

Comparative efficacy of thiazolidinediones and metformin for polycystic ovary syndrome

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ABSTRACT

الأهداف: مقارنة فعالية عقار الثيازولدينديونز وميتفورمين في علاج المرضى المصابين بداء تكيس المبايض المتعدد.

الطريقة: أجريت دراسة منهجية في مستشفى جامعة شنق هنج، شنيانج، الصين، قمنا بالبحث في أدوات البحث الطبية الالكترونية ومكتبة كوكرين وقاعدة بيانات الصين الوطنية للمعرفة حتى يناير 2012 م.

النتائج: تم استرجاع 6 دراسات عشوائية والتي شملت 267 مريض. كان تأثير عقار الثيازولدينديونز على مؤشر كتلة الجسم أقل بشكل إحصائي من الميتفورمين القيمة الإحصائية=0.001 واختلاف المعدل الطبيعي=0.40، وفترة الثقة=95% (0.16-0.65)، ولم يختلف مؤشر مناعة الانسولين اختلافاً إحصائياً عن الميتفورمين ومعدل الاستنابات المقدر (-0.38-0.40، $p=0.955$, SMD = 0.01). بينما لم يكن هنالك اختلاف إحصائي بين مستوى هرمون الاندوجين من الميتفورمين معدل مصال التستوستيرون القيمة الإحصائية=0.287، اختلاف المعدل الطبيعي=0.20، فترة الثقة 95% (-0.17-0.57).

خاتمة: بالمقارنة مع الميتفورمين أظهر عقار الثيازولدينديونز الفعالية نفسها في التقليل من مستويات الاندروجين في المرضى المصابين بداء تكيس المبايض المتعدد ولكن أثرها في خفض الوزن ليس جيداً بالمقارنة مع الميتفورمين.

Objectives: To compare the efficacy of thiazolidinediones (TZDs) and metformin in polycystic ovary syndrome (PCOS) patients.

Methods: This systematic review study was conducted at Shengjing Hospital of China Medical University, Shenyang, China between January and February 2012. We searched the following databases MEDLINE, EMBASE, the Cochrane Library, and Chinese National Knowledge Infrastructure until January 2012.

Results: Six randomized controlled trials records involving 267 patients were retrieved. The effect of TZDs on body mass index (BMI) was significantly lower than metformin ($p=0.001$; standardized mean difference [SMD] = 0.40, 95% confidence interval [CI]; 0.16-0.65). The effect of TZDs on the Homeostasis Model of Assessment-Insulin Resistance Index was not significantly different from metformin ($p=0.955$, SMD = 0.01, 95% CI: -0.38-0.40). The effect of TZDs on the androgen level was not significantly different from metformin (serum total testosterone: $p=0.287$, SMD = 0.20, 95% CI: -0.17-0.57).

Conclusion: Compared to metformin, TZDs had the same effectiveness in treating insulin sensitivity and lowering androgen in PCOS patients, but the effect on weight loss was not as good as metformin.

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Polycystic ovary syndrome (PCOS) affects 4-10% of females of reproductive age,^{1,2} which is a disorder of ovarian follicular development that originates from multiple factors. The clinical manifestation of PCOS includes menstrual abnormalities, infertility, hirsutism, and obesity. Patients with PCOS are more likely to have insulin resistance (IR), and have a higher risk of atherosclerosis and cardiovascular diseases.³ The mechanism of PCOS is not clear, and may be associated with increased androgen levels,⁴ IR (hyperinsulinemia), and obesity. The insulin gene, variable number of

tandem repeats (VNTR) is a sensitive site of PCOS, and further supports the role of hyperinsulinemia and IR in PCOS.⁵

The treatment options for PCOS include drug-induced ovulation and IR therapy. The choice for drug-induced ovulation is clomiphene.⁶ Insulin resistance can be treated with insulin sensitizers, biguanides, and thiazolidinediones (TZDs).⁷ Biguanides act through suppressing glucose excretion from the liver, and activating glucose transporters to increase insulin sensitivity of the surrounding tissues. Phenethylbiguanide, a type of biguanide, is rarely used due to the adverse effect of lactic acidosis;⁸ metformin is currently the most often used biguanide. The TZDs is a type of selective peroxisome proliferator-activated receptor (PPAR- γ) agonist that acts by combining with, and activating PPAR- γ receptors to increase the protein expression of several genes, and enhance the expression of the insulin receptors that accelerate the differentiation of adipose cells, decrease adiposity, and improves insulin resistance.⁹ The PPAR- γ receptors also effect the reproductive system by improving IR, and indirectly reducing the synthesis of androgen in the ovaries. The ovaries are directly targeted to reduce hyperandrogenemia and stimulate ovulation.¹⁰ Troglitazone is seldom used due to severe liver toxicity,¹¹⁻¹³ rosiglitazone and pioglitazone are more frequently used. For the treatment of PCOS, evidence shows that metformin, an insulin sensitizer, is widely recognized for improving IR, reducing weight, and decreasing androgen levels.^{14,15} However, the mechanism underlying TZDs action is unclear. Thus, we aim to compare the efficacy of TZDs and metformin in PCOS patients.

Methods. The systematic search included MEDLINE, EMBASE, Cochrane, CENTRAL electronic databases, and Chinese National Knowledge Infrastructure from their inception between January and February 2012, in Shengjing Hospital of China Medical University, Shenyang, China. The references listed in the articles thus identified, were further hand-searched for additional relevant citations. Search terms included those for patient selection: PCOS; exposure (rosiglitazone, pioglitazone,

thiazolidinediones, peroxisome proliferator-activated receptor- γ , PPAR- γ agonist, insulin-sensitizing drugs, insulin-sensitizing agents, metformin); and study type (randomized controlled trial, randomized). The detailed strategy is available upon request. Reviewers working independently and in duplicate, considered all titles and abstracts, to determine whether they met the eligibility criteria. Whenever an abstract suggested that the article could fulfill the entry criteria, the corresponding full text was assessed. References and review articles were obtained for additional relevant studies. The diagnosis of PCOS was made based on the Rotterdam European Society for Human Reproduction & Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), or National Institute of Child Health and Human Development (NICHD) criteria.^{16,17} Age, disease progression, and race did not influence the diagnosis of PCOS. The inclusion criteria were as follows: the experimental group was given rosiglitazone or pioglitazone; and the control group was given metformin. The exclusion criteria were as follows: animal trials; reviews; trials without control groups; non-randomized trials; retrospective studies; or studies with other treatments in the experimental or control groups. The outcomes included androgen level, fasting plasma glucose level, serum insulin concentration, homeostasis model assessment of insulin resistance (HOMA-IR) index, body mass index (BMI), and adverse events. Four researchers used Jadad scoring¹⁸ to evaluate literature quality, and for those studies lacking information, we contacted the corresponding authors to provide supplementary information for the trials. If there was no reply from the authors, these research were listed as "pending evaluation."

The statistical package, Stata software version 11.0 (Stata Corp, College Station, Texas, USA) was used to conduct the systematic review. The measurement was expressed in standardized mean differences (SMDs) and the confidence interval (CI) was uniform (95%). The heterogeneity between research was estimated with a χ^2 test. If there was no statistical significance based on the heterogeneity test ($p > 0.1$), the fixed inverse variance method was used. If there was statistical significance based on the heterogeneity test ($p \leq 0.1$), the random DerSimonian and Laird method was used.

Results. We identified 161 studies by searching the databases. We included 6 randomized trials after reading the titles, abstracts, and full texts based on the inclusion and exclusion criteria in Figure 1. The basic information for the experimental and control groups was comparable with detailed descriptions. The

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basic information is listed in Table 1. Six randomized controlled trials included had descriptions regarding the method of randomization, and 5 of the trials described allocation concealment. Two studies adopted double-blinding. The comparable baselines were described in each study. The 6 studies included were of high quality.

The effect on BMI in PCOS patients. Six studies compared the effects of the 2 groups of medications on BMI, and included 267 participants.¹⁹⁻²⁴ The TZDs was used in 130 patients, and metformin was used in 137 patients. There was not heterogeneity between the studies ($p=0.219$, $I^2=28.8%$). The fixed inverse variance method was used to evaluate the variance combination. The results of the systematic review showed that the

effect of TZDs on BMI was significantly lower than metformin ($p=0.001$; $SMD=0.40$; $95\% CI: 0.16-0.65$) (Figure 2).

The effect of lowering androgen levels in PCOS patients. Five studies studied the effect of lowering serum total and free testosterone levels separately in 237 patients.^{19,20,22-24} One hundred and fifteen patients were treated with TZDs, and 122 with metformin. The statistics of the heterogeneity test of the serum total and free testosterone levels were as follows: $p=0.966$, $I^2=0.0%$; and $p=0.919$, $I^2=0.0%$. The fixed inverse variance method was used to evaluate the variance combination. The results of systematic review showed that the effect of TZDs on lowering androgen levels was

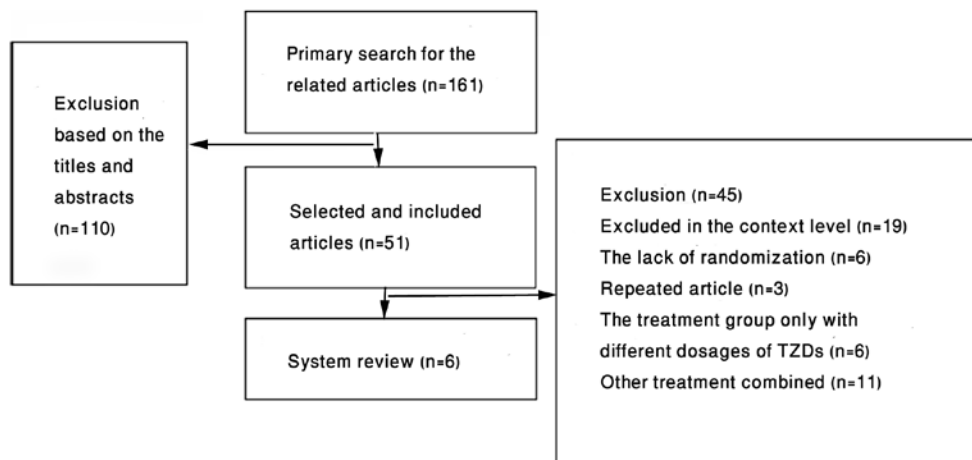


Figure 1 - The selection process of the randomized controlled trials. We included 6 randomized trials after reading the titles, abstracts, and full texts based on the inclusion and exclusion criteria. TZD - thiazolidinediones

Table 1 - Characteristics of the included studies according to age groups, treatment and course of treatment.

Trials	Sample size, groups		Age, groups		Treatment, groups, mg/day		Course of treatment	Randomization	Concealed randomization	Blinding
	1	2	1	2	1	2				
Baillargeon JP, ¹⁹ 2004	22	28	27.9 ± 1.1	27.7 ± 0.9	Rosiglitazone 8	Metformin 1700	6 months	Yes	Yes	Yes
Jensterle M, ²⁰ 2008	17	18	25.2 ± 4.8	22.9 ± 4.5	Rosiglitazone 4	Metformin 1700	6 months	Yes	Yes	Unclear
Kilicdag EB, ²¹ 2005	15	15	25.53 ± 1.68	24.13 ± 1.42	Rosiglitazone 4	Metformin 1700	3 months	Yes	Yes	Unclear
Yilmaz M, ²² 2005	45	43	25.13 ± 4.43	24.67 ± 4.60	Rosiglitazone 4	Metformin 1700	6 months	Quasi-random	No	Yes
Ortega-González C, ²³ 2005	17	18	28.8 ± 0.9	29.0 ± 0.8	Pioglitazone 30	Metformin 2550	6 months	Yes	Yes	Yes
Naka KK, ²⁴ 2011	14	15	23.6 ± 5.1	22.2 ± 3.6	Pioglitazone 30	Metformin 1700	6 months	Yes	Yes	Yes

Group 1 - Experiment, Group 2 - Control

not significantly different from that of metformin (for serum total testosterone - $p=0.287$, SMD=0.20, 95% CI: -0.17 to 0.5, **Figure 3A**; for serum free testosterone - $p=0.878$, SMD=0.02, 95% CI: -0.29 to 0.34, **Figure 3B**).

The effect of improving IR in PCOS patients. The commonly used and relatively simple HOMA-IR index was used in 3 studies,^{20,21,23} to compare the effect of 2 medications in 100 patients. Forty-nine patients were treated with TZDs, and 51 patients were treated with metformin. The heterogeneity test between studies was not significant ($p=0.712$, $I^2=0.0\%$); the fixed inverse variance method was used to combine the variance. The results of the systematic review showed that the effect of TZDs on the HOMA index was not significantly different from metformin ($p=0.955$, SMD=0.01, 95% CI: -0.38 to 0.40, **Figure 4A**).

Five studies compared the effects of these 2 medications on the level of fasting insulin and glucose levels in 237 patients.^{19,20,22-24} One hundred and fifteen patients were treated with TZDs, and 112 patients were treated with metformin. The heterogeneity tests for studies in fasting insulin ($p=0.835$, $I^2=0.0\%$), or glucose ($p=0.492$, $I^2=0.0\%$) were not significant. The fixed inverse variance method was used to combine the variance. The results of the systematic review showed that there was no statistically significant difference in the effect of TZD or metformin on fasting insulin ($p=0.532$, SMD=-0.09, 95% CI: -0.38 to 0.20, **Figure 4B**) or fasting glucose ($p=0.233$, SMD=0.16, 95% CI: -0.10 to 0.41, **Figure 4C**).

Evaluation of drug safety. Only a few patients experienced light headaches in the TZDs group, and several patients in the metformin group suffered from

adverse effects involving gastrointestinal discomfort. The incidence of adverse effects was lower in the TZDs group, and these effects were minor without causing any withdrawal.

Discussion. The systematic review suggested that TZDs is effective in treating PCOS, and had the same effect on improving insulin sensitivity as metformin, including the effect on the levels of fasting glucose and insulin. The effect of TZDs on weight loss was not as much as that of metformin, and the incidence of adverse effects induced by TZDs was lower than the effect induced by metformin. Therefore, TZDs was suitable to treat PCOS patients, especially for those who were obese, and did not tolerate gastrointestinal adverse effects induced by metformin. Because the use of TZDs is not common clinically to treat PCOS patients, the diagnosis criteria of PCOS were not uniform, and increased the heterogeneity between studies. The small number of patients in each group, and the different measurement units used in studies might contribute to the insufficiency of test power and large variation of the results. The studies included were publicly available, and most of the studies were small scale. The possibility of publication bias could not be excluded, and the precision of systematic review might be influenced. Some of the studies did not follow proper methodology, including complete allocation concealment, and blinding. The number of included studies was too small to construct the funnel-plot analysis, and the results were only for reference.

Although the studies included had limitations and shortcomings, the systemic and exhaustive search of the literature strengthened the power of this analysis.

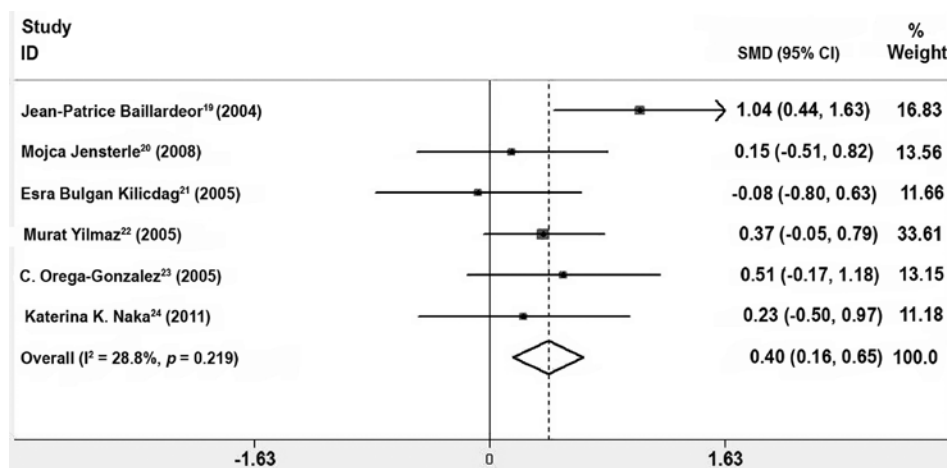


Figure 2 - The effect of thiazolidinediones or metformin treatments on body mass index in polycystic ovary syndrome patients. SMD - standard mean difference, identification number.

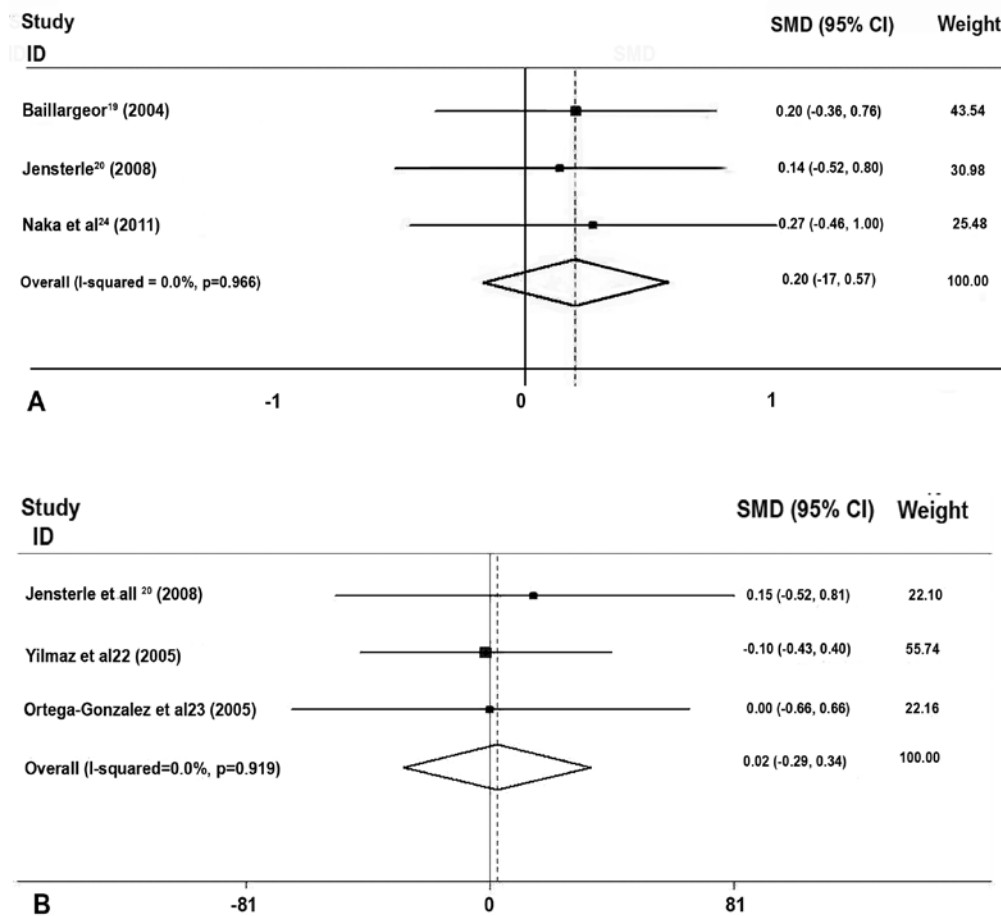


Figure 3 - The effect of thiazolidinediones or metformin treatments on lowering serum A) total and B) free testosterone levels in polycystic ovary syndrome (PCOS) patients. CI - Confidence interval, SMD - standardized mean difference

For related literature published by the authors, the inclusion and exclusion criteria were strictly enforced. The measurement units were unified according to international standards. Research work was divided, and several researchers performed data checking separately. The systematic review helped the clinicians clarify the results of several vague and small clinical trials. These trials were applied to a much-specified group of patients due to its imprecise results, and the summarized conclusion helped to a more widely used results.

This study summarized the efficacy of TZDs compared to metformin on PCOS, but most of the randomized controlled trials did not describe the adverse events in detail. Based on the previous literature, the major adverse effect of metformin was gastrointestinal events, and diabetic patients had weight gain as the most common adverse effect of rosiglitazone, while some patients developed water and sodium retention that induced heart failure, and increased the risk of

myocardial infarction.^{25,26} There was no documentation regarding the adverse effects induced by pioglitazone. The lack of documentation of adverse effects in PCOS patients by rosiglitazone, pioglitazone, and other TZDs was noted. Some of the patients in the study had pregnancy after taking TZDs and metformin. The details in the long-term follow-up were not recorded. The safety instructions on the use of TZDs by pregnant women is still absent.

The evidence and methodology in this field was not clear. More high-quality, large-enrollment, and multi-center trials are expected to be realized by institutes without a conflict of interest. The prolonged study time, the observation on the safety and effectiveness of TZDs in PCOS patients (especially on the indicators for cardiovascular events and other long-term outcomes), and the investigation on the time- and dose-dependent relationships were to find a more safe and effective medication. The randomized controlled trials

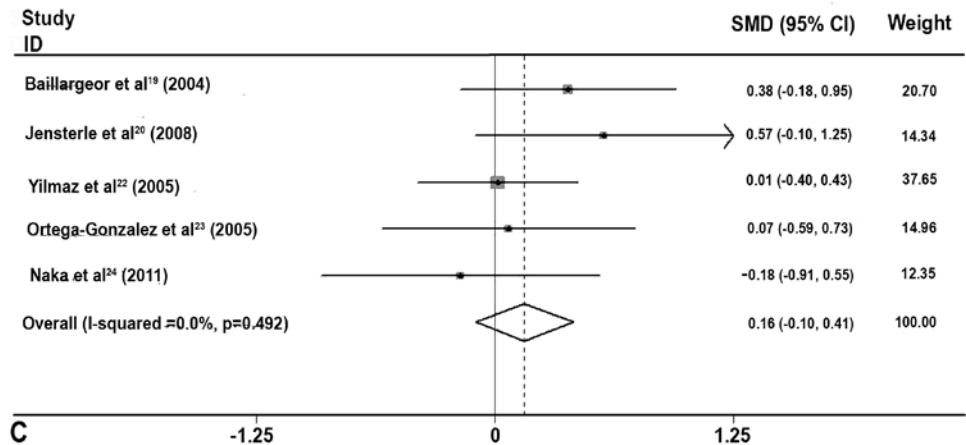
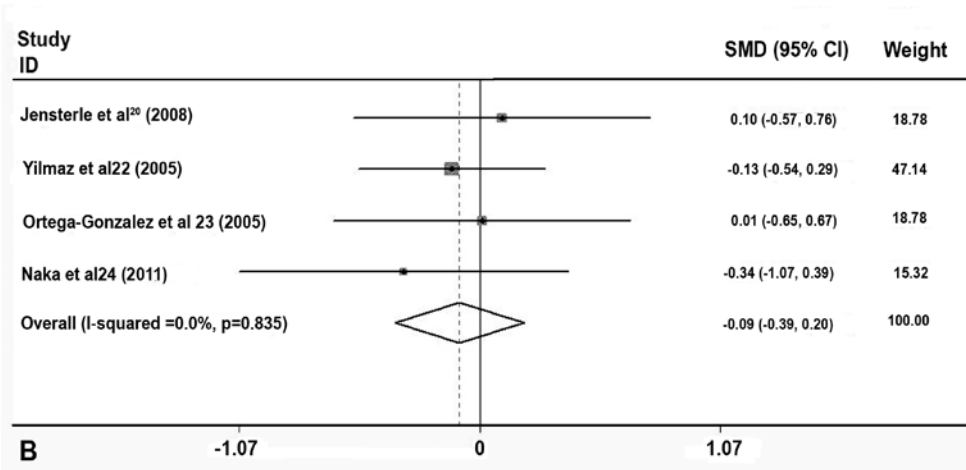
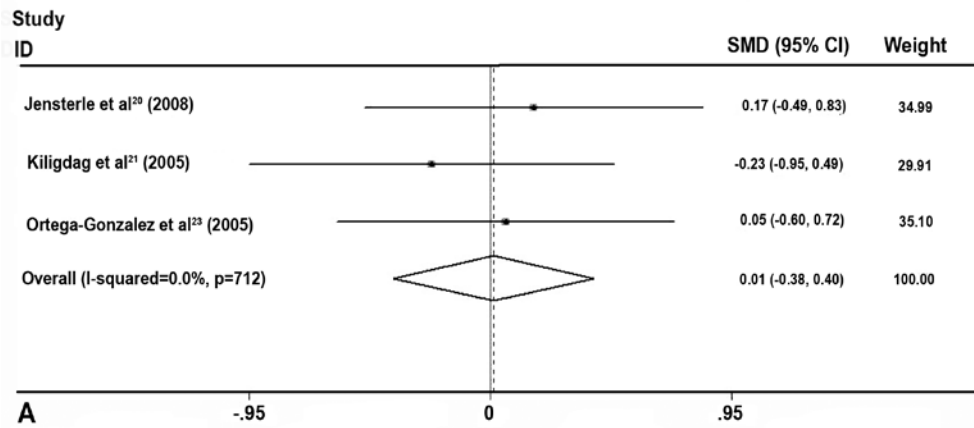


Figure 4 - The effect of A) thiazolidinediones or metformin treatments on improving insulin resistance (HOMA index) in polycystic ovary syndrome (PCOS) patients, B) thiazolidinediones or metformin treatments on improving fasting insulin in PCOS patients, and C) thiazolidinediones or metformin treatments on improving fasting glucose in PCOS patients. SMD - standardized mean difference

with placebo control could reveal the mechanism of TZDs clearer to provide objective evidence for clinical decision-making and benefit the patients. Moreover, the incidence of PCOS might be related to the changes in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), especially when the LH/FSH >2-3.^{27,28}

Few of the trials included in this systematic review had LH and FSH measurements, and the ratio of LH and FSH was not well-studied. The studies on the changes in the ratio of LH and FSH were expected in the future.

In conclusion, in the treatment of PCOS, TZDs lowered the level of androgen and improved the insulin sensitivity as did metformin, but the weight loss effect on patients was not as good as metformin. The statistics available so far might determine the precision of systematic review, and the evidence from large-scale randomized controlled trials would be more desirable.

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