Arbas *et al.*
The Egyptian Journal of Internal Medicine (2023) 36:5
https://doi.org/10.1186/s43162-023-00269-2

The Egyptian Journal of Internal Medicine

RESEARCH

Open Access

A meta-analysis of randomized clinical trials on the effect of metformin vs. pioglitazone monotherapy on plasma adiponectin levels among patients with diabetes mellitus

Roselle Arbas[1], Sofia Alexis Dayrit[2], Arah Dimalanta[1], John Ashley Flores[2], Arch Raphael Mañalac[2], Dinah Rose Soriano[1], Johana Vallo[1], Raphael Enrique Tiongco[2*] and Maria Ruth Pineda-Cortel[3,4]

Abstract

Background Limited and contradicting findings were observed on the effects of both metformin (MET) and pioglitazone (PIO) on adiponectin (ADP) levels. Hence, we performed a meta-analysis of randomized control trials to obtain more precise estimates. Studies were searched, screened, and identified through different database sites. Data from included studies were extracted, pooled, and analyzed. Mean and standardized mean differences were computed with their corresponding confidence intervals.

Results Overall, five studies were included in the meta-analysis. Pooled outcomes suggest that patients with diabetes receiving PIO treatment have significantly increased ADP levels. On the other hand, no significant differences were observed for those treated with MET. Other diabetes-related parameters were tested, comparing the effect of MET vs. PIO treatment, and yielded significant results for HOMA-IR and BMI.

Conclusion Our study suggests that PIO significantly affects ADP levels compared to MET among patients with diabetes mellitus. However, further studies are needed to verify these claims.

Keywords Pioglitazone, Metformin, Adiponectin, Diabetes, Meta-analysis

Introduction

Metformin (MET) is a biguanide class of hypoglycemic agent. It is used as the first-line therapy for the treatment of type 2 diabetes mellitus (T2DM) for its glucose-lowering effects, efficacy in glucose metabolism, and other diabetes-related complications [14]. Another drug used to treat T2DM comes from the class of thiazolidinediones, such as pioglitazone (PIO). This drug helps individuals with T2DM manage their blood sugar levels and insulin resistance (IR). TZD functions as insulin sensitizers, enhancing insulin activity and increasing insulin sensitivity in important tissues, and are the only pharmacologic agents that specifically treat IR [8, 16].

IR is a condition shared by many diseases other than prediabetes and T2DM [11]. MET exerts therapeutic effects on diseases where IR plays an important role. MET works by altering the expression of microRNAs in diseases. Since MET is considered safe, cheap, and therapeutically effective in IR-related illnesses that

*Correspondence:
Raphael Enrique Tiongco
tiongco.raphael@auf.edu.ph
[1] Department of Pharmacy, College of Allied Medical Professions, Angeles University Foundation, 2009 Angeles, Philippines
[2] Department of Medical Technology, College of Allied Medical Professions, Angeles University Foundation, 2009 Angeles, Philippines
[3] Department of Medical Technology, Faculty of Pharmacy, University of Santo Tomas, 1008 Manila, Philippines
[4] Research Center for the Natural and Applied Sciences, University of Santo Tomas, 1008 Manila, Philippines

involve different miRNAs, it can be considered as the drug of choice for treating such illnesses [1]. MET does not appear to have a single mechanistic target: rather, it counters IR through multiple effects that are individually modest but collectively substantial. MET is also said to impact metabolic, vascular, and other physiological functions [2].

On the other hand, PIO is a drug that promotes insulin sensitivity in impaired glucose tolerance subjects through the decrease and redistribution of muscle lipids into subcutaneous adipose tissue [24]. PIO has been shown to increase the secretion of adiponectin (ADP) by activating the peroxisome proliferator-activated receptor-γ in adipose tissues. This leads to an increased level of ADP, and consequently, the improvement of IR [17]. Compelling in vitro studies show that both MET and PIO may increase the levels of ADP, leading to improved IR [10, 21, 22, 26, 27]. However, studies are limited and contradictory, prompting us to perform a meta-analysis to obtain more precise estimates. The primary purpose of this meta-analysis is to compare the effect of MET vs. PIO monotherapy in patients with diabetes on the levels of serum ADP. Further, the study also determines the effect of MET vs. PIO monotherapy on other diabetes-related parameters among the study population.

Materials and methods

Literature search strategy, study assessment, and eligibility criteria

Articles used in this review were retrieved from PubMed, Google Scholar (title search only), and Science Direct up to April 24, 2023, using a combination of the following key search terms: "pioglitazone" AND "metformin" AND "adiponectin" AND "diabetes." No restrictions were applied to the date of publication. Papers marked as reviews, case reports, case studies, and commentaries were excluded. Only studies written in English were considered. The resulting studies' title and abstract were initially extracted and screened for eligibility. Studies were included if they had data on plasma ADP levels before and after treatment with PIO and MET. The full text was retrieved from those who passed the screening for further evaluation.

Data extraction and analysis

From the full text included, the following data were obtained from each study: (i) first author's last name, (ii) year of publication, (iii) the country where the study was conducted, (iv) the total number of participants, (v) the number of T2DM patients involved, (vii) duration and dosage of treatment, (viii) ADP assay used, (ix) pre- and post-intervention data for ADP, and (x) pre- and post-intervention data for diabetes-related markers such as homeostatic model assessment-insulin resistance (HOMA-IR), HbA1c, body mass index (BMI), and fasting plasma glucose (FPG). Data obtained were then tabulated using a customized spreadsheet.

Quality assessment of the included studies

A tool drafted by the National Heart, Lung, and Blood Institute designed for before-after (pre-post) studies with no control group (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to assess the quality of the included studies. The results obtained were described accordingly.

Meta-analysis

Data were analyzed using Review Manager 5.4.1. by computing the pooled mean difference (MD) and standardized mean difference (SMD). The MD (for dependent groups) and 95% confidence interval (CI) of the levels of plasma ADP, HOMA-IR, HbA1c, BMI, and FPG among patients with T2DM before and after therapy with either PIO or MET were computed. Consequently, the SMD (for independent groups) and 95% CI of the levels of plasma ADP, HOMA-IR, HbA1c, BMI, and FPG between T2DM patients who underwent PIO therapy and those who received MET were also computed. The pooled MD and SMD were calculated either by the fixed- (absence of heterogeneity) or random-effects (presence of heterogeneity) model [7, 19]. Heterogeneity in the pooled outcomes was assessed using a chi-based Q test and I^2 statistics [13, 15]. All p values (P^A) used for association were two-sided with a significance level of <0.05, whereas the p value (P^H) for heterogeneity is set at <0.10 due to the low power of the test [12].

Results

Characteristics of the included studies

Out of the 75 studies identified, only five [10, 21, 22, 26, 27] qualified to be included in the meta-analysis. Overall, a total of 232 patients with T2DM were included. All studies included were conducted in Asia and among Asian participants. Patients included were divided into two cohorts, treatment with either MET or PIO. Those treated with MET were given 500, 750, or 1000 mg/day doses for around 12 or 24 weeks. On the other hand, those receiving PIO were given a dose of either 15 or 30 mg/day for around 12 or 24 weeks. Regarding ADP measurement, most used enzymelike immunoassay (ELISA) for analysis, and one study used radioimmunoassay (RIA). The quality of studies was determined and showed an overall low result for bias. Publication bias analysis was no longer performed due to the limited number of eligible studies in this meta-analysis Fig. 1.

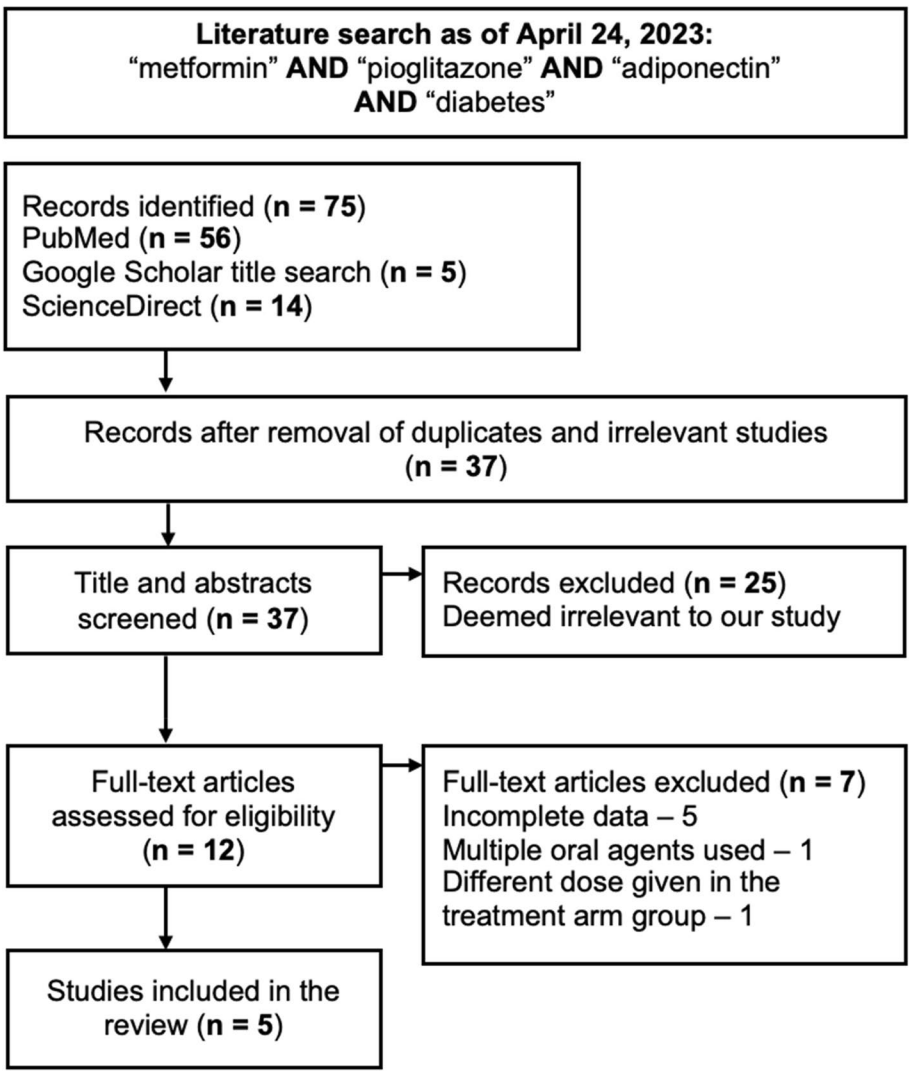

Fig. 1 Summary of the literature search

Effect of metformin vs. pioglitazone monotherapy on ADP levels

ADP levels were compared before and after MET or PIO treatment (Fig. 2a, b). Between the two cohorts, the PIO treatment arm showed a significant difference in ADP after treatment (MD 6.15, 95% CI 3.04, 9.25, $P^A = 0.0001$); however, the outcomes are heterogenous ($I^2 = 86\%$, $P^H < 0.00001$), whereas non-significant (MD 0.66, 95% CI −0.05, 1.37, $P^A = 0.07$) and homogenous ($I^2 = 17\%$, $P^H = 0.31$) outcomes were observed for the MET treatment arm Table 1.

A comparison of the levels of ADP after treatment with either MET or PIO was also done (Table 2). Initial results showed heterogeneous outcomes, which prompted us to identify the source using a Funnel plot (Fig. 3). After the removal of the study of Sharma et al., the analysis was repeated and showed homogenous ($I^2 = 0\%$, $P^H = 0.53$) and significant (SMD 0.82, 95% CI 0.53, 1.11, $P^A < 0.0001$) outcomes.

Effect of metformin vs. pioglitazone monotherapy on HOMA-IR, HbA1c, BMI, and FPG levels

Further analysis of the effect of both MET and PIO on diabetes-related parameters was done. After the intervention, BMI, HbA1c, HOMA-IR, and FPG levels were compared between the MET and PIO treatment arms. The results are summarized in Table 2. Out of the four parameters, only HOMA-IR (SMD −0.52, 95% CI −0.79, −0.26 1.11, $P^A = 0.0001$) and BMI (SMD 0.30, 95% CI 0.05, 0.56, $P^A = 0.02$) showed significant differences with homogenous outcomes ($I^2 = 0$–40%, $P^H = 0.15$–0.77).

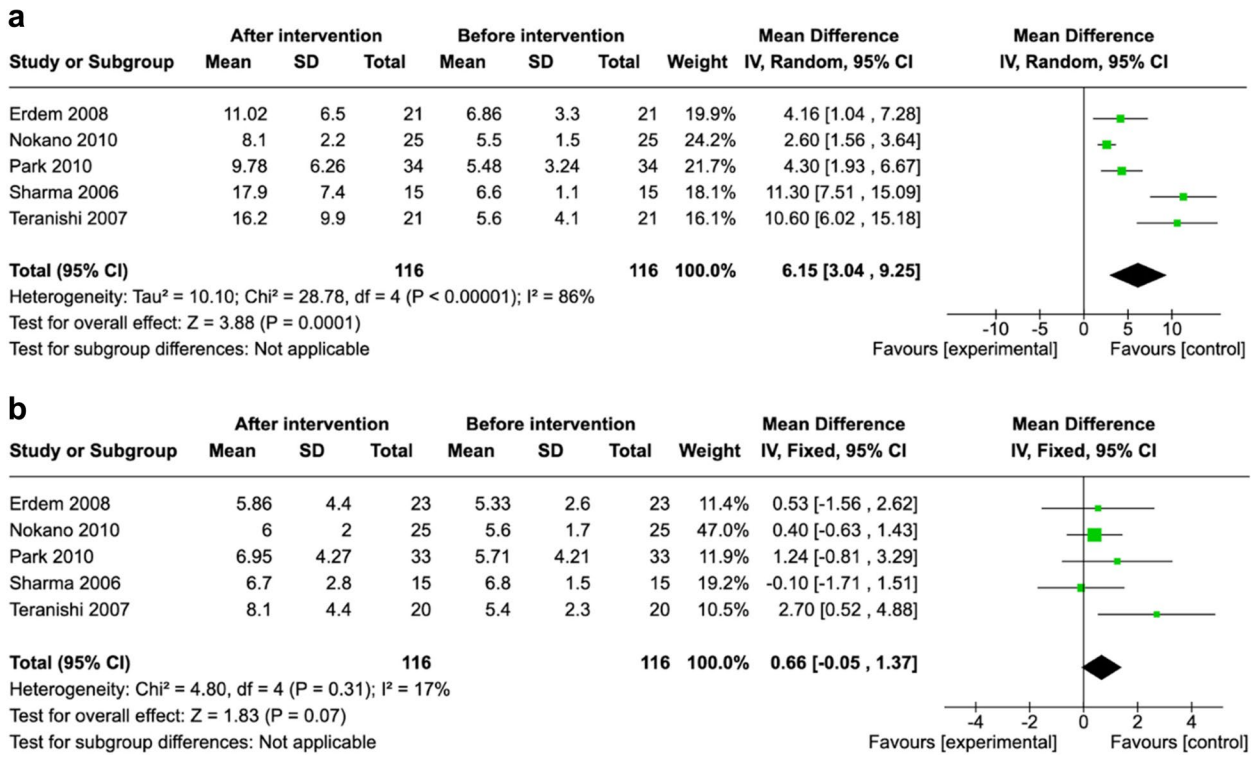

Fig. 2 **a** Comparison of ADP levels in patients with T2DM before and after treatment with PIO. **b** Comparison of ADP levels in patients with T2DM before and after treatment with MET. SD standard deviation, CI confidence interval

Table 1 Characteristics of the included studies

First author and year	Country	*N*	T2DM	Other medications	Pioglitazone		Metformin		ADP assay
					Duration	Dose	Duration	Dose	
[10]	Turkey	44	Newly diagnosed from outpatient clinics	None	12 weeks	15 mg/day	12 weeks	1 g/day	RIA
[21]	Japan	50	Newly diagnosed from outpatient clinics	Glimepiride (*n*=6), anti-hypertensive (*n*=11), low-dose lipid-lowering agent (*n*=8)	12 weeks	15 mg/day	12 weeks	500 mg/day	ELISA
[22]	Korea	67	T2DM inadequately managed by glimepiride or sulfonylurea	None	24 weeks	15 mg/day	24 weeks	1 g/day	ELISA
[26]	India	30	Newly diagnosed from outpatient clinics	None	12 weeks	15-30 mg/day	12 weeks	1 g/day	ELISA
[27]	Japan	41	Diagnosed from a hospital and no treatment was started	Some patients are treated with sulfonylureas even before the start of the study and was not discontinued.	24 weeks	30 mg/day	24 weeks	750 mg/day	ELISA

N Total number of participants, *T2DM* Type 2 diabetes mellitus, *ADP* Adiponectin, *RIA* radioimmunoassay, *ELISA* Enzyme-linked immunoassay

Discussion

The results of this meta-analysis suggest that between MET and PIO, those receiving PIO had significantly higher levels of ADP than those receiving MET. Further analysis of diabetes-related parameters further support these results. As observed in this meta-analysis, IR (as measured using HOMA-IR) is lower in the MET treatment arm than in the PIO treatment arm. This suggests

Table 2 Comparison of ADP, HOMA-IR, HbA1c, BMI, and FPG between T2DM patients who underwent pioglitazone vs. metformin monotherapy

PIO vs. MET	Pre-outlier analysis							Post-outlier analysis							Effect of outlier analysis
	n	AM	SMD	95% CI	P^A	I^2	P^H	n	AM	SMD	95% CI	P^A	I^2	P^H	
ADP	5	R	0.99	0.06, 1.39	<0.00001*	49%	0.10**	4[a]	F	0.82	0.53, 1.11	<0.0001*	0%	0.53 ns	HO
HOMA-IR	5	F	−0.52	−0.79, −0.26	0.0001*	40%	0.15 ns	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HbA1c	4	R	−0.22	−0.69. 0.25	0.36 ns	61%	0.05**	3[b]	F	0.02	−0.30, 0.35	0.88 ns	0%	0.51 ns	HO
BMI	5	F	0.30	0.05, 0.56	0.02*	0%	0.77 ns	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
FPG	4	F	−0.05	−0.34, 0.23	0.71 ns	0%	0.89 ns	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

ADP Adiponectin, *HOMA-IR* Homeostatic model assessment-insulin resistance, *BMI* Body mass index, *FPG* Fasting plasma glucose, *T2DM* Type 2 diabetes mellitus, *PIO* Pioglitazone, *MET* Metformin, *n* Number of studies, *AM* Analysis model, *SMD* Standardized mean difference, *CI* Confidence interval, P^A *p* value for association, I^2 Degree of heterogeneity, P^H *p* value for heterogeneity, *R* Random effects model, *F* Fixed effects model, *ns* Not significant, *n/a* Not applicable, *HO* Homogenous outcomes

* *p* value is significant if <0.05

** *p* value is significant if <0.10

[a] Study of [26] was omitted from the post-outlier analysis

[b] Study of [10] was omitted from the post-outlier analysis

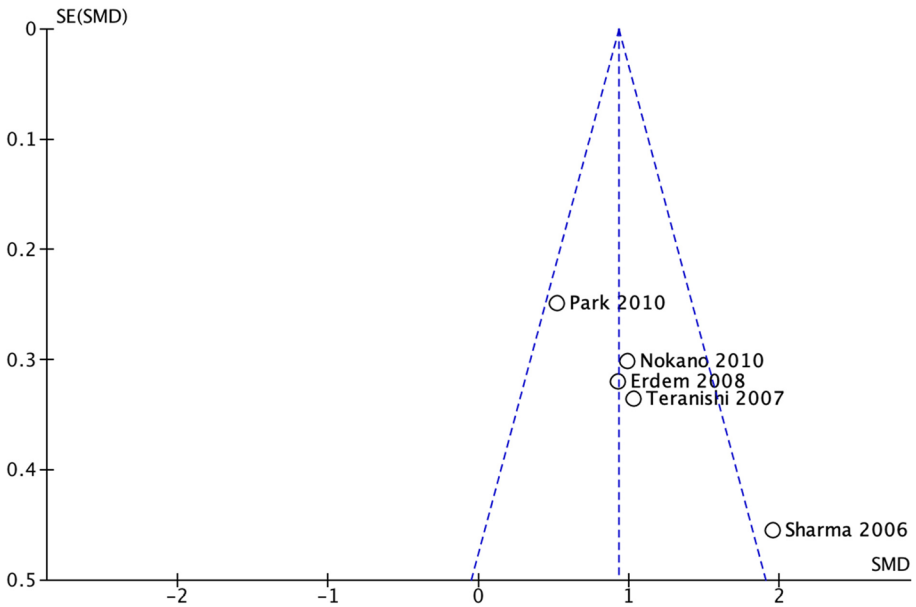

Fig. 3 Funnel plot analysis to identify outlier studies

that those treated with PIO have better IR than those receiving MET. However, MET showed more promising results in lowering BMI. These results are supported by the homogeneity of the post-outlier results indicating the combinability of the studies. Moreover, a high degree of significance, consistent precision of effects, and robustness of the post-outlier outcomes enhance the evidence presented in this meta-analysis. Consequently, studies included in this meta-analysis all come from Asian ethnicity, despite not limiting the search criteria. Hence, findings may be limited to interpretation in the Asian group given the difference in diet, environmental exposure, and drug metabolism with Western countries.

Based on the results of this meta-analysis, the pooled outcomes suggest the following significant findings: (**a**) ADP levels are significantly increased among those treated with PIO than those treated with MET, (b) HOMA-IR levels are lower among those treated with PIO than those treated with MET, and (c) BMI is higher among those treated with PIO than those treated with MET.

Studies included in this meta-analysis have shown that PIO influences ADP levels. Aside from human studies,

in vivo animal studies have also shown such an effect of the drug on ADP levels [6, 18]. A well-known effect of PIO is increasing plasmatic levels of ADP in humans and mice. ADP plays a significant role in lipid and glucose metabolism modulation in human insulin-sensitive tissues [10]. It helps improve insulin sensitivity and combat IR by activating the AMP-activated protein kinase (AMPK) pathway, considered the master switch that regulates glucose and lipid metabolism [21]. This activation increases glucose uptake in skeletal muscle and enhances fatty acid oxidation, contributing to lower blood glucose levels. ADP also prevents the development of lipid-induced IR by promoting fatty acid oxidation and inhibiting triglyceride synthesis. Consequently, the activity of enzymes in fatty acid oxidation increases, reducing lipid accumulation in tissues such as the liver and skeletal muscle. Low ADP levels are commonly observed in individuals with obesity and T2DM. ADP levels are also low in people with cardiovascular disease [22]. Conversely, higher ADP levels are associated with improved insulin sensitivity and a lower risk of metabolic disorders. Investigating the role of ADP in metabolic regulation and its implications for health conditions is essential for advancing our understanding of these diseases and developing effective therapeutic approaches.

HOMA-IR is a reliable technique for predicting IR [4, 5, 9]. In the present meta-analysis, the decrease in HOMA-IR levels of patients taking PIO compared to those taking MET may be attributed to the effect of PIO in increasing ADP levels and may not be a direct correlation. As supported by the study of Eboka-Loumingou Sakou et al. in 2021, a strong correlation is observed between ADP levels and IR,hence, an increase in ADP levels means increasing the sensitivity of the cells to insulin. Regarding BMI reduction, MET was shown to be superior to PIO because of the latter's effect in increasing adipocyte levels in the body. While this association is unclear, PIO is said to redistribute white adipose tissue in the body via a reduction in visceral adipose tissue and the promotion of adipose expansion (i.e., adipogenesis), which in turn may result to increase in lower-body fat [3, 20, 23, 25]. Another study suggested that PIO treatment in non-diabetic obese individuals is associated with an increase in the relative and total number of small adipose cells and increased variability in the size of the large adipose cells. Furthermore, PIO significantly increased two subcutaneous fat depots but decreased visceral abdominal fat [20].

Even with the promising results of this paper, care should be taken when findings are interpreted and applied clinically, given its limitations. Some of the inconsistencies noted in the study include the ethnicity of the participants given that all studies included were conducted within Asia, duration of treatment, dosage of the drug, the criteria used for the recruitment of the participants, other medications being taken, and the participants' environment during the study period. Also, it is important to note that both clinical (differences in the study population included—T2DM) and methodological (differences in drug dosage and intervention time) heterogeneity are present in the study which may further limit the interpretation.

Conclusion

Overall, this meta-analysis shows that individuals treated with PIO are associated with increased ADP production compared to those who received MET among Asians with T2DM. Further, HOMA-IR levels were significantly decreased in patients who received PIO. However, individuals receiving PIO were shown to have higher BMI levels compared to those treated with MET.

Abbreviations

MET	Metformin
PIO	Pioglitazone
ADP	Adiponectin
T2DM	Type 2 diabetes mellitus
HOMA-IR	Homeostatic model assessment-insulin resistance
BMI	Body mass index
FPG	Fasting plasma glucose
MD	Mean difference
SMD	Standardized mean difference
CI	Confidence interval

Acknowledgements

None.

Authors' contributions

All authors participated in the conceptualization, data gathering, data analysis, and writing of the manuscript.

Funding

None.

Availability of data and materials

Associated data from the study are included in the manuscript.

Declarations

Ethics approval and consent to participate

None.

Consent for publication

All authors agree to publish the results of the output.

Competing interests

None.

Received: 30 September 2023 Accepted: 17 December 2023
Published: 2 January 2024

References

1. Alimoradi N, Firouzabadi N, Fatehi R (2021) Metformin and insulin-resistant related diseases: Emphasis on the role of microRNAs. Biomed Pharmacother 139:111662. https://doi.org/10.1016/j.biopha.2021.111662

2. Bailey CJ (2017) Metformin: historical overview. Diabetologia 60(9):1566–1576. https://doi.org/10.1007/s00125-017-4318-z
3. Basu A, Jensen MD, McCann F, Mukhopadhyay D, Joyner MJ, Rizza RA (2006) Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. Diabetes Care 29:510–514. https://doi.org/10.2337/diacare.29.03.06.dc05-2004
4. Behiry EG, El Nady NM, AbdEl Haie OM, Mattar MK, Magdy A (2019) Evaluation of TG-HDL ratio instead of HOMA ratio as insulin resistance marker in overweight and children with obesity. Endocr Metab Immune Disord Drug Targets 19:676–682. https://doi.org/10.2174/1871530319666190121123535
5. de Abreu VG, de Martins CJ, M, de Oliveira PAC, Francischetti EA, (2017) High-molecular weight adiponectin/HOMA-IR ratio as a biomarker of metabolic syndrome in urban multiethnic Brazilian subjects. PLoS One 12:e0180947. https://doi.org/10.1371/journal.pone.0180947
6. de Mendonça M, dos Santos B, de AC, de Sousa É, Rodrigues AC, (2019) Adiponectin is required for pioglitazone-induced improvements in hepatic steatosis in mice fed a high-fat diet. Mol Cell Endocrinol 493:110480. https://doi.org/10.1016/j.mce.2019.110480
7. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2
8. Devchand PR, Liu T, Altman RB, FitzGerald GA, Schadt EE (2018) The pioglitazone trek via human PPAR gamma: from discovery to a medicine at the FDA and beyond. Front Pharmacol. 9.https://doi.org/10.3389/fphar.2018.01093
9. Eboka-Loumingou Sakou RF, Longo-Mbenza B, Nkalla-Lambi M, Mokondjimobe E, Monabeka HG, Moukassa D, Abena AA, Mekieje Tumchou MP, Tchokonte-Nana V (2021) Inflammatory biomarkers and prediction of insulin resistance in Congolese adults. Heliyon 7:e06139. https://doi.org/10.1016/j.heliyon.2021.e06139
10. Erdem G, Dogru T, Tasci I, Bozoglu E, Muhsiroglu O, Tapan S, Ercin CN, Sonmez A (2008) The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Res Clin Pract 82:214–218. https://doi.org/10.1016/j.diabres.2008.07.021
11. Herman R, Kravos NA, Jensterle M, Janež A, Dolžan V (2022) Metformin and Insulin Resistance: A Review of the Underlying Mechanisms behind Changes in GLUT4-Mediated Glucose Transport. Int J Mol Sci 23(3):1264. https://doi.org/10.3390/ijms23031264
12. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558. https://doi.org/10.1002/sim.1186
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560. https://doi.org/10.1136/bmj.327.7414.557
14. Kaneto H, Kimura T, Obata A, Shimoda M, Kaku K (2021) Multifaceted Mechanisms of Action of Metformin Which Have Been Unraveled One after Another in the Long History. Int J Mol Sci 22(5):2596. https://doi.org/10.3390/ijms22052596
15. Lau J, Ioannidis JPA, Schmid CH (1997) Quantitative synthesis in systematic reviews. Ann Intern Med 127:820–826
16. Lebovitz HE (2019) Thiazolidinediones: the forgotten diabetes medications. Curr Diab Rep 19:151. https://doi.org/10.1007/s11892-019-1270-y
17. Li P, Shibata R, Unno K, Shimano M, Furukawa M, Ohashi T, Cheng X, Nagata K, Ouchi N, Murohara T (2010) Evidence for the importance of adiponectin in the cardioprotective effects of pioglitazone. Hypertension 55:69–75. https://doi.org/10.1161/HYPERTENSIONAHA.109.141655
18. Li Y, Xia T, Li R, Tse G, Liu T, Li G (2019) Renal-protective effects of the peroxisome proliferator-activated receptor-γ agonist pioglitazone in ob/ob mice. Med Sci Monit. 25:1582–1589. https://doi.org/10.12659/MSM.913461
19. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748. https://doi.org/10.1093/jnci/22.4.719
20. Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA (2002) Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 87:2784–2791. https://doi.org/10.1210/jcem.87.6.8567
21. Nakano K, Hasegawa G, Fukui M, Yamasaki M, Ishihara K, Takashima T, Kitagawa Y, Fujinami A, Ohta M, Hara H, Adachi T, Ogata M, Obayashi H, Nakamura N (2010) Effect of pioglitazone on various parameters of insulin resistance including lipoprotein subclass according to particle size by a gel-permeation high-performance liquid chromatography in newly diagnosed patients with type 2 diabetes. Endocr J 57:423–430. https://doi.org/10.1507/endocrj.K10E-006
22. Park JS, Cho MH, Nam JS, Yoo JS, Ahn CW, Cha BS, Kim KR, Lee HC (2011) Effect of pioglitazone on serum concentrations of osteoprotegerin in patients with type 2 diabetes mellitus. Eur J Endocrinol 164:69–74. https://doi.org/10.1530/EJE-10-0875
23. Pramyothin P, Karastergiou K (2016) What can we learn from interventions that change fat distribution? Curr Obes Rep 5:271–281. https://doi.org/10.1007/s13679-016-0215-x
24. Rasouli N, Raue U, Miles LM, Lu T, Di Gregorio GB, Elbein SC, Kern PA (2005) Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. Am J Physiol Endocrinol Metab. https://doi.org/10.1152/ajpendo.00522.2004
25. Shadid S, Jensen MD (2003) Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. Diabetes Care 26:3148–3152. https://doi.org/10.2337/diacare.26.11.3148
26. Sharma PK, Bhansali A, Sialy R, Malhotra S, Pandhi P (2006) Effects of pioglitazone and metformin on plasma adiponectin in newly detected type 2 diabetes mellitus. Clin Endocrinol (Oxf) 65:722–728. https://doi.org/10.1111/j.1365-2265.2006.02658.x
27. Teranishi T, Ohara T, Maeda K, Zenibayashi M, Kouyama K, Hirota Y, Kawamitsu H, Fujii M, Sugimura K, Kasuga M (2007) Effects of pioglitazone and metformin on intracellular lipid content in liver and skeletal muscle of individuals with type 2 diabetes mellitus. Metabolism 56:1418–1424. https://doi.org/10.1016/j.metabol.2007.06.005

Publisher's Note