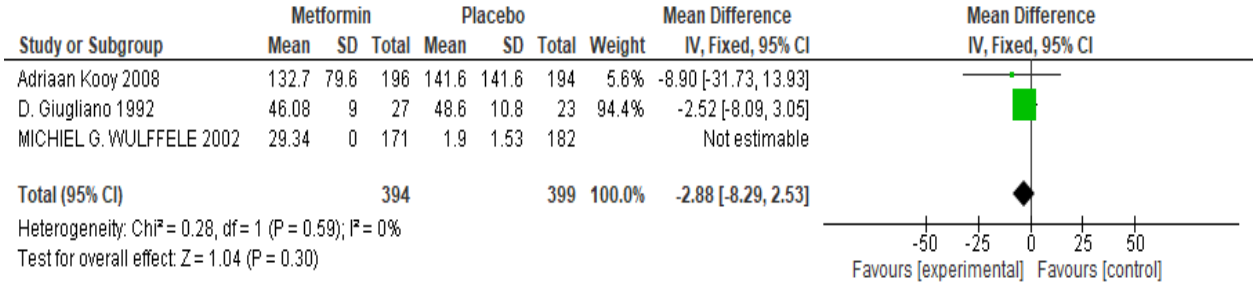
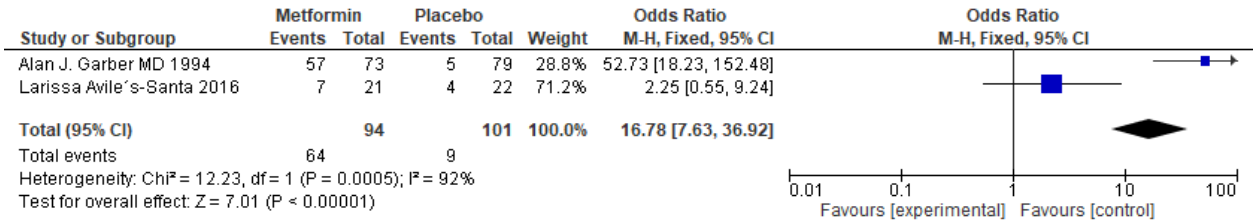


Figure 19. Forest plot of Triglycerides at follow up demonstrates non-statistically significant difference between Metformin and Placebo groups.

Side Effect

Two studies reported (Side Effect) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 92%, P <0.001). The combined mean difference and 95% CIs was 16.78 (7.63to 36.92). The combined result demonstrates highly statistically significant difference between groups regarding (Side Effect) (Z = 7.01, P <0.001).



Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Figure 20. Forest plot of side effects demonstrates highly statistically significant difference between Metformin and Placebo groups.

Discussion

In the current meta-analysis, 4 studies reported (Duration of diabetes) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 51%, P=0.11). The combined mean difference and 95% CIs was 0.73 (0.15 to 1.30). The combined result demonstrates statistically significant difference between groups regarding (Duration of diabetes) (Z = 2.48, P =0.01).

In line with **Holden et al., (6)** aimed to determine if concomitant metformin reduced the risk of death, major adverse cardiac events (MACE), and cancer in people with type 2 diabetes treated with insulin, reported that there was statistically significant difference between groups regarding duration of diabetes, p<0.001.

On the other hand, **(Relimpio et al., (7)** who aimed to compare the effect of adding metformin to insulin therapy with a moderate increase in insulin dose alone in insulin-treated, poorly controlled Type 2 diabetic patients, reported that there was no statistically significant difference between groups regarding duration of diabetes.

Also, contrast with **(Lundby-Christensen et al.,(8)** who aimed to assess the effect of metformin versus placebo both in combination with insulin analogue treatment on changes in carotid intima-media thickness (IMT) in patients with type 2 diabetes, reported that there was no statistically significant difference between groups regarding duration of diabetes.

In the current meta-analysis, 3 studies reported (Duration of insulin therapy) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.79). The combined mean difference and 95% CIs was 1.02 (0.08 to 1.95). The combined result demonstrates statistically significant difference between groups regarding (Duration of insulin therapy) (Z = 2.12, P =0.03).

On the other hand, **Hermann et al., (9)** who aimed to assess the adjunct effect of metformin to insulin in type 2 diabetes, reported that there was no statistically significant difference between groups regarding duration of insulin therapy.

In contrast **Strowig et al.,(10)** aimed to evaluate the safety and efficacy of treatment with insulin alone, insulin plus metformin, or insulin plus troglitazone in individuals with type 2 diabetes, reported that there was no statistically significant difference between groups regarding duration of insulin therapy.

In the current meta-analysis, 3 studies reported (GHb (% Hb) at Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.79). The combined mean difference and 95% CIs was -0.01 (-0.18 to0.16). The combined result demonstrates no statistically significant difference between groups regarding (GH b (% Hb) at Baseline) (Z = 0.15, P =0.88).

In line with **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding HbA1c at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding HbA1c at baseline.

Moreover **Kooy et al.,(11)** aimed to investigate whether metformin hydrochloride has sustained beneficial metabolic and (cardio) vascular effects in patients with type 2 diabetes mellitus (DM2), reported that plasma HbA1c level was comparable between both groups at baseline.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

In the current meta-analysis, 3 studies reported (GHb (% Hb) at follow up) and all can be used. A significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P=0.001). The combined mean difference and 95% CIs was -0.37 (-0.56 to -0.18). The combined result demonstrates statistically significant difference between groups regarding (GH b (% Hb) at follow up) (Z = 3.73, P =0.0002).

In line with **Hemmingsen et al.,(12)** who conducted a systematic review and meta-analysis to compare the benefits and harms of metformin and insulin versus insulin alone as reported in randomised clinical trials of patients with type 2 diabetes, reported that the achieved percentage of HbA1c decreased with metformin and insulin compared with insulin alone (mean difference −0.60%, 95% confidence interval −0.89 to −0.31, P<0.001; 20 trials; heterogeneity I2=82%, P<0.001).

As well **Lundby-Christensen et al.,(8)** reported that HbA1c decreased with metformin and insulin compared with placebo and insulin at follow up, p<0.006.

Moreover **Ebrahim et al., (13)** aimed to study the effect, safety and efficacy of metformin in poorly controlled insulin treated type II diabetes, reported that there was insulin requirement less in metformin treated group with 14% reduction in HbA1c.

In the current meta-analysis, 3 studies reported (Change in GHb (% Hb) and all can be used. A significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 76%, P=0.04). The combined mean difference and 95% CIs was -0.78 (-0.91 to -0.66). The combined result demonstrates statistically significant difference between groups regarding (Change in GH b (% Hb)) (Z = 12.46, P < 0.00001).

In line with **(Relimpio et al.,(7)** reported that there was statistically significant difference between groups regarding change in HbA1c, p<0.01.

As well **Wulffele et al.,(14)** aimed to investigate the metabolic effects of metformin, as compared with placebo, in type 2 diabetic patients intensively treated with insulin, reported that there was significant difference between the studied groups regarding Change in GHb (% Hb), p<0.001.

In the current meta-analysis, four studies reported (Daily dose of insulin (IU/day) at baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.76). The combined mean difference and 95% CIs was 0.30 (-2.94 to 3.55). The combined result demonstrates non-statistically significant difference between groups regarding (Daily dose of insulin (IU/day) at baseline) (Z = 0.18, P =0.85).

In line with **Relimpio et al.,(7)** who reported that there was no statistically significant difference between groups regarding Daily dose of insulin at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding daily dose of insulin at baseline.

Moreover **Kooy et al.,(11)** didn't report significance between two groups regarding daily dose of insulin at baseline.

In the current meta-analysis, four studies reported (Daily dose of insulin (IU/day) at follow up) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P <0.001). The combined mean difference and 95% CIs was -11.00 (-15.63 to -6.38). The combined result demonstrates highly statistically significant difference between groups regarding (Daily dose of insulin (IU/day) at follow up) (Z = 4.66, P <0.001).

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

In line with **Hemmingsen et al., (12)** reported that Insulin dose was significantly reduced when metformin was combined with insulin, compared with insulin alone (mean difference−18.65 U/day, 95% confidence interval −22.70 to −14.60, P<0.001; heterogeneity I2=81%, P<0.001).

As well **Lundby-Christensen et al.,(8)** reported that Insulin dose was significantly reduced when metformin was combined with insulin compared with placebo and insulin at the end of trail, p<0.001.

Moreover **Strowig et al.,(10)** reported that the mean total daily insulin dose significantly decreased in the insulin plus metformin group compared to insulin alone, p<0.001.

In the current meta-analysis, four studies reported (change in Daily dose of insulin (IU/day)) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 99%, P <0.001). The combined mean difference and 95% CIs was 0.39 (-1.22 to -2.00). The combined result demonstrates non-statistically significant difference between groups regarding (change in Daily dose of insulin (IU/day)) (Z = 0.47, P =0.64).

In contrast, **Relimpio et al.,(7)** reported that there was statistically significant difference between groups regarding change in Daily dose of insulin, p<0.001.

In disagreement **Yilmaz et al.,(15)** aimed to compare the efficacy of treatment with insulin alone, insulin plus acarbose, insulin plus metformin, or insulin plus rosiglitazone in type 2 diabetic subjects who were previously on insulin monotherapy, reported that mean total daily insulin dose was significantly decreased at the end of 6 month in insulin plus metformin group, p=0.00.

Also disagreed with **Lundby-Christensen et al.,(8)** who reported that there was statistically significant difference between groups regarding change in dose of insulin from baseline, p<0.001.

In the current meta-analysis, one study reported (Fasting plasma glucose level at baseline) and all can be used. The combined mean difference and 95% CIs was -21.30 (-64.23 to 21.63). The combined result demonstrates no statistically significant difference between groups regarding (Fasting plasma glucose level at baseline) (Z = 0.97, P =0.33).

In line with **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding Fasting plasma glucose level at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding Fasting plasma glucose level at baseline.

In the current meta-analysis, one study reported (Fasting plasma glucose level at follow up) and all can be used. The combined mean difference and 95% CIs was -19.70 (-33.53 to -5.87). The combined result demonstrates statistically significant difference between groups regarding (Fasting plasma glucose level at follow up) (Z = 2.79, P =0.005).

In line with **Ponssen et al.,(16)** aimed to assess the effects of combined treatment with insulin and metformin in patients with type 2 diabetes mellitus in whom dietary measures, weight control, and oral antihyperglycemic therapy had failed, reported that Metformin plus insulin produced significant reductions in fasting blood glucose levels compared to placebo plus insulin (9.46 mmol/L vs 8.26 mmol/L, P = 0.055).

On the other hand **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding Fasting plasma glucose level at follow up.

In contrast, **Lundby-Christensen et al.,(8)** reported that there was no statistically significant difference between groups regarding Fasting plasma glucose level at follow up.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

In the current meta-analysis, one study reported (change in Fasting plasma glucose level) and all can be used. The combined mean difference and 95% CIs was 1.60 (-8.21 to 11.41). The combined result demonstrates no statistically significant difference between groups regarding (change in Fasting plasma glucose level) (Z = 0.32, P =0.75).

In line with, **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding change in Fasting plasma glucose level.

In the current meta-analysis, 4 studies reported (Total cholesterol level at Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.69). The combined mean difference and 95% CIs was 0.04 (-0.11 to 0.19). The combined result demonstrates no statistically significant difference between groups regarding (Total cholesterol level at Baseline) (Z = 0.51, P =0.61).

In line with, **(Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding total cholesterol level at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding Total cholesterol at baseline.

In the current meta-analysis, 3 studies reported (Total cholesterol level at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 58%, P=0.09). The combined mean difference and 95% CIs was -0.11 (-0.22 to 0.00). The combined result demonstrates statistically significant difference between groups regarding (Total cholesterol level at follow up) (Z = 1.97, P =0.25).

In line with, **Relimpio et al.,(7)** reported that there was statistically significant difference between groups regarding Total cholesterol level at follow up, $p<0.05$.

As well **Ponssen et al.,(16)** reported that metformin plus insulin produced significant reductions in mean total serum cholesterol levels compared to placebo plus insulin, P = 0.005.

In the current meta-analysis, three studies reported (LDL Baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 45%, P =0.16). The combined mean difference and 95% CIs was 4.24 (-2.00 to 10.48). The combined result demonstrates non-statistically significant difference between groups regarding (LDL Baseline) (Z = 1.33, P =0.18).

In line with, **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding LDL level at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding LDL at baseline.

In the current meta-analysis, two studies reported (LDL Follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.52). The combined mean difference and 95% CIs was -2.66 (-5.67 to 0.36). The combined result demonstrates non-statistically significant difference between groups regarding (LDL Follow up) (Z = 1.73, P =0.08).

In line with, **Relimpio et al.,(7)** reported that there was statistically significant difference between groups regarding LDL level follow up, $p<0.05$.

In contrast, **Yilmaz et al.,(15)** reported that there was no significant difference between the studied groups regarding LDL after 6 months.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

In the current meta-analysis, four studies reported (HDL at baseline) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P =0.59). The combined mean difference and 95% CIs was 0.05 (-0.03 to 0.12). The combined result demonstrates non-statistically significant difference between groups regarding (HDL at Baseline) (Z = 1.22, P =0.22).

In line with, **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding HDL at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding HDL at baseline.

In the current meta-analysis, three studies reported (HDL at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 18%, P =0.30). The combined mean difference and 95% CIs was 0.07 (-0.00 to 0.14). The combined result demonstrates non-statistically significant difference between groups regarding (HDL at follow up) (Z = 1.87, P =0.06).

In line with, **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding HDL at follow up.

As well **Ponssen et al.,(16)** reported that there was no statistically significant difference between groups regarding HDL.

In the current meta-analysis, four studies reported (Triglycerides at Baseline) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P < 0.0001). The combined mean difference and 95% CIs was 44.19 (36.30 to 52.08). The combined result demonstrates highly statistically significant difference between groups regarding (Triglycerides at Baseline) (Z = 10.97, P < 0.00001).

In line with, **Relimpio et al.,(7)** reported that there was no statistically significant difference between groups regarding Triglycerides at baseline.

As well **Hermann et al.,(9)** reported that there was no statistically significant difference between groups regarding Triglycerides at baseline.

In the current meta-analysis, three studies reported (Triglycerides at follow up) and all can be used. A non-significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.59). The combined mean difference and 95% CIs was -2.88 (-8.29 to 2.53). The combined result demonstrates non-statistically significant difference between groups regarding (Triglycerides at follow up) (Z = 1.04, P=0.30).

In line with **Lundby-Christensen et al.,(8)** reported that there was no significant difference between both group regarding Triglycerides after 18 months follow-up.

On the other hand, **Relimpio et al.,(7)** reported that there was statistically significant difference between groups regarding Triglycerides at follow up, P<0.05.

In the current meta-analysis, two studies reported (Side Effect) and all can be used. A highly significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 92%, P <0.001). The combined mean difference and 95% CIs was 16.78 (7.63to 36.92). The combined result demonstrates highly statistically significant difference between groups regarding (Side Effect) (Z = 7.01, P <0.001).

However, **Yilmaz et al.,(15)** reported that only three patients in insulin plus metformin group experienced gastrointestinal side effects, which were resolved within few weeks, there were no significant differences

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

among the groups in the rate of hypoglycemic episodes, and no serious adverse event was noted in any group.

In contrast **Hemmingsen et al.,(12)** showed no significant difference between intervention groups (relative risk 1.28, 95% confidence interval 0.69 to 2.37; heterogeneity I2=75%, P=0.003).

Conclusion

In conclusion, this meta-analysis demonstrate that metformin significantly improves the duration of diabetes, duration of insulin therapy, and glycated hemoglobin (HbA1c) levels at follow-up, with a notable reduction in HbA1c change, fasting plasma glucose levels and the daily dose of insulin at follow-up. However, side effects related to metformin were also significantly more common in the treatment group, highlighting the importance of monitoring adverse events in clinical settings. Overall, the findings support the beneficial role of metformin in improving glycemic control and reducing insulin requirements in insulin-treated Type 2 diabetes patients, with a moderate risk of side effects. Further studies with larger sample sizes and longer follow-up periods are warranted to confirm these effects and explore long-term safety

References

Hu N, Zhang Q, Wang H, Yang X, Jiang Y, Chen R, Wang L. Comparative evaluation of the effect of metformin and insulin on gut microbiota and metabolome profiles of type 2 diabetic rats induced by the combination of streptozotocin and high-fat diet. Frontiers in Pharmacology. 2022 Jan 3;12:794103.

Gebrie D, Manyazewal T, A Ejigu D, Makonnen E. Metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes: a comparative study of glycemic control and risk of cardiovascular diseases in Addis Ababa, Ethiopia. Diabetes, Metabolic Syndrome and Obesity. 2021 Jul 24:3345-59.

Gebrie D, Manyazewal T, A Ejigu D, Makonnen E. Metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes: a comparative study of glycemic control and risk of cardiovascular diseases in Addis Ababa, Ethiopia. Diabetes, Metabolic Syndrome and Obesity. 2021 Jul 24:3345-59.

Paczkowska A, Hoffmann K, Michalak M, Bryl W, Kopciuch D, Zaprutko T, Ratajczak P, Nowakowska E, Kus K. A comparison between the therapeutic effect of metformin alone versus a combination therapy with insulin in uncontrolled, non-adherence patients with type 2 diabetes: six months follow-up. Diabetes, Metabolic Syndrome and Obesity. 2021 Jul 14:3243-52.

Nordklint AK, Almdal TP, Vestergaard P, Lundby-Christensen L, Boesgaard TW, Breum L, Gade-Rasmussen B, Sneppen SB, Gluud C, Hemmingsen B, Perrild H. Effect of metformin and insulin vs. placebo and insulin on whole body composition in overweight patients with type 2 diabetes: a randomized placebo-controlled trial. Osteoporosis International. 2021 Sep 1:1-2.

Holden SE, Jenkins-Jones S, Currie CJ. Association between insulin monotherapy versus insulin plus metformin and the risk of all-cause mortality and other serious outcomes: a retrospective cohort study. PLoS One. 2016 May 6;11(5):e0153594.

Relimpio F, Pumar A, Losada F, Mangas MA, Acosta D, Astorga R. Adding metformin versus insulin dose increase in insulin-treated but poorly controlled Type 2 diabetes mellitus: an open-label randomized trial. Diabetic medicine. 1998 Dec;15(12):997-1002.

Lundby-Christensen L, Tarnow L, Boesgaard TW, Lund SS, Wiinberg N, Perrild H, Krarup T, Snorgaard O, Gade-Rasmussen B, Thorsteinsson B, Røder M. Metformin versus placebo in combination with insulin analogues in patients with type 2 diabetes mellitus—the randomised, blinded Copenhagen Insulin and Metformin Therapy (CIMT) trial. BMJ open. 2016 Feb 1;6(2):e008376.

Hermann LS, Kalen J, Katzman P, Lager I, Nilsson A, Norrhamn O, Sartor G, Ugander L. Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients. Diabetes, Obesity and Metabolism. 2001 Dec;3(6):428-34.

Strowig SM, AvilEs-Santa ML, Raskin P. Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes. Diabetes care. 2002 Oct 1;25(10):1691-8.

Kooy A, De Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Archives of internal medicine. 2009 Mar 23;169(6):616-25.

Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. Bmj. 2012 Apr 19;344.

Ebrahim MA, Jamal QA, Shah MA. The effect of metformin in poorly controlled insulin treated type II diabetes mellitus. Diabetes Research and Clinical Practice. 2000(50):49.

Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes care. 2002 Dec 1;25(12):2133-40.

Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 14425 – 14441
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6753

Yilmaz H, Gursoy A, Sahin M, Guvener Demirag N. Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and rosiglitazone or insulin and acarbose in type 2 diabetes. Acta diabetologica. 2007 Dec;44:187-92.

Ponssen HH, Elte JW, Lehert P, Schouten JP, Bets D. Combined metformin and insulin therapy for patients with type 2 diabetes mellitus. Clinical therapeutics. 2000 Jun 1;22(6):709-18..