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Review Article

Metformin Immediate and Extended-Release Adverse Events and Effects on Metabolic Parameters: A Meta-Analysis

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Abstract: Metformin is the first-line antidiabetic medication, and face-to-face comparisons between immediate-release and extended-release are scarce. The current meta-analysis aimed to compare metformin's immediate and extended-release effects on glycemic control, adverse events, and lipid profile. We searched PubMed, Cochrane Library, and the first 100 articles in Google Scholar from inception until September 2022. Studies were eligible if they were randomized controlled trials and compared metformin's immediate and extended-release effects on glycemic control, adverse events, and lipid profile. The keywords used were metformin immediate-release, extended-release, glycated hemoglobin, HbA1c, high-density lipoproteins, low-density lipoproteins triglycerides, total cholesterol, adverse effects, and side effects. The retrieved data were exported to an Excel sheet detailing the authors' names, the country of origin of the study, the number of patients and control subjects, and the total number of events in the interventional and control groups. No significant statistical difference was found between metformin immediate-release and metformin extended-release regarding the reduction of $HbA1_c$, overall adverse effects, low-density lipoproteins, and high-density lipoproteins; odd ratio, 0.08, 95% *CI,* -0.14-0.29; 1.34, 95% *CI,* 0.86-2.08; -0.03, 95% *CI,* -0.22-0.17; and -0.26, 95% *CI,* -1.32-0.80 respectively. Metformin immediate-released reduced total cholesterol better than the extended-release; odd ratio, -2.35, 95% *CI,* -2.57-2.12. However, a paradox was observed regarding triglycerides (increment on extended-release and reduction with extended-release); odd ratio, -0.36, 95% *CI,* -0.44-0.28. No significant differences were found between the two formulations except for a better triglyceride reduction and total cholesterol in the immediate-release arm.

Keywords: Metformin immediate-release, extended-release, HbA1c, lipid profile, adverse events.

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1. INTRODUCTION

Diabetes mellitus is rising globally; 9.3% of the adult population is currently affected. The projection for the years 2030 and 2045 is 10.2% (578 million) and 10.9% (700 million).[1] The Kingdom of Saudi Arabia is among the countries with the highest prevalence of diabetes (18.7% are suffering from the disease, according to the International Diabetes Federation).[2] Metformin is the first-line oral therapy for type II diabetes and is available in several formulations, either alone or combined with other oral hypoglycemic drugs. Metformin's immediate release is usually taken several times with meals, and its action peaks three hours after the 1000mg dose.[3] Metformin is the first-line oral drug for patients with type II diabetes due to its lower risk of hypoglycemia, low-neutral effect, and glucose-lowering ability.[4] Due to the frequent dosing of metformin immediate-release, metformin extended-release was introduced and was shown to improve compliance.[5] The pharmacokinetic properties of metformin formulations are generally similar. However, metformin extended-release peaks seven to eight hours after dosing (two grams). Metformin extended-release is effective and safe and reduces the glycated hemoglobin compared to a placebo.[6] Although face-to-face comparisons between metformin immediate-release and metformin extended-release lack, few previous researchers found improved adherence and reduced gastrointestinal side effects with metformin extended-release.[3,7] Recent research in Australia showed that metformin extended-release is safe and tolerable among patients with pre-diabetes and stroke.[8] Many patients on metformin developed gastrointestinal disturbances. A study conducted among elderly patients showed no difference in gastrointestinal side effects of different doses of metformin (1000mg and 2000mg), but larger doses improved glycemic control.[9] Severe metformin intolerance leading to treatment discontinuation was observed among patients with a specific phenotype, including ABO group imbalance, left-handedness, and an iron load.[10] The American Diabetes Association and the European Association for the Study of Diabetes recommended glycated hemoglobin by < 7%.[11,12] Tighter glycemic control was desired in young, recently diagnosed patients, while elderly patients with comorbidities need a more flexible approach. Strict maintenance of blood glucose and the glycated hemoglobin to normal or close to the normal range was crucial to avoid the harmful complications of diabetes, including retinopathy, neuropathy, and nephropathy.[13] Diabetic dyslipidemia is mainly mixed dyslipidemia [increase in triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), and small-dense (atherogenic), low-density lipoprotein cholesterol (LDL-C) particles]. Metformin effects on lipid profiles were discussed controversially, and some studies reported beneficial effects on lipid profiles.[14] In contrast, other studies showed no added benefits.[15] Therefore, the current meta-analysis aimed to compare metformin's immediate and extended-release effects on glycemic control, adverse events, and lipid profile.

2. SUBJECTS AND METHODS

2.1. Eligibility criteria

Studies were eligible if they were randomized controlled trials. Prospective cohorts, retrospective studies, case-control studies, case series, case reports, and studies on animals were not included. Studies were approached if they compare the effect of metformin immediate-release and extended-release on glycemic control, adverse effects, and lipid profile.

2.2. Primary outcomes

- The effect of metformin is immediate-release and extended-release on glycated hemoglobin ($HbA1_{c)}$.
- The effect of metformin is immediate-release and extended-release on triglycerides, total cholesterol, low-density lipoproteins, and high-density lipoproteins.

2.3. Secondary outcomes

- The comparison of metformin is immediate-release and extended-release regarding adverse effects.

2.4. Search strategy and study selection

We searched PubMed, Cochrane Library, and the first 100 articles in Google Scholar from inception until September 2022. Out of 307 articles retrieved, 57 full texts were screened, and twelve studies were included in the meta-analysis. (Figure 1). We included 36 cohorts from twelve randomized controls. The following keywords were used: Metformin immediate-release, metformin extended-release, glycated hemoglobin, HbA1c, high-density lipoproteins, low-density lipoproteins triglycerides, total cholesterol, adverse effects, and side effects. The retrieved data were exported to an Excel sheet detailing the authors' names, the country of origin of the study, the number of patients and control subjects, and the total number of events in the interventional and control groups. Continuous data (lipid profile and HbA1c) were also reported.

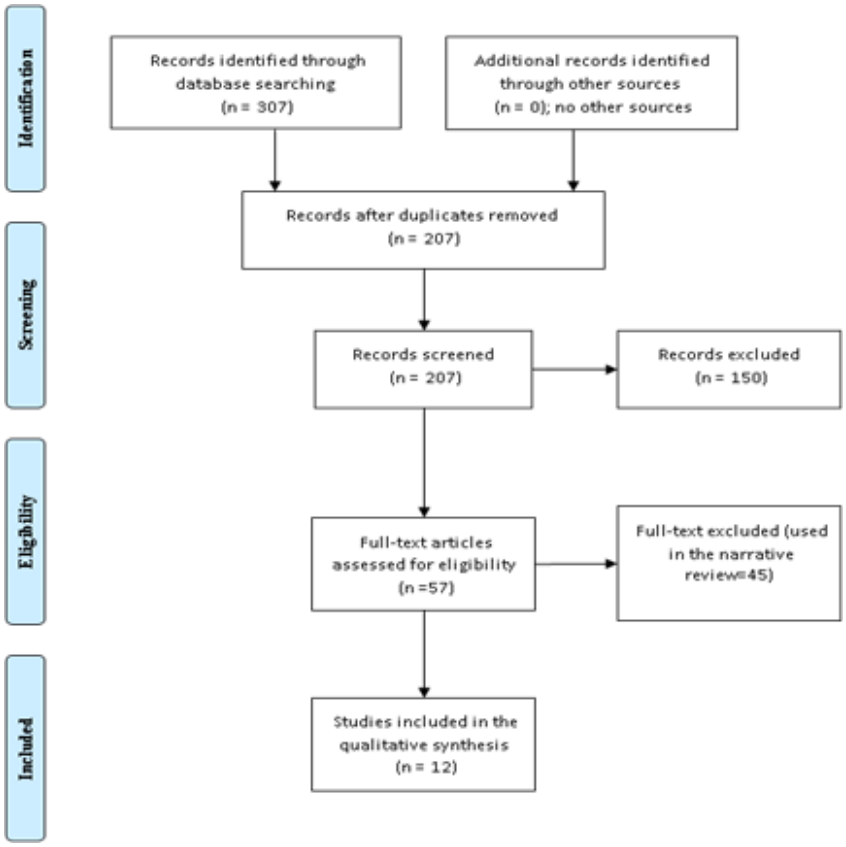

Fig 1: Literature search and data extraction of metformin immediate-release and extended-release comparison.

2.5. Risk of bias assessment

The quality of the included studies was assessed using a modified Cochrane risk of bias assessment tool. Five trials showed some concerns; three had a high risk of bias, while four showed a low risk. (Table 1).

Table 1: The risk of bias in the included trials. (The bias was estimated using the Cochrane risk of bias)

Author	Randomization bias	Deviation from intervention	Missing outcome data	Outcome measurement bias	Bias is a selection of reported result	Overall bias
Aggarwal et al., 2018 [3]	Some concerns	Low	Some concerns	Low	Low	Some concerns
Derosa et al., 2017 [7]	Some concerns	Low	Low	Some concerns	Low	Low
Gao et al., 2008 [16]	Some concerns	High	Some concerns	Some concerns	Some concerns	High
Hameed et al., 2017 [17]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Henry et al., 2018, [18]	Low	Some concerns	Low	Some concerns	Low	Low
Hsieh et al., 2007 [19]	High	Some concerns	Low	Some concerns	high	High
Ji et al., 2018, [20]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Schwartz et al., 2006 [21]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Blonde et al., 2004 [22]	High	Some concerns	Low	Some concerns	high	High
Zhang et al., 2007 [23]	Low	Low	High	High	Low	Low
Fujioka et al. 2003 [24]	Some concerns	Some concerns	Low	Low	Low	Low
Ghorpade et al. 2016 [25]	Some concerns	Low	Some concerns	Low	Low	Some concerns

Table 1 illustrates the risk of bias among the included trials. Four of the included studies showed a low risk of bias, five trials with some concerns regarding the risk of bias, and three trials showed a high risk of bias. The above results imply that the evidence concluded from this meta-analysis is medium at best. Significant concerns were observed in randomization, which was explainable as it is very difficult to conceal the prescription from the patients in the real world.

2.6. Imputations

Not applicable.

2.7. Data analysis

We used the RevMan (version 5.4) for data analysis, the data were entered manually, and dichotomous and continuous variables were compared using the random effect due to the significant heterogeneity. Therefore, a P-value of 0.05 is significant.

3. RESULTS

Table 2: Metformin IR and XR's effects on the glycated hemoglobin ($HbA1_c$).

Author	Country	Patients and duration	Metformin IR	Metformin XR	Results
Aggarwal et al., 2018 [3]	Canada	568, 6 months	0.96±0.05	0.93±0.05	Not sig.
Derosa et al., 2017 [7]	Italy	235, 6 months	0.40±0.02	0.80±0.02	More reduction in XR
Gao et al., 2008 [16]	China	140, 4 months	0.3±0.1	0.3±0.3	Not sig.
Hameed et al., 2017 [17]	Pakistan	60, 3 months	1.02±1.27	0.68±1.42	Not sig.
Henry et al., 2018, [18]	USA	190, 4 months	1.10±0.13	0.62±0.12	More reduction in IR
Hsieh et al., 2007 [19]	Taiwan	55, 3 months	1.4±0.4	1.3±0.5	Not sig.
Ji et al., 2018 [20]	China	532, 4 months	1.61±0.03	1.54±0.03	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	1.05±0.13	0.9±0.12	More reduction in IR

Table 2 compares metformin immediate-release and extended-release regarding their effects on HbA1c. Three trials reported more reduction among the immediate-release arm, five studies reported no difference, while one study showed the superiority of the extended-release. The pooled analysis is shown in Figure 2.

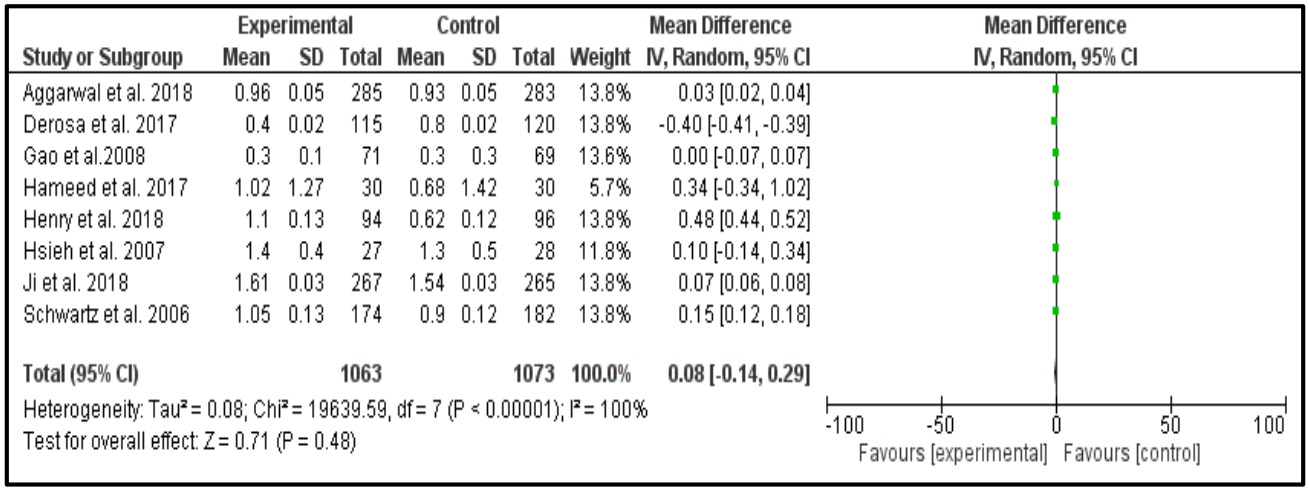

Fig 2: A comparison between metformin IR and metformin XR regarding the effect on glycated hemoglobin ($HbA1_c$).

In the current meta-analysis, we pooled eight trials, including 2136 patients.[3,7,16-21] No significant statistical difference was found between metformin immediate-release and metformin extended-release regarding the reduction of $HbA1_c$. Odd ratio, 0.08, 95% *CI,* -0.14-0.29. P-value, 0.48. However, substantial heterogeneity was observed, I^2=100%. The P-value for heterogeneity <0.001, the Chi-square was 19639.59, and the degree of freedom=7. (Figure 2).

Table 3: Drug-related adverse effects of metformin IR and metformin XR.

Author	Country	Methodology	Metformin IR	Metformin XR	Results
Aggarwal et al., 2018 [3]	Canada	568, 6 months	25/285	30/283	Not sig.
Derosa et al., 2017 [7]	Italy	235, 6 months	42/115	10/120	Higher among IR
Gao et al., 2008 [16]	China	140, 4 months	8/71	6/69	Not sig.
Hameed et al., 2017 [17]	Pakistan	180, 3 months	32/90	12/90	Higher among IR
Henry et al., 2018, [18]	USA	190, 4 months	29/94	22/96	Higher among IR
Hsieh et al., 2007 [19]	Taiwan	55, 3 months	4/27	4/28	Not sig.

Ji et al., 2018, [20]	China	532, 4 months	66/267	85/265	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	58/174	58/182	Not sig.
Blonde et al., 2004 [22]	USA	468, 8 months	18/158	37/310	Not sig.
Zhang et al., 2007 [23]	China	140, 3 months	5/71	7/69	Not sig.

Table 3 depicts the adverse events of metformin-immediate release and metformin-extended release. Most trials (seven) showed similar adverse events; three studies reported more side effects with the immediate release, and one trial showed higher side effects with the extended-release. The above results are shown in Figure 3.

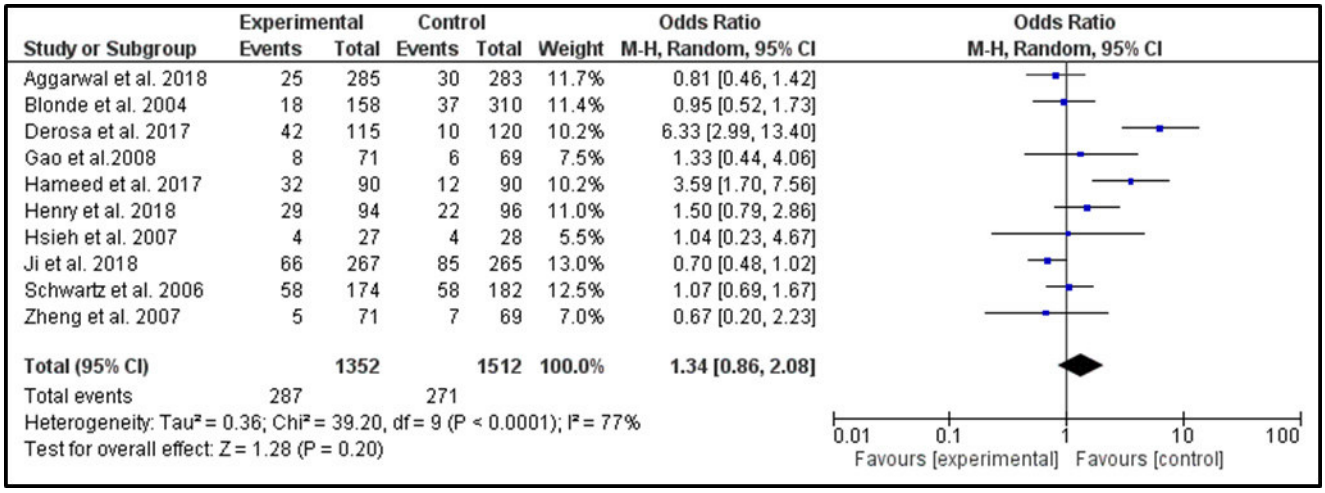

Fig 3: A comparison between metformin IR and XR regarding the adverse effects.

Ten trials were included regarding the overall adverse effects.[3,7,16-23] No difference was evident between the two formulations. Odd ratio, 1.34, 95% *CI,* 0.86-2.08. P-value, 0.20 with significant heterogeneity, I^2=77%. The P-value for heterogeneity <0.001, the Chi-square was 39.20, and the degree of freedom=9. (Figure 3).

Table 4: The effects of metformin IR and metformin XR on triglycerides.

Author	Country	Patients and duration	Metformin IR	Metformin XR	Results
Derosa et al., 2017 [7]	Italy	235, 6 months	-6.6±5.3	-18.3±8.6	Sig.
Gao et al., 2008 [16]	China	140, 4 months	-0.1±0.3	0.2±0.2	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	-4.3±17.1	4.2±17.1	Sig.
Fujioka et al., 2017 [24]	Pakistan	434, 3 months	1±8	34±9	Sig.
Ghorpade et al., 2003 [25]	India	40, 4 months	-1.15±0.30	-2.55±2.82	Sig.

Table 4 shows a comparison between metformin immediate-release regarding their effects on triglycerides. Three studies reported that the immediate release was more effective in reducing triglycerides, while two reported that the extended formulation was more effective. The results of the analysis are illustrated in Figure 4.

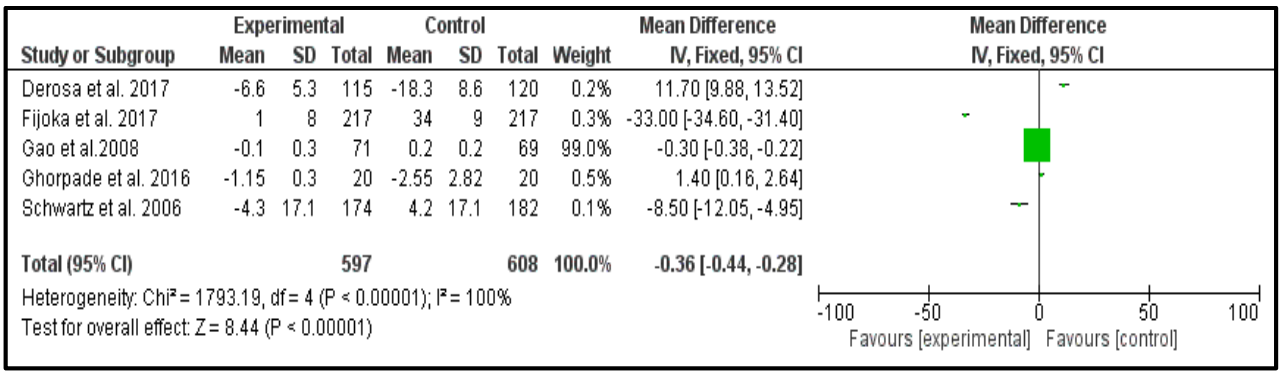

Fig 4: A comparison between metformin IR and XR regarding the effect on triglycerides.

Regarding the effects of metformin formulations on lipid profile, out of the five studies included [7,16,21,24,25], four studies showed a reduction of triglycerides with immediate release, and only one showed a slight increment. In contrast, only two studies showed a reduction of triglycerides while using the extended-release. Odd ratio, -0.36, 95% *CI,* -0.44-0.28. P-value <0.001. However, substantial heterogeneity was observed, I^2=100%. The P-value for heterogeneity <0.001, the Chi-square was 1793.19, and the degree of freedom=4. The above results imply a triglycerides paradox with the extended release. (Figure 4).

Table 5: Metformin IR and XR's effects on total cholesterol.

Author	Country	Patients and duration	Metformin IR	Metformin XR	Results
Derosa et al., 2017 [7]	Italy	235, 6 months	-9.1±8.0	-20.6±13.7	Sig.
Gao et al., 2008 [16]	China	140, 4 months	5.0 ± 0.8	5.2 ± 1.2	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	-5.7±2.8	2.6±2.7	More reduction in IR
Fujioka et al., 2017 [24]	Pakistan	434, 3 months	-1±3	2±3	Not sig.
Ghorpade et al., 2003 [25]	India	40, 4 months	-3.75±0.98	-1.37±0.40	Not sig.

No significant differences were evident between the two formulations regarding total cholesterol (four trials), and only one trial showed the superiority of the immediate formulation. (Table 5, Figure 5).

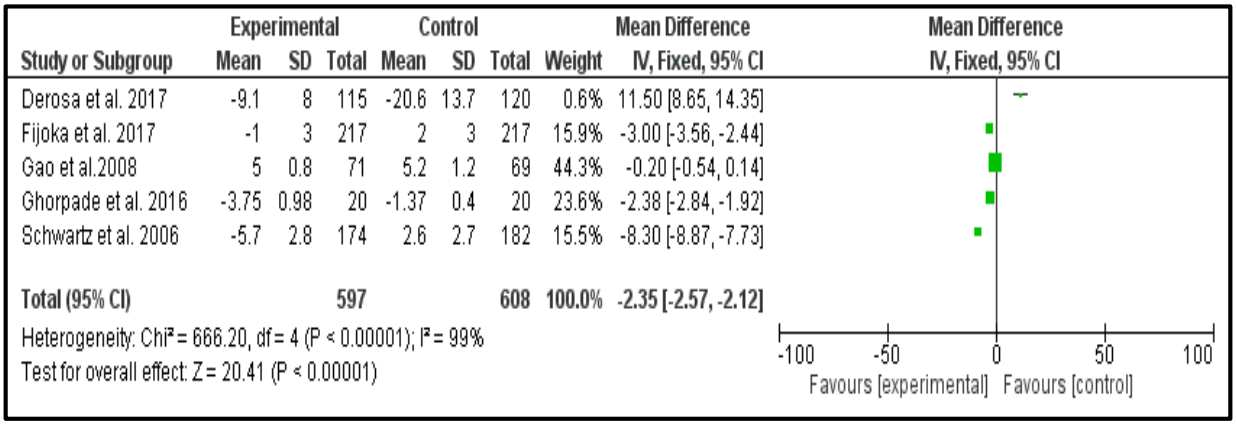

Fig 5: A comparison between metformin IR and XR regarding the effect on total cholesterol.

Metformin immediate-release showed more reduction of cholesterol compared to the extended-release.[7,16,21,24,25] P-value <0.001; odd ratio, -2.35, 95% *CI,* -2.57--2.12; I^2, 99%. The P-value for heterogeneity <0.001, the Chi-square was 666.20, and the degree of freedom=4. (Figure 5).

Table 6: Metformin IR and XR's effects on low-density lipoproteins.

Author	Country	Patients and duration	Metformin IR	Metformin XR	Results
Derosa et al., 2017 [7]	Italy	235, 6 months	-8.4±3.7	-18.8±7.9	Sig.
Gao et al., 2008 [16]	China	140, 4 months	3.0±0.7	3.0±0.9	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	-11.0±3.8	4.5±3.4-	More reduction in IR
Fujioka et al., 2017 [24]	Pakistan	434, 3 months	-4±2	-6±2	Not sig.
Ghorpade et al., 2003 [25]	India	40, 4 months	-2.85±0.66	-0.35±1.14	Not sig.

The effects of metformin-immediate release and extended-release on low-density lipoproteins are shown in Table 6 and Figure 6. There was no significant statistical difference in the three trials; one reported a higher reduction in the immediate-release formulation, while another showed more reduction in the extended-release arm.

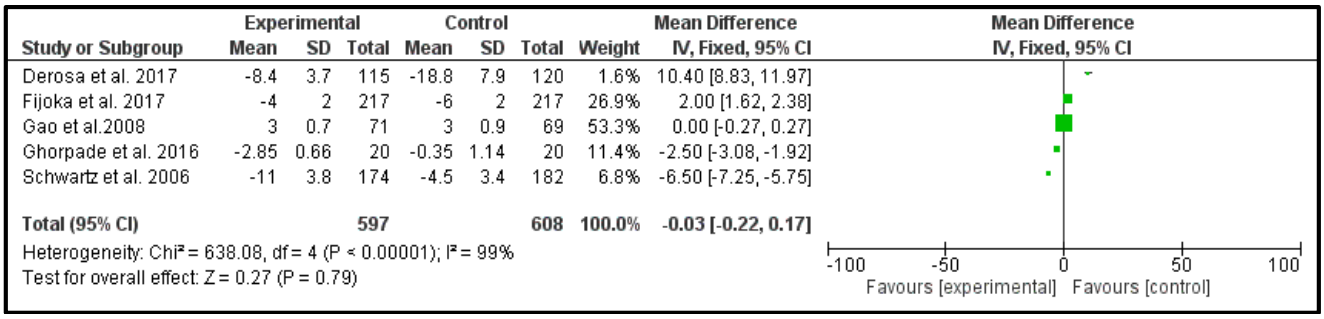

Fig 6: A comparison between metformin IR and XR regarding the effect on low-density lipoproteins.

No significant statistical difference was observed between metformin immediate-release and the extended-release regarding the effects on low-density lipoproteins.[7,16,21,24,25] P-value, 0.79, odd ratio, -0.03, 95% *CI,* -0.22-0.17; I^2, 99%. The P-value for heterogeneity <0.001, the Chi-square was 638.08, and the degree of freedom=4. (Figure 6).

Table 7: Metformin IR and XR's effects on high-density lipoproteins.

Author	Country	Patients and duration	Metformin IR	Metformin XR	Results
Derosa et al., 2017 [7]	Italy	235, 6 months	0.7±0.4	1.7±1.4	Not sig.
Gao et al., 2008 [16]	China	140, 4 months	1.4±0.3	1.4±0.4	Not sig.
Schwartz et al., 2006 [21]	USA	356, 6 months	2.1±1.2	2.0±0.44	Not sig.
Fujioka et al., 2017 [24]	Pakistan	434, 3 months	2±1	0±1	Not sig.
Ghorpade et al., 2003 [25]	India	40, 4 months	-0.50±0.16	2.0±1.14	Not sig.

Table 7 and Figure 7 show the effects of the immediate-release and the extended-release metformin on high-density lipoproteins. All the trials reported no significant statistical difference.

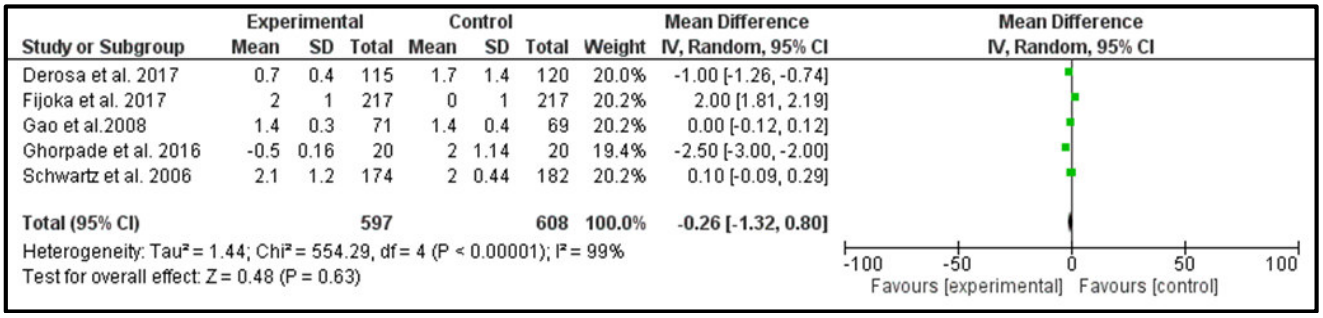

Fig 7: A comparison between metformin IR and XR regarding the effect on high-density lipoproteins.

Both metformin immediate-release and extended-release increased high-density lipoproteins with no significant statistical difference.[7,16,21,24,25] P-value, 0.63, odd ratio, -0.26, 95% *CI,* -1.32-0.80; I^2, 99%. The P-value for heterogeneity <0.001, the Chi-square was 554.29, and the degree of freedom=4. (Figure 7).

4. DISCUSSION

Although metformin is widely used, there must be clear guidelines on which formulation is better.[26] The current meta-analysis showed no difference between metformin immediate-release and extended-release formulations regarding the effects on HbA1c, low-density lipoproteins, and overall adverse events (although a reduction was found in both formulations). In contrast, immediate-release reduced total cholesterol more than extended-release. Regarding triglycerides, the immediate release reduced the level, while an increasing trend was observed with the extended-release. Both formulations showed increasing high-density lipoproteins with no significant statistical difference. Our results agree with Tan et al. (2021),[15], who conducted a meta-analysis and found no difference between the two formulations regarding glycemic control and adverse events. However, Tan and colleagues did not assess the differences in lipid profiles. Tarry-Adkins et al. (2021)[27] assessed HbA1c and lipid profile. They found no difference in HbA1c, total cholesterol, triglycerides, and high-density lipoproteins, with a significantly lower rate of low-density lipoproteins among extended-release users. Tarry-Adkins et al. (2021)[27] results align with the current observation regarding glycated hemoglobin and high-density lipoproteins. The clinical significance of the current findings is to be determined by other studies due to the high risk of heterogeneity[28,29]. However, Tarry-Adkins et al. (2021)[27] findings were different from the current results; we found a paradoxical increase of triglycerides when using the extended-release and a better reduction of serum cholesterol in the immediate-release arm (both immediate-release and extended-release reduced total cholesterol). The current findings supported Abrilla et al. (2021)[30] findings of equivalent reduction of HbA1c and adverse events; Abrilla and colleagues found a better reduction of total cholesterol and triglycerides when taking immediate release in agreement with our findings. However, the current results did not report a better elevation of high-density lipoproteins. The difference in study duration and the cumulative rate estimation put the current findings in question. The effects of metformin on lipid profile are contradicting. Some studies found a reduction of triglycerides and total cholesterol,[31] while others showed no impact on total cholesterol.[32] The dose might affect the contradiction as lower doses did not benefit lipids.[33] Body mass index plays a role in modulating metformin effects on lipid profile.[34] An interesting study found the superiority of green tea over metformin in obese women.[35]

5. METFORMIN PARADOX

Metformin was found to increase saturated free fatty acid and hence hypoxia and vessel stiffness.[36] Some studies reported worsening insulin resistance.[37] Whether the observed favorable effects of metformin immediate-release on total cholesterol and triglycerides had clinical implications open the door for future studies. In addition, the severity and frequency of gastrointestinal side effects might subside as a function of the time the drug is taken.[38] Future randomized controlled trials estimating the incidence rate are needed. The current study was limited by the limitation of the search engine to the English language and the substantial heterogeneity observed.

6. CONCLUSION

Metformin immediate-release and extended-release showed similar effects on HbA1c, low-density lipoproteins, high-density lipoproteins, and comparable overall adverse events. Although both formulations showed reduced total cholesterol, the immediate release was better. In contrast, a paradox was observed regarding triglycerides as the immediate release decreases the level with a slight increment in the extended-release arm.

7. AUTHORS CONTRIBUTION STATEMENT

Hisham Alshadfan, Marai Alamri, Hyder Mirghani, and Samar Aljohani conceptualized the manuscript and gathered the data. Mansuor Alanazi, Faisal Altemani, and Majed Alqahtani analyzed the data and provided the necessary information regarding the research design. All the authors discussed the methodology and results and contributed to the final manuscript. All the authors revised the manuscript critically and approved it before submission.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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