This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature's AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: https://doi.org/10.1007/s12325-024-02848-3

The effect of thiazolidinediones in polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials

Running title: Pharmacological Interventions in PCOS

Mohammed A. Abdalla[1], Najeeb Shah[1], Harshal Deshmukh[1], Amirhossein Sahebkar[2,3,4], Linda Östlundh [5], Rami H. Al-Rifai[6], Stephen L. Atkin[7], Thozhukat Sathyapalan[1]

[1] Allam Diabetes Centre, academic Diabetes, Endocrinology and Metabolism. The University of Hull, Hull York Medical School (HYMS), Hull, UK.

[2]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.

[3]Applied Biomedical Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran.

[4]School of Medicine, The University of Western Australia, Perth, Australia.

[5]College of Medicine and Health Sciences, the National Medical Library, United Arab Emirates University, United Arab Emirates.

[6]College of Medicine and Health Sciences, Institute of Public Health, United Arab Emirates University, Al Ain, United Arab Emirates.

[7]School of Postgraduate Studies and Research, RCSI Medical University of Bahrain, Kingdom of Bahrain.

Correspondence: Dr Mohammed A Abdalla

Dasman Diabetes Institute, Department of Translational Research, State of Kuwait.

Email: mohammed.ahmed@dasmaninstitute.org

PROSPERO registarion No: CRD42020178783

Prior Publication

This work was part of Dr Mohammed A Abdalla's PhD thesis which was deposited at the University of Hull repository website https://hull-repository.worktribe.com.

Abstract

Context: Polycystic ovary syndrome (PCOS) is a complex endocrine condition affecting women of reproductive age. It is characterised by insulin resistance and is a risk for type 2 diabetes mellitus (T2DM).

Objective. To review the literature on the effect of pioglitazone and rosiglitazone in women with PCOS.

Data sources: We searched PubMed, MEDLINE, Scopus, Embase, Cochrane Library and the Web of Science in April 2020 and updated in March 2023.

Study selection. Studies were deemed eligible if they were randomised controlled trials (RCTs) reporting the effect of pioglitazone and rosiglitazone in PCOS. The study follows the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data extraction. Two reviewers independently extracted data and assessed the risk of bias using the Cochrane risk of bias tool.

Results. Out of 814 initially retrieved citations, 24 randomised clinical trials (RCTs) involving 976 participants were deemed eligible. Among women with PCOS, treatment with rosiglitazone compared to metformin resulted in a significant increase in the mean body weight (Mean difference (MD): 1.95 kg; 95% CI: 0.03-3.87, p = 0.05). Metformin treatment was associated with a reduction in mean body mass index (BMI) compared to pioglitazone (MD: 0.85 kg/m²; 95% CI: 0.13-1.57, p = 0.02). Both pioglitazone compared to placebo (MD: 2.56 kg/m²; 95% CI: 1.77-3.34, p < 0.00001), and rosiglitazone compared to metformin (MD: 0.74 kg/m²; 95% CI: 0.07-1.41, *p = 0.03)* were all associated with a significant increase in BMI. Treatment with pioglitazone compared to placebo showed a significant reduction in triglycerides (MD: -0.20 mmol/L; 95% CI: -0.38 to -0.03, p = 0.02), and fasting insulin levels (MD: -11.47 mmol/L; 95% CI: -20.20, -2.27, p= 0.01). Rosiglitazone compared to metformin was

marginally significantly associated with a reduction in the luteinising hormone (LH) (MD: -0.62; 95% CI: -1.25-0.00, p = 0.05).

Conclusion. Both pioglitazone and rosiglitazone were associated with significant increases in body weight, and BMI when compared with metformin or placebo. Pioglitazone significantly reduced triglycerides and fasting insulin when compared with placebo while rosiglitazone showed a modest reduction of LH when compared with metformin.

Keywords: polycystic ovary syndrome, PCOS, glitazones, pioglitazone, rosiglitazone, metformin, FBG, FI, HOMA-IR, HOMA-B, pharmacological therapy.

Key message

- In women with Polycystic ovary syndrome (PCOS), treatment with pioglitazone and rosiglitazone increases body weight, and body mass index (BMI), while only pioglitazone is associated with increased waist circumference.
- In women with PCOS, pioglitazone significantly reduces fasting insulin compared with placebo, while rosiglitazone is more effective than metformin in reducing LH levels.
- Pioglitazone could be used as add-on therapy or as a monotherapy for insulin-resistant women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting women of reproductive age, with a prevalence ranging from 5% to 20% depending on ethnicity and diagnostic criteria[1,2]. PCOS is characterized by high androgen levels, menstrual irregularities, and polycystic ovarian morphology[3]. While the exact cause of PCOS is not fully understood, insulin resistance plays a significant role in its development. Elevated insulin levels in PCOS contribute to increased ovarian androgen release and exacerbate its clinical features[4]. Additionally, increased body weight, often seen in PCOS, can further elevate androgen and insulin levels[5].

Insulin stimulates the release of the androgens from both the ovaries and adrenal glands leading to hirsutism and reduced fertility in women with PCOS [6,7]. Women with PCOS also have a higher prevalence of impaired glucose tolerance and insulin resistance, both of which are features of type 2 diabetes mellitus (T2DM)[8]. Nearly 70 % of women with PCOS will develop metabolic syndrome (MS), characterised by dyslipidaemia, central adiposity, hypertension, and impaired glucose tolerance, all of which are predisposing factors for cardiovascular disease (CVD)[9,10]. The primary approach to managing PCOS focuses on weight loss and improving insulin sensitivity[11,12].

Thiazolidinediones (TZDs) are insulin sensitisers primarily used in the management of T2DM. They work by activating the gamma isoform of the nuclear receptor peroxisome proliferator-activated receptors (PPRA-gamma)[13]. TZDs reduce insulin resistance in adipose tissue, muscle, and the liver by increasing the transcription of several insulin-sensitive genes. Pioglitazone is the main TZD currently used in clinical practice for the management of T2DM. However, rosiglitazone, another TZD, has been withdrawn from the market in many countries due to concerns over its cardiovascular safety. While troglitazone, another TZD, has been formally withdrawn from the market due to significant hepatotoxicity[14,15,16]. TZDs have shown beneficial effects on PCOS. Small clinical trials comparing the effectiveness of TZDs as monotherapy or add-on therapy to metformin in women with PCOS have reported variable metabolic benefits[17]. Therefore, this systematic review aims to evaluate thoroughly

the effectiveness of pioglitazone and rosiglitazone as an add-on therapy to metformin or as monotherapy in the management of PCOS.

Method

This systematic review was prospectively registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020178783) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement[18].

A statement of ethics compliance

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search and identification of the studies

The eligibility criteria for the included studies are presented in Table 1. Only trials that included women of reproductive age diagnosed with PCOS were eligible. These trials employed a randomised design to assess the effect of pioglitazone and rosiglitazone compared to placebo or other treatments. We accepted all methods of randomisations, including cross-over, double-blinded, single-blinded, open-label and parallel trials.

A medical librarian specialising in systematic reviews (L.Ö.) developed and performed the literature search in collaboration with the subject experts (MA and TS). The search covered biomedical databases PubMed, EMBASE, MEDLINE, Scopus, Cochrane Central Library, and Web of Science, performed in April 2020 with an update in PubMed in March 2021. Grey literature sources (European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), Open Grey and ClinicalTrial.gov) were also included. The search strategy, initially developed in PubMed, was replicated in each database without any publication year or language restrictions. A combination of Medical Subject Headings (MeSH)/Thesaurus terms and searches in the Title and Abstract fields (alternatively "Topic" or "title, abstract keywords") were applied to ensure the best possible search outcome. All records in

the literature search were exported to Covidence systematic review software[19] for automatic deduplication and blinded screening. Cabell's Predatory Report[20] was used to verify the quality of the open-access publications reported in this review.

Study selection

Two reviewers (M.A and N.S) initially screened titles and abstracts of all retrieved studies for their potential eligibility. Subsequently, the full text of those eligible studies was then retrieved for further detailed evaluation. Any disagreement between the reviewers was resolved by discussion, consensus, or mediation of a third reviewer (T.S). We only included RCTs that compared pioglitazone and rosiglitazone with placebo or other treatments. The detailed study selection process is presented in Figure 1- PRISMA flow diagram[18].

From all the eligible RCTs, two reviewers (M.A, NS) extracted information on the country of the trial, the year of the publication, the baseline characteristics of the included cohort, PCOS diagnostic criteria, trial duration and the reported outcomes. All reported outcomes were considered for inclusion, but the primary outcomes were anthropometric parameters, indices for insulin resistance, lipid profiles, C-reactive protein (CRP), and androgen hormones.

Risk of bias assessment in the included studies

The Cochrane Collaboration's tool for assessing the risk of bias (RoB) was used as recommended by Higgins et al[21]. Six domains, including (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias) were assessed by two reviewers (M.A, N.S), and a third reviewer (T.S) arbitrated any conflict that arises between the two reviewers. In addition, we followed the recommendation from the *Cochrane handbook*[22], and any RoB was graded as either 'high RoB', 'low RoB', or 'unclear RoB'. The overall RoB of the included RCTs is presented in Figure 1-Supplementary Material.

GRADE scoring

We assessed the strength of evidence for each outcome using the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) system[23]. GRADEpro GDT software was used to summarise the findings for each outcome, which is presented in Table 1 A, B, C, and D-Supplementary Material. Four points were given for each outcome then we assessed factors reducing the quality of the evidence. For each outcome, points were reduced based on the presence of the following: the overall RoB for each RCT, inconsistency (significant heterogeneity), indirectness (significant differences in the population, comparisons, and outcomes), imprecision (the size of the cohort, width and significance of the confidence intervals (CIs). Accordingly, we graded the evidence in four categories based on the overall GRADE scores for each intervention: high-grade evidence (at least 4 points), moderate-grade evidence (3 points), low-grade evidence (2 points) and very low-grade evidence (1 point). All the grades of evidence are shown in Table 1 A, B, C, D-Supplementary Material.

Investigation for heterogeneity

The I-squared (I^2) statistic was used to evaluate the statistical heterogeneity for each outcome across the RCTs. We described heterogeneity as insignificant (I^2= *0-40%*), moderate (I^2 = 30-60%), substantial (I^2= 50-90%), or considerable heterogeneity (I^2= 75-100%). Heterogeneity with $p < 0.1$ was statistically significant, if this was the case, the source of the heterogeneity was investigated by observing and removing the largest outlier. Where significant heterogeneity has not been resolved, subgroup analysis has been performed using the random-effects model.

Subgroup analysis

Subgroup analysis was performed at different levels where data from ≥ 2 RCTs were available. RCTs were grouped based on the dosages of the pioglitazone and rosiglitazone (e.g. 30 mg, 45 mg, and 4 mg) and metformin (850 mg, 1500 mg and 2000 mg), frequencies of administration (once a day QD or

twice a day-BID), duration of the intervention (weeks/months) and the subtotal results were presented.

Statistical analysis

All the meta-analyses were conducted using the statistical methods outlined in the *Cochrane Handbook for Systematic Reviews and Meta-analysis*[22]. Data from two or more RCTs were available, and their pooled estimates and the 95% confidence intervals (95%CIs) were presented. For outcomes reported using the same scale, continuous data were pooled using (unstandardised) mean difference (MD) with inverse-variance (IV) and random-effects model of the analysis based on *Cochrane recommendation 22*. Where scales were different, if possible, the unit of measurement was converted to the most common unit. If this was not convenient, the standardised mean difference (SMD) was used to pool the estimated effect of the same outcomes measured using different scales. Where necessary, data presented as standard error (SE), confidence intervals (CIs) and p-values were converted into SD using the RevMan calculator. For RCTs with more than one intervention arm, the desired outcome was pooled by combining data of the same outcome in all arms. When an RCT used a cross-over design, data were used from the point of cross-over only. All the meta-analysis was performed using the Review Manager software (RevMan version 5.4, The Cochrane Collaboration) and differences with two-tailed p- p-values of ≤ 0.05 were considered statistically significant.

Results

Literature search

After deduplication, a total of 3,186 unique records were identified in the literature search, of which 2,372 were excluded after the title and abstract screening against the pre-set inclusion and exclusion criteria. Of the 814 records screened in full text, 24 RCTs met the eligibility criteria and were included in the systematic review and the meta-analysis Figure 1.

Characteristics of the included RCTs

The 24 RCTs (976 participants) were published until 2020, of which 11 RCTs[24-34] diagnosed PCOS based on the Rotterdam criteria-2003[35], while six RCTs[36-41] diagnosed PCOS using the National Institute of Health (NIH/NICHD) criteria[42]. No diagnostic criteria were specified for the remaining seven RCTs. The characteristics of the included RCTs are presented in Table 2.

Sensitivity analysis

Small sample-sized RCTs (< 10 patients) and those with high RoB were eliminated from the analysis while monitoring their impact on the results. No significant effect was found, and hence none of the 24 RCTs was removed from the meta-analysis. No assessment of publication bias as less than 10 RCTs were included in each comparison.

<u>Effect of glitazones on anthropometric outcomes</u>

Body weight

Rosiglitazone vs metformin

In three RCTs, rosiglitazone 4 mg QD was compared with metformin. Rosiglitazone has significantly increased the mean body weight by 1.95 kg (95% CI: 0.03-3.87; I^2 = 3 %; p = 0.05) (Figure 2-A) (very low-grade evidence).

The meta-analysis did not find any effect on body weight when pioglitazone was compared with metformin (Figure 2-B) and rosiglitazone compared with placebo (Figure 2-C).

Body mass index (BMI)

Pioglitazone vs metformin

Two RCTs comparing pioglitazone 45 mg QD with metformin 850 mg BID showed no effect on the mean BMI (MD: 0.35 kg/m^2; 95% CI: -1.10, 1.80). In four RCTs, pioglitazone 45 mg QD compared with metformin 1500 mg QD significantly increased the BMI by 1.01 kg/m^2 (95% CI: 0.18-1.85). Overall, metformin has significantly reduced the mean BMI by 0.85 kg/m^2 (MD: 0.13-1.57; I^2= 0%; p = 0.02) compared to pioglitazone (Figure 2-D) (very low-grade evidence).

Pioglitazone vs placebo

In one RCT, pioglitazone 45 mg QD significantly increased the mean BMI by 3.33 kg/m^2 (95% CI: 1.60-5.06). In four RCTs pioglitazone 30 mg QD compared with placebo significantly increased the mean BMI by 2.35 kg/m^2 (95% CI: 1.47-3.23). Overall, pioglitazone at various dosages compared with placebo significantly increased the mean BMI by 2.56 kg/m^2 (95% CI: 1.77-3.34; I^2= 0 %, p < 0.00001) (Figure 2-E) (low-grade evidence).

Rosiglitazone vs metformin

Eight RCTs comparing rosiglitazone 4 mg QD with metformin showed a significant increase in the mean BMI by 0.74 kg/m^2 (95% CI: 0.07-1.41; I^2= 23 %, *p = 0.03)* (Figure 2-F) (moderate grade evidence).

The meta-analysis did not establish any effect on the mean BMI when rosiglitazone was compared with placebo (Figure 2-G).

Waist circumference (WC)

Pioglitazone vs placebo

One RCT compared pioglitazone 45 mg QD with placebo showed a significant increase in the mean WC by 6.60 cm (95% CI: 2.78-10.42). Two RCTs compared pioglitazone 30 mg QD with placebo showed a significant increase in the mean WC by 2.30 cm (95% CI: -4.0-8.60). Overall, pioglitazone at various

doses compared with placebo significantly increased the mean WC by 5.45 cm (95%CI: 2.18-8.71; I^2= 0 %, *p = 0.001*) (Figure 2-H) (very-low grade evidence).

The meta-analysis did not find any effect on the WC when pioglitazone and rosiglitazone were compared with metformin (Figure 2-I and J).

Waist-to-hip ratio (WHR)

Rosiglitazone vs placebo

Three RCTs comparing rosiglitazone 4 mg QD with placebo showed a significant reduction in the mean WHR by 0.08 cm (95 % CI: -0.11, -0.04; I^2= 0 %, *p < 0.0001)* (Figure 2-K) (very-low grade evidence).

The meta-analysis did not find any significant effect on the mean WHR when pioglitazone was compared with metformin and placebo (Figure 2-L and M) and when rosiglitazone was compared with metformin (Figure 2-N).

<u>Effect of glitazones on C-reactive protein (CRP) and lipid profiles</u>

C-reactive protein (CRP)

Rosiglitazone vs metformin

Three RCTs comparing rosiglitazone 4 mg QD with metformin showed no effect on the mean CRP (MD: -0.21; 95% CI: -0.53, 0.10; I^2= 0 %, *p* = 0.18) (Figure 3-A) (low-grade evidence).

Triglycerides

Pioglitazone vs placebo

Two RCTs comparing pioglitazone 30 mg QD with placebo showed a significant reduction in the mean triglycerides by 0.20 mmol/L (95% CI: -0.38,-0.03; I^2= 0 %, *p* = 0.02) (Figure 3-B) (low-grade evidence).

The meta-analysis did not find any effect on the triglycerides when pioglitazone and rosiglitazone were compared with metformin (Figure 3-C and D).

Total cholesterol

There was no significant effect on the mean total cholesterol when pioglitazone was compared with metformin and placebo (Figure 3-E and F), and when rosiglitazone was compared with metformin (Figure 3-G).

Low-density lipoprotein cholesterol (LDL-C)

Rosiglitazone vs metformin

Four RCTs comparing rosiglitazone with metformin showed a nonsignificant reduction in the mean LDL-C (SMD: -0.34; 95% CI: -0.72, 0.04; I^2= 50 %, *p* = 0.08) (Figure 3-H) (low-grade evidence).

The meta-analysis did not find any effect on the mean LDL-C when pioglitazone was compared with metformin (Figure 3-I).

High-density lipoprotein cholesterol (HDL-C)

When both pioglitazone and rosiglitazone were compared with metformin, no effect on the mean HDL-C was observed (Figure 3-J and K).

<u>Effect of glitazones on insulin resistance</u>

Fasting insulin

Pioglitazone vs placebo

In three RCTs, pioglitazone 30 mg QD showed a significant reduction in the mean fasting insulin by 16.76 pmol/L (95 % CI: -25.81, -7.72) compared with placebo. One RCT compared pioglitazone 45 mg QD with placebo and showed no significant effect on the mean fasting insulin (MD: -5.34 pmol/L; 95%

CI: -14.54, 3.86). Overall, pioglitazone compared with placebo significantly reduced the mean fasting insulin by 11.47 pmol/L (95% CI: -20.20, -2.74; I^2= 35 %, *p*= 0.01) (Figure 4-A) (very-low grade evidence).

The meta-analysis did not find any effect on the mean fasting insulin when pioglitazone and rosiglitazone were compared with metformin (Figures 4-B and C).

Fasting blood glucose

The meta-analysis did not find any effect on the mean fasting blood glucose when pioglitazone was compared with placebo and metformin (Figure 4-D and E) and when rosiglitazone was compared with metformin (Figure 4-F).

Homeostatic model of insulin resistance (HOMA-IR)

Pioglitazone vs metformin

Two RCTs comparing pioglitazone 45 mg QD with metformin 850 mg BID showed no effect in the mean HOMA-IR (SMD: -0.23; 95% CI: -0.66, 0.21). Two RCTs compared pioglitazone 45 mg QD with metformin 1500 mg QD showed no effect in the mean HOMA-IR (SMD: -0.35; 95% CI: -0.94, 0.23). Overall, pioglitazone showed a nonsignificant reduction in HOMA-IR compared with metformin (SMD: -0.30; 95% CI: -0.61, 0.01; I^2= 35 %, *p* = 0.06) (Figure 4-G) (very-low grade evidence).

The meta-analysis did not find any effect on the mean HOMA-IR when pioglitazone was compared with placebo (Figure 4-H) and when rosiglitazone was compared with metformin (Figure 4-I).

<u>Effect of glitazones on androgen hormones</u>

Total testosterone

Pioglitazone vs metformin

Three RCTs compared pioglitazone 45 mg QD with metformin 1500 mg QD. Metformin showed a superior effect in the mean total testosterone level (SMD: 0.35; 95% CI: 0.00-0.70; I^2= 0 %, *p* = 0.05) compared to pioglitazone (Figure 5-A) (very low-grade evidence).

The meta-analysis did not find any effect on the total testosterone, DHEAS and SHBG when rosiglitazone and pioglitazone were compared with metformin (Figure 5-B, C, D and E).

Luteinising hormone (LH)

Rosiglitazone vs metformin

Four RCTs comparing rosiglitazone 4 mg QD with metformin showed a significant reduction in the mean LH (MD: -0.62; 95% CI: -1.25, 0.00; I^2= 0 %, *p* = 0.05) (Figure 5- F) (very low-grade evidence).

The meta-analysis did not establish any effect on the mean LH when pioglitazone was compared with metformin (Figure 5-G).

The meta-analysis did not find any effect on the mean FSH, free testosterone and androstenedione when pioglitazone and rosiglitazone were compared with metformin (Figure 5- H, I, J and K).

Discussion

This review is the most comprehensive and up-to-date systematic review and meta-analysis on the effect of glitazones in women with PCOS with a comprehensive analysis reporting the effects of pioglitazone and rosiglitazone, either as an add-on or monotherapy, on anthropometric outcomes, insulin resistance indices, lipid profiles, CRP, and androgen hormones in women with PCOS. When pioglitazone and rosiglitazone were administered at various therapeutic doses and compared with placebo and metformin, there was a statistically significant increase in the mean body weight, BMI, and WC along with a significant reduction in triglycerides, LDL-C, fasting insulin, HOMA-IR, and LH. However, neither drug had an effect on fasting blood glucose, total cholesterol, HDL-C, CRP, SHBG,

DHEAS, FSH, free testosterone and androstenedione. These findings are in accord with the findings of previous studies. A systematic review and meta-analysis of six randomised controlled trials showed pioglitazone was more effective in reducing fasting insulin, and HOMA-IR (P = 0.02 and P = 0.014, respectively) and significantly increased the mean BMI compared to metformin mainly due to increased fluid retention and fat mass[43]. In another systematic review and meta-analysis of eleven RCTs comparing pioglitazone and metformin, pioglitazone significantly increased the mean BMI compared to metformin (P = 0.006)[44]. In this systematic review, we found that rosiglitazone significantly reduced the mean LH when compared with metformin. These results will add to the existing evidence on the effect of ZTDs. A similar effect was also reported in a network meta-analysis of 28 RCTs that compared the effect of rosiglitazone and pioglitazone on the hormonal parameters in PCOS, which showed a significant effect of rosiglitazone in reducing the mean LH compared to metformin[45]. A recent network meta-analysis compared the efficacy of TZDs and metformin concerning endocrine and metabolic profiles in women with PCOS. The results suggested a superior efficacy for the TZDs as an add-on therapy to metformin than as monotherapy in ameliorating insulin resistance, lipid profile and testosterone levels[46]. Another network meta-analysis of 14 RCTs assessing the efficacy of TZDs in overweight women with PCOS reported that TZDs as an add-on therapy to metformin had superior efficacy in improving hyperandrogenaemia compared to monotherapy 47. However, this systematic review and meta-analysis showed a superior effect of metformin on mean total testosterone compared to pioglitazone. There are several contraindications for using TZDs, including heart failure due to its fluid retention effect[47]. Also due to it is teratogenic potential, TZDs would not be the right choice for women with PCOS who are pregnant or actively seeking pregnancy[48]. Thus, in such cases, women should be switched to other insulin sensitisers.

This study employed a comprehensive and systematic approach to searching for relevant databases and grey literature sources, focusing exclusively on RCTs. Several steps were taken to minimise the risk of bias including excluding observational studies and non-randomised clinical trials. This systematic review outlines the up-to-date evidence supporting the effectiveness of glitazones used in

the management of PCOS; however, most of the RCTs were small, and the statistical power used to calculate sample size was not fully reported. Moreover, all the trials were of short duration leaving the long-term effects of TZDs in women with PCOS unclear.

This systematic review acknowledges the poor quality of the included trials, as reflected in the summary of evidence of the GRADE score. The trials exhibited a high level of heterogeneity and performance bias. The findings indicate a lack of robust clinical trials assessing the efficacy of TZDs in managing PCOS. Moreover, trials examining the clinical effectiveness of pioglitazone and rosiglitazone were of low or very low quality. Therefore, the available data are insufficient to draw definite conclusions or propose recommendations for clinical practice. Additionally, the small sample sizes of these trials undermined the statistical power to calculate significant effects on the outcomes. Further clinical trials with robust designs are needed to make better-informed decisions and recommendations and to establish guidelines for the effectiveness of pioglitazone and rosiglitazone in women with PCOS.

Conclusion

Pioglitazone demonstrated effectiveness in reducing fasting insulin levels, while rosiglitazone showed efficacy in reducing luteinising hormone (LH) levels compared to metformin. However, both pioglitazone and rosiglitazone were associated with significant increases in mean body weight, body mass index (BMI), and waist circumference (WC). There was no significant effect observed in the mean levels of follicle-stimulating hormone (FSH), C-reactive protein (CRP), dehydroepiandrosterone sulfate (DHEAS), total cholesterol, and androstenedione. Therefore, thiazolidinediones (TZDs) could be considered for use either as monotherapy or as an add-on to metformin in women with PCOS who are insulin-resistant.

Acknowledgement

Authors contributions

Mohammed Altigani Abdalla; designed the review, completed the screening, assessed the quality, extracted, collected, and analysed the data, written, revised, and edited the final manuscript. Najeeb Shah; assessed the quality, extracted, and collected the data, and revised and edited the final manuscript. Harshal Deshmukh; revised and edited the final manuscript. Amirhossein Sahebkar; revised and edited the final manuscript; Linda Östlundh; developed and performed the systematic search, assessed for predatory journals, and revised and edited the final manuscript. Rami H. Al-Rifai; participated in the critical discussion and revised and edited the final manuscript. Stephen L. Atkin: participated in the critical discussion and revised the final draft of the manuscript. Finally, Thozhukat Sathyapalan; acted as a mediator for assessing the quality of the evidence, supervised the study, participated in the critical discussion, and revised, and edited the final manuscript.

Funding

The rapid service fee and open access fee were funded by the authors.

Medical writing/Editorial assistance

There was no assistance in writing or editing this manuscript.

Availability of data

The datasets generated and analysed for this review are available upon compelling request to the authors.

Ethical approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Thus, no ethical approval was required.

Conflict of interest

There is nothing to declare.

Disclosure

Dr Mohammed A Abdalla is currently affiliated with Dasman Diabetes Institute, Department of Translational Research, State of Kuwait, Kuwait.

Ms Linda Östlundh is now affiliated with Örebro University, Sweden.

References

1. Barnard L, Ferriday D, Guenther N, Strauss B, Balen AH, Dye L. Quality of life and psychological well being in polycystic ovary syndrome. *Hum Reprod.* 2007;22(8):2279-2286.
2. Abdalla MA, Deshmukh H, Atkin S, Sathyapalan T. The potential role of incretin-based therapies for polycystic ovary syndrome: a narrative review of the current evidence. *Ther Adv Endocrinol Metab.* 2021;12:2042018821989238.
3. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *P T.* 2013;38(6):336-355.
4. Witchel SF, Oberfield SE, Pena AS. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. *J Endocr Soc.* 2019;3(8):1545-1573.
5. Abdalla M, Deshmukh H, Atkin SL, Sathyapalan T. miRNAs as a novel clinical biomarker and therapeutic targets in polycystic ovary syndrome (PCOS): A review. *Life Sci.* 2020;259:118174.
6. Wu S, Divall S, Wondisford F, Wolfe A. Reproductive tissues maintain insulin sensitivity in diet-induced obesity. *Diabetes.* 2012;61(1):114-123.
7. Azziz R, Ehrmann DA, Legro RS, Fereshetian AG, O'Keefe M, Ghazzi MN. Troglitazone decreases adrenal androgen levels in women with polycystic ovary syndrome. *Fertility and sterility.* 2003;79(4):932-937.
8. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome--a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab.* 2007;92(12):4546-4556.
9. Garruti G, Depalo R, Vita MG, et al. Adipose tissue, metabolic syndrome and polycystic ovary syndrome: from pathophysiology to treatment. *Reprod Biomed Online.* 2009;19(4):552-563.
10. Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. *Clin Obstet Gynecol.* 2007;50(1):205-225.
11. Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005;353(20):2111-2120.
12. Abdalla MA, Deshmukh H, Atkin S, Sathyapalan T. A review of therapeutic options for managing the metabolic aspects of polycystic ovary syndrome. *Ther Adv Endocrinol Metab.* 2020;11:2042018820938305.
13. Hauner H. The mode of action of thiazolidinediones. *Diabetes Metab Res Rev.* 2002;18 Suppl 2:S10-15.
14. Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. *N Engl J Med.* 2007;356(24):2522-2524.
15. Ajjan RA, Grant PJ. The cardiovascular safety of rosiglitazone. *Expert Opin Drug Saf.* 2008;7(4):367-376.
16. Bailey CJ. Thiazolidinediones. In: *xPharm: the comprehensive pharmacology reference.* Elsevier; 2011.
17. Valsamakis G, Lois K, Kumar S, Mastorakos G. Metabolic and other effects of pioglitazone as an add-on therapy to metformin in the treatment of polycystic ovary syndrome (PCOS). *Hormones (Athens).* 2013;12(3):363-378.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
19. Babineau J. Product review: covidence (systematic review software). *Journal of the Canadian Health Libraries Association/Journal de l'Association des bibliothèques de la santé du Canada.* 2014;35(2):68-71.
20. Das S, Chatterjee SS. Cabell's blacklist: A new way to tackle predatory journals. *Indian journal of psychological medicine.* 2018;40(2):197-198.
21. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
22. Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions.* John Wiley & Sons; 2019.

23. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
24. Shahebrahimi K, Jalilian N, Bazgir N, Rezaei M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. *Indian journal of endocrinology and metabolism.*20(6):805-809.
25. Sohrevardi SM, Nosouhi F, Hossein Khalilzade S, et al. Evaluating the effect of insulin sensitizers metformin and pioglitazone alone and in combination on women with polycystic ovary syndrome: An RCT. *International journal of reproductive biomedicine (Yazd, Iran).* 2016;14(12):743-754.
26. Cetinkalp S, Karadeniz M, Erdogan M, Ozgen G, Saygl F, Ylmaz C. The effects of rosiglitazone, metformin, and estradiol-cyproterone acetate on lean patients with polycystic ovary syndrome. *Endocrinologist.* 2009;19(3):94-97.
27. Kilicdag EB, Bagis T, Zeyneloglu HB, et al. Homocysteine levels in women with polycystic ovary syndrome treated with metformin versus rosiglitazone: a randomized study. *Human reproduction (Oxford, England).* 2005;20(4):894-899.
28. Lam PM, Tam WH, Ma RC, et al. The reproductive and metabolic effect of rosiglitazone on Chinese women with polycystic ovarian syndrome--a double-blind randomized placebo-controlled study. *Fertility and sterility.* 2011;96(2):445-451.e441.
29. Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL. Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. *Clinical endocrinology.* 2009;70(2):233-237.
30. Li Y, Tan J, Wang Q, Duan C, Hu Y, Huang W. Comparing the individual effects of metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial. *Fertility and sterility.* 2020;113(1):197-204.
31. Ziaee A, Oveisi S, Abedini A, Hashemipour S, Karimzadeh T, Ghorbani A. Effect of metformin and pioglitazone treatment on cardiovascular risk profile in polycystic ovary syndrome. *Acta medica Indonesiana.* 2012;44(1):16-22.
32. Brettenthaler N, De Geyter C, Huber PR, Keller U. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism.* 2004;89(8):3835-3840.
33. Mohiyiddeen L, Watson AJ, Apostolopoulos NV, Berry R, Alexandraki KI, Jude EB. Effects of low-dose metformin and rosiglitazone on biochemical, clinical, metabolic and biophysical outcomes in polycystic ovary syndrome. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2013;33(2):165-170.
34. Yilmaz M, Karakoç A, Törüner FB, et al. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2005;21(3):154-160.
35. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19-25.
36. Aroda VR, Ciaraldi TP, Burke P, et al. Metabolic and hormonal changes induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial. *The Journal of clinical endocrinology and metabolism.* 2009;94(2):469-476.
37. Cataldo NA, Abbasi F, McLaughlin TL, et al. Metabolic and ovarian effects of rosiglitazone treatment for 12 weeks in insulin-resistant women with polycystic ovary syndrome. *Human reproduction (Oxford, England).* 2006;21(1):109-120.
38. Jensterle M, Janez A, Mlinar B, Marc J, Prezelj J, Pfeifer M. Impact of metformin and rosiglitazone treatment on glucose transporter 4 mRNA expression in women with polycystic ovary syndrome. *European journal of endocrinology.* 2008;158(6):793-801.

39. Jensterle M, Sebestjen M, Janez A, et al. Improvement of endothelial function with metformin and rosiglitazone treatment in women with polycystic ovary syndrome. *European journal of endocrinology.* 2008;159(4):399-406.
40. Steiner CA, Janez A, Jensterle M, Reisinger K, Forst T, Pfützner A. Impact of treatment with rosiglitazone or metformin on biomarkers for insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome. *Journal of diabetes science and technology.* 2007;1(2):211-217.
41. Dereli D, Dereli T, Bayraktar F, Ozgen AG, Yilmaz C. Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. *Endocrine journal.* 2005;52(3):299-308.
42. Anaforoglu I, Algun E, Incecayir O, Ersoy K. Higher metabolic risk with National Institutes of Health versus Rotterdam diagnostic criteria for polycystic ovarian syndrome in Turkish women. *Metab Syndr Relat Disord.* 2011;9(5):375-380.
43. Du Q, Wang YJ, Yang S, Wu B, Han P, Zhao YY. A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. *Curr Med Res Opin.* 2012;28(5):723-730.
44. Xu Y, Wu Y, Huang Q. Comparison of the effect between pioglitazone and metformin in treating patients with PCOS:a meta-analysis. *Arch Gynecol Obstet.* 2017;296(4):661-677.
45. Huang R, Zhao PF, Xu JH, Liu DD, Luo FD, Dai YH. Effects of placebo-controlled insulin-sensitizing drugs on hormonal parameters in polycystic ovary syndrome patients: A network meta-analysis. *J Cell Biochem.* 2018;119(3):2501-2511.
46. Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. *Reprod Health.* 2021;18(1):171.
47. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ.* 2009;339:b2942.
48. Froment P, Touraine P. Thiazolidinediones and Fertility in Polycystic Ovary Syndrome (PCOS). *PPAR Res.* 2006;2006:73986.
49. Naka KK, Kalantaridou SN, Kravariti M, et al. Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study. *Fertil Steril.* 2011;95(1):203-209.
50. Ortega-González C, Luna S, Hernández L, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism.* 2005;90(3):1360-1365.
51. Batista JG, Soares JM, Maganhin CC, Simões RS, Tomaz G, Baracat EC. Assessing the benefits of rosiglitazone in women with polycystic ovary syndrome through its effects on insulin-like growth factor 1, insulin-like growth factor-binding protein-3 and insulin resistance: a pilot study. *Clinics (Sao Paulo, Brazil).* 2012;67(3):283-287.
52. Li T, Zhang T, Cui T, et al. Involvement of endogenous testosterone in hepatic steatosis in women with polycystic ovarian syndrome. *J Steroid Biochem Mol Biol.* 2020;204:105752.
53. Glintborg D, Støving RK, Hagen C, et al. Pioglitazone treatment increases spontaneous growth hormone (GH) secretion and stimulated GH levels in polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism.* 2005;90(10):5605-5612.
54. Glintborg D, Hermann AP, Andersen M, et al. Effect of pioglitazone on glucose metabolism and luteinizing hormone secretion in women with polycystic ovary syndrome. *Fertility and sterility.* 2006;86(2):385-397.
55. Glintborg D, Frystyk J, Højlund K, et al. Total and high molecular weight (HMW) adiponectin levels and measures of glucose and lipid metabolism following pioglitazone treatment in a randomized placebo-controlled study in polycystic ovary syndrome. *Clinical endocrinology.* 2008;68(2):165-174.

56. Dereli D, Dereli T, Bayraktar F, Ozgen AG, Yilmaz C. Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. *Endocr J.* 2005;52(3):299-308.
57. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Endocrine and metabolic effects of rosiglitazone in overweight women with PCOS: a randomized placebo-controlled study. *Human reproduction (Oxford, England).* 2006;21(6):1400-1407.

Table 1

The inclusion/exclusion criteria for the included studies in this systematic review

Inclusion Criteria
Study design: randomised controlled trials including (randomised open-label trials, double-blind controlled trials, cross-over randomised trials, parallel randomised trials). **Population:** adult females aged 18 and over with a diagnosis of PCOS based on a robust diagnostic criterion. **Comparator:** studies reported pioglitazone and rosiglitazone compared to placebo or other Treatment. **Outcomes:** reported outcomes such as BMI, body weight, waist circumference and waist, Waist hip ratio, CRP, LDL-C, HDL-C, TC, TGs, TT, FT, FAI, A4, 17-OHP, LH, FSH, FBG, FI, HMOA-IR SHBG and DHEAS.
Exclusion criteria
Study design: case studies, cross-sectional studies, and animal studies. **Patients' population:** paediatric and adolescents females, postmenopausal women, and women without PCOS. **Comparators:** non-glitazones interventions, pharmacological interventions versus dietary interventions, pharmacological interventions versus physical activities or surgery

PCOS: polycystic ovary syndrome, **BMI**: body mass index, **CRP:** c-reactive protein, **LDL-C:** low-density lipoprotein cholesterol, **HDL-C:** high-density lipoprotein cholesterol, **TC:** total cholesterol, **TGs:** triglycerides, **TT:** total testosterone, **FT:** free testosterone F**AI: f**ree androgen index, **A4**: androstenedione, **LH:** luteinising hormone**, FSH:** follicular Stimulating hormone, **FBG:** fasting blood glucose, **FI:** fasting insulin, **HOMA-IR:** the homeostatic model of insulin resistance, SHBG**:** sex hormone-binding globulin, **DHEAS:** dehdroepianderostendione sulphate.

Table 2: Characteristics of the studies included in the systematic review and meta-analysis.

Author	*Year of publication*	*Country of the trial*	*PCOS diagnostic criteria*	*Duration of the trial (month)*	*Measured outcome(s)*
Naka et al.[49]	2011a	Greece	N/A	6	Bodyweight, BMI, WC and WHR, FI
Ortega Gonzlez et al.[50]	2005	Mexico	N/A	6	Bodyweight, BMI,WHR
Shahebrahimi et al.[24]	2016	Iran	Rotterdam	3	Bodyweight ,BMI,WC, FBG, LDL,HDL,TG
Sohrevardi et al.[25]	2016	Iran	Rotterdam	3	BMI,WHR, HOMA-IR, FBG, FI
Batista et al.[51]	2012	Brazil	AES-2006	3	FBG.FI,HOMA-IR
Cataldo et al.[37]	2006	USA	NICHD	3	BMI, WHR
Lam et al.[28]	2011	China	Rotterdam	12	BMI, FI,FBG,TC, TG
Cetinkalp et al.[26]	2009	Turkey	Rotterdam	4	TG,HDL,LDL, BMI, HOMA-IR, TC,
Kilicdag et al.[27]	2005	Turkey	Rotterdam	3	BMI, FI,FBG,TC, TG, HOMA-IR
Li et al.[52]	2020	China	Rotterdam	6	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Cho et al.[29]	2009	UK	Rotterdam	12	BMI, HOMA-IR
Ziaee et al.[31]	2012	Iran	Rotterdam	3	BMI,HOMA-IR,HDL,LDL,TG,TC
Aroda et al.[36]	2009	USA	NIH	6	Bodyweight, BMI, WHR, WC, FBG,FI
Brettenthaler et al.[32]	2004	Switzerland	Rotterdam	3	BMI,WHR,FBG, FI, HOMA-IR
Glintborg et al.[53]	2005	Denmark	N/A	4	BMI,WHR, WC, FI
Glintborg et al.[54]	2006	USA	N/A	4	BMI, CRP, LDL
Glintborg et al.[55]	2008	USA	N/A	4	FI, HOMA-IR
Dereli et al.[56]	2005	Turkey	NICHD	8	BMI, WHR
Rautio et al.[57]	2006	Finland	N/A	4	BMI, WHR
Mohiyiddeen et al.[33]	2013	UK	Rotterdam	3	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Steiner et al.[40]	2007	Germany	NIH	6	BMI,HOMA-IR, FBG,FI
Yilmaz et al.[34]	2005	Turkey	Rotterdam	24	FBG, FI,BMI, WHR
Jensterle et al.[38]	2008a	Slovenia	NIH	6	FBG, FI,BMI, HOMA-IR
Jensterle et al.[39]	2008b	Slovenia	NIH	6	LDL,HDL,HOMA-IR,WC,BMI, FI,FBG,TC

NIH: national institute for health, **NICHD**: national institute of child health and development. **USA:** the United States of America, **UK**: United Kingdom, **PCOS:** polycystic ovary syndrome, **BMI:** body mass index, **WC:** waist circumference, **FI:** fasting insulin; **FBG**: fasting blood glucose **LDL:** low density-lipoprotein; **HDL:** high density-lipoprotein; **TG:** triglycerides**, HOMA-IR**: a homeostatic model of insulin resistance, **TC**: Total Cholesterol, **WHR:** waist-to-hip ratio, **CRP:** c-reactive protein.

Figure 1: PRISMA flow diagram

Figure 2: Forest plot of comparisons on anthropometric indices

Bodyweight

A)

B)

C)

Body mass index (BMI)

D)

E)

F)

G)

Waist circumference (WC)

H)

I)

J)

Waist-to-hip ratio (WHR)

K)

L)

M)

N)

Figure 3: Forest plot of comparisons on C-reactive protein (CRP) and lipid profiles

C-reactive protein (CRP)

A)

Triglycerides

B)

C)

D)

Total cholesterol

E)

F)

G)

Low-density lipoprotein cholesterol (LDL-C)

H)

I)

High-density lipoprotein cholesterol (HDL-C)

J)

K)

Figure 4: Forest plot of comparisons on insulin resistance

Fasting insulin

A)

B)

C)

Fasting blood glucose

D)

E)

F)

Homeostatic model of insulin resistance (HOMA-IR)

G)

H)

I)

Figure 5: Forest plot of comparisons on androgen hormones

Total testosterone

A)

B)

DHEAS

C)

D)

Sex hormone-binding globulin (SHBG)

E)

Luteinising Hormone (LH)

F)

G)

Follicular stimulating hormone (FSH)

H)

I)

Free testosterone

J)

Androstenedione

K)