Systematic Review and Meta-Analysis

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Effects of atorvastatin on the insulin resistance in women of polycystic ovary syndrome

A systematic review and meta-analysis

Lin-Lin Chen, MM, Jian-Hong Zheng, MB*

Abstract

Background: Atorvastatin treatment has been suggested as a therapeutic method for women with polycystic ovary syndrome (PCOS) in many clinical studies. Nonetheless, the effects of atorvastatin on insulin resistance in PCOS patients still remain controversial.

Objective: The aim of this report was to evaluate the effects of atorvastatin therapy on the insulin resistance in the treatment of PCOS compared to that of placebo, in order to confer a reference for clinical practice.

Methods: Randomized controlled trials (RCTs) of atorvastatin for PCOS published up to August, 2020 were searched. Standardized mean difference (SMD) and 95% confidence interval (CI) were calculated, and heterogeneity was measured by the I^2 test. Sensitivity analysis was also carried out. The outcomes of interest were as follows: fasting glucose concentration, fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR) or body mass index (BMI) value.

Results: Nine RCTs with 406 participants were included. The difference of fasting glucose concentration in PCOS patients between atorvastatin group and placebo group was not statistically significant (8 trials; SMD −0.06, 95% CI −0.31 to 0.20, $P = .66$). PCOS patients in atorvastatin group had lower fasting insulin level than those in placebo group (7 trials; SMD −1.84, 95% CI −3.06 to −0.62, $P < .003$). The homeostasis model assessment of insulin resistance (HOMA-IR) value showed significant decrease in the atorvastatin therapy compared to placebo (6 trials; SMD −4.12, 95% CI −6.00 to −2.23, $P < .0001$). In contrast to placebo, atorvastatin therapy did not decrease the BMI value significantly in PCOS patients (7 trials; SMD 0.12, 95% CI −0.07 to 0.31, $P = .22$).

Conclusions: Atorvastatin therapy can reduce insulin resistance in the treatment of patients with PCOS. In addition, further large-sample, multi-center RCTs are needed to identify these findings.

Abbreviations: BMI = body mass index, CI = confidence interval, HOMA-IR = homeostasis model assessment of insulin resistance, PCOS = polycystic ovary syndrome, RCTs = randomized controlled trials, RE = random-effect, SMD = standardized mean difference.

Keywords: atorvastatin, fasting insulin, homeostasis model assessment of insulin resistance, meta-analysis, polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS), a common endocrine disease in women of reproductive age, is characterized by ovulation dysfunction and hyperandrogenism. PCOS can affect the lives and health of 3.5% to 10% of fertile-age women around the world.[1] The occurrence of PCOS is often accompanied by high risk of abdominal obesity, insulin resistance, metabolic disorders or cardiovascular diseases. The pathogenesis of PCOS is not only related to the female reproductive endocrine system, but also associated with multiple important physiological functions, such as lipid metabolism, glucose metabolism, chronic inflammation, thyroid function.[2] Glycometabolic disorder and insulin resistance play an important role in the progress of PCOS, the glucose intolerance rate among American patients with PCOS is as high as 40%, insulin resistance can cause obesity in 60% of PCOS patients, and 20% of them suffer from type 2 diabetes.[3,4] Endocrine dysfunction and metabolic disturbance are the main causes of obesity in PCOS patients. Studies have indicated that more than 40% of obese PCOS patients have insulin resistance, which is due to the weakening of insulin receptor function after the increase in human insulin secretion.[5]

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Department of Gynecology, Tongde Hospital of Zhejiang Province, Hangzhou, China.

** Correspondence: Jian-Hong Zheng, Department of Gynecology, Tongde Hospital of Zhejiang Province, No.234 Gucui Road, Hangzhou 310012, Zhejiang Province, China (e-mail: jhgelx@163.com).*

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Insulin resistance is an important pathological feature in PCOS patients with infertility. The continuous increase of insulin level directly or indirectly stimulates the ovarian secretion of androgen. Endometrial hyperplasia is prone to occur under the stimulation of estrogen and insulin for a long time, leading to a significant decrease in pregnancy rate of PCOS patients.[6,7] So, improving insulin resistance is very necessary for PCOS women. The mechanisms of insulin resistance are very complex, they are usually related to obesity, metabolic abnormalities, gene expression and so on.[8] Therefore, reducing body weight, improving glucose and lipid metabolism, inhibiting sex hormone secretion and inflammatory response are all conducive to alleviating insulin resistance,[9,10] which is of great significance for increasing ovulation rate and pregnancy rate in women with PCOS.

Statins therapy is a new method for the treatment of PCOS. A large number of studies have exhibited that statins can not only reduce cholesterol biosynthesis, but also decrease androgen levels, restore ovarian function, inhibit the expression of inflammatory factors, and even have intrinsic antioxidant properties in PCOS patients.[11] For example, long-term simvastatin treatment for young women with PCOS was associated with significant decrease of testosterone, luteinizing hormone, follicle-stimulating hormone, total cholesterol, low-density lipoprotein and triglycerides, along with a clear improvement of ovarian dysfunction as well.[12] The results of study conducted by Sathyapalan et al illustrated that 12 weeks of atorvastatin therapy in PCOS patients resulted in a significant reduction in the adipose tissue dysfunction marker acylation stimulating protein and adipocyte inflammation markers (interleukin-6 and monocyte-chemoattractant-protein-1).[13] Several clinical studies have demonstrated that statins can improve insulin sensitivity in PCOS patients. In the research conducted by Kaya et al, atorvastatin treatment resulted in a significant reduction in the homeostasis model assessment of insulin resistance (HOMA-IR) index and fasting insulin, and had a noticeable effect on insulin sensitivity in patients with PCOS.[14] After 12 weeks of atorvastatin treatment, there was a significant reduction in insulin resistance as measured by HOMA-IR.[15] Simvastatin could reduce the activation of insulin and insulin-like growth factor-I signaling pathways in ovarian cells, alleviate ovarian hyperthecosis and inhibit the expression of steroidogenic enzymes, thereby promoting ovulation.[16]

Atorvastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, can reduce serum cholesterol and low-density lipoprotein levels by disturbing cholesterol biosynthesis in the liver, and may impair glucose homeostasis by inhibiting the secretion of insulin from pancreatic β cells.[17] Luotol et al pointed out that moderately elevated testosterone concentrations together with obesity-related inflammatory factors in PCOS patients could disrupt glucose homeostasis by increasing insulin resistance and early insulin secretion.[18] However, there are few studies on the effects of atorvastatin on blood sugar concentration and insulin level in PCOS patients, and there are some differences and controversies in the results of clinical trials. A study carried out by Raja-Khan et al revealed that insulin secretion increased during 6 weeks atorvastatin therapy (40 mg/d) in women with PCOS.[19] Puurunen et al demonstrated that 6-month atorvastatin therapy improved the lipid profile and alleviated chronic inflammation in women with PCOS, however, several parameters measuring insulin sensitivity and glucose tolerance worsened during atorvastatin therapy in these women.[20] In the present study, evidence-based medicine methodology was used to analyze the results of randomized controlled trials (RCTs) of atorvastatin in women with PCOS, the aim of this report was to explore the relationship between atorvastatin treatment and insulin resistance in PCOS patients.

2. Methods

2.1. Guidelines and search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[21] The electronic databases of PubMed, Web of Science, Google Scholar, Embase, Cochrane Library, Chinese BioMedical Database, Chinese National Knowledge Infrastructure Database and Wanfang Database were searched without language restrictions, from the earliest available date to August 1, 2020. The key terms used in this search were (polycystic ovary syndrome or polycystic ovarian syndrome or PCOS) and (atorvastatin or lipitor).

2.2. Study selection criteria

Studies were included if they met all eligibility criteria, stated as follows:

1. study types were RCTs.
2. Patients were clinically diagnosed with any stage of PCOS, and none of the patients received statin therapy in the past.
3. Patients in experimental group were treated with atorvastatin or atorvastatin combined with metformin, and patients in control group were correspondingly treated with placebo or placebo combined with metformin.
4. Data on changes in fasting glucose, fasting insulin, Homeostasis model assessment of insulin resistance (HOMA-IR) or body mass index (BMI) could be extracted,
5. A full-text publication was available.

The exclusion criteria included the following:

1. cross-over trials and quasi-randomized trials.
2. Trials with some deficiencies in data, or original data displayed as figures.
3. Participants had nonclassical 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease, androgen-secreting tumors, type 2 diabetic mellitus or pregnancy.
4. Patients had taken drugs affecting glucose tolerance, lipid metabolism, or steroid synthesis in the preceding 3 months before enrollment.
5. Participants suffered from contraindications to the use of atorvastatin.
6. Animal or basic experiments.

2.3. Data extraction

Data of the independent variables, including patient baseline characteristics, publication year, diagnostic criteria, drug intervention methods and study durations, were summarized independently by investigators from the included studies. The outcomes of interest included fasting glucose, fasting insulin, HOMA-IR, and BMI.

2.4. Quality assessment

The established Jadad scale was used to measure the methodological quality of included studies by the authors, 4 to 7 points

indicated high-quality trials, and 0 to 3 points indicated poor or low-quality trials.[22] The risk of bias within included studies was judged as low, unclear, or high by the Risk of Bias Tool from the Cochrane Collaboration.[23] In case of disagreements regarding the quality assessment, discussion was conducted until a consensus was reached.

2.5. Ethical approval

All the data in present meta-analysis were extracted from the previous published studies, no ethical approval or patient consent was required.

2.6. Statistical analysis

The weighted standardized mean difference (SMD) and 95% confidence intervals (95% CIs) were estimated for continuous data. Heterogeneity test was executed by Q test (a P value less than .10 indicated a problem with heterogeneity) and I^2 statistics (a I^2 value of at least 50% was taken as indicator of substantial heterogeneity).[24] When heterogeneity existed ($I^2 > 50\%$ and $P < .10$), the random-effect (RE) model was used for analysis, otherwise, the fixed-effect model was used for analysis.[25] The possibility of publication bias was tested by funnel plot. The influence of a single study on the overall pooled estimate was investigated by excluding 1 trial in each turn.[26] Subgroup analyses were also carried out based on the study duration ($\leq$3 months or 6 months). A P value less than .05 was judged as statistically significant. All statistical analysis were performed using RevMan 5.3 software.

3. Results

3.1. Description of included studies

The study selection process was plotted in Figure 1. Eighty three potentially relevant articles were identified from the initial searches, but only 9 studies[15,19,20,27–32] satisfying the inclusion

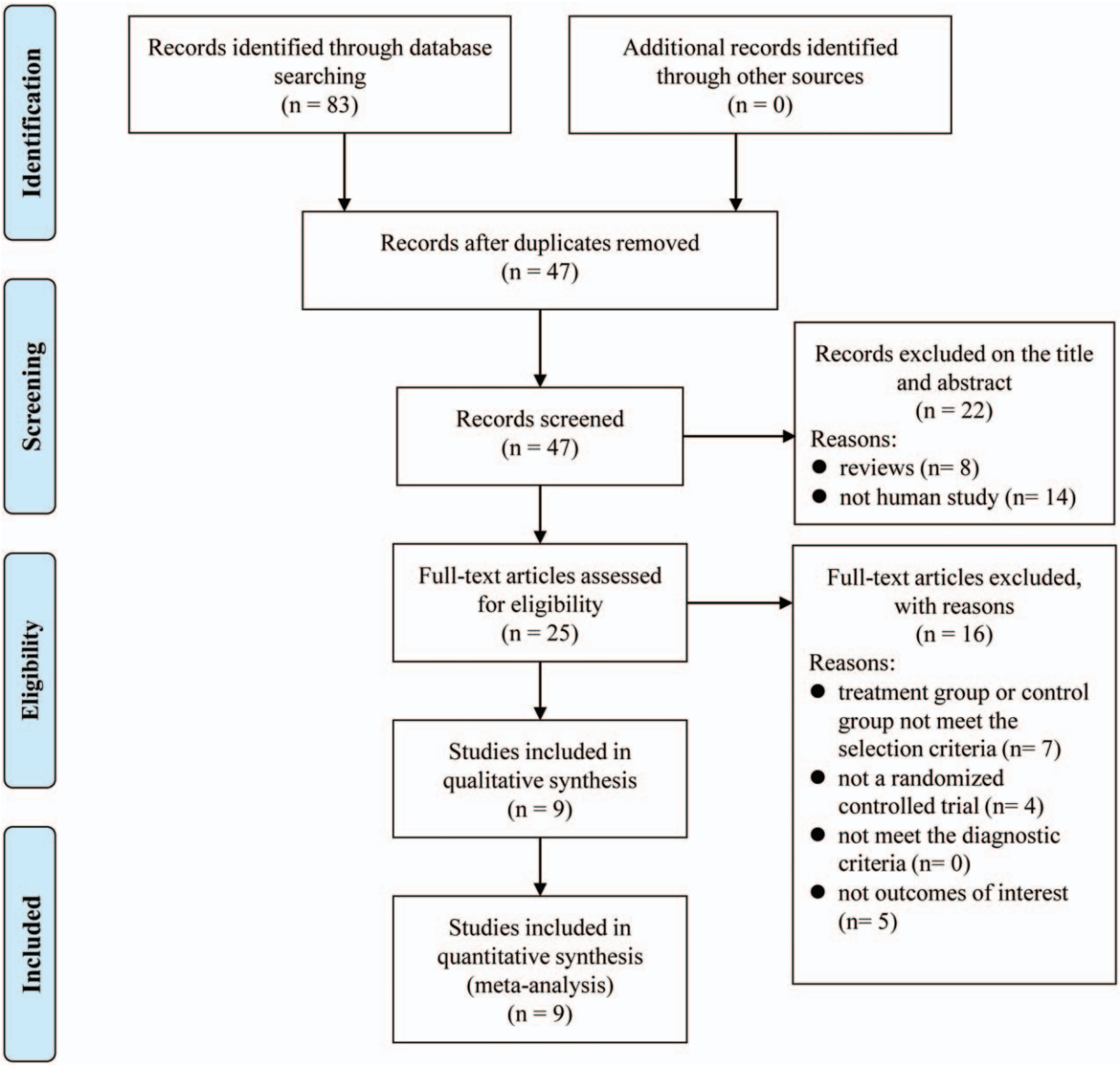

Figure 1. Flowchart of study selection in the meta-analysis.

Table 1

Characteristics of the studies included in the meta-analysis.

Study	Number atorvastatin group/ placebo group	Age (yr) atorvastatin group/ placebo group	Diagnostic criteria	Weight (kg) atorvastatin group/ placebo group	BMI (kg/m^2) atorvastatin group/ placebo group	Waist size (cm) atorvastatin group/ placebo group	Interventions		Study duration (months)	Outcomes	Quality
							atorvastatin group	placebo group			
Akbari M et al, 2016	20/20	27.7 ± 3.4/30.9 ± 4.8	the Rotterdam consensus	69.7 ± 9.2/66.7 ± 10.2	26.7 ± 3.6/26.3 ± 4.4	NR	atorvastatin 40 mg daily for 6 wks	placebo for 6 wks	1.5	fasting glucose, BMI	6
Jia XZ et al, 2015	25/25	18-35	the Rotterdam consensus	NR	29.8 ± 1.0/29.4 ± 1.1	NR	atorvastatin 20 mg daily for 3 mo	placebo for 3 mo	3	HOMA-IR, BMI	5
Puurunen J et al, 2013 d1	15/13	40.5 ± 5.9/38.5 ± 4.8	the Rotterdam consensus	NR	30.4 ± 8.6/26.7 ± 4.7	NR	atorvastatin 20 mg daily for 3 mo	placebo for 3 mo	3	fasting glucose, fasting insulin, BMI	7
Puurunen J et al, 2013 d2	15/13	40.5 ± 5.9/38.5 ± 4.8	the Rotterdam consensus	NR	30.4 ± 8.6/26.7 ± 4.7	NR	atorvastatin 20 mg daily for 6 months	placebo for 6 months	6	fasting glucose, fasting insulin, BMI	7
Raja-Khan N et al, 2011	9/11	33.8 ± 4.3/29.4 ± 5.8	the 1990 National Institutes of Health criteria	NR	40.1 ± 11.8/36.0 ± 10.4	NR	atorvastatin 40 mg daily for 6 wks	placebo for 6 wks	1.5	fasting glucose, fasting insulin, BMI	7
Sathyapalan T et al, 2009	19/18	26.6 ± 5.2/28.8 ± 7.6	the Rotterdam consensus	91.3 ± 14.8/93.1 ± 20.4	33.2 ± 6.1/33.9 ± 5.9	98.1 ± 14.0/99.3 ± 10.2	atorvastatin 20 mg daily for 3 months	placebo for 3 mo	3	fasting glucose, fasting insulin, HOMA-IR	7
Sathyapalan T et al, 2017	19/18	26.6 ± 5.2/28.8 ± 7.6	the Rotterdam consensus	91.3 ± 14.8/93.1 ± 20.4	33.2 ± 6.1/33.9 ± 5.9	98.1 ± 14.0/99.3 ± 10.2	atorvastatin 20 mg daily for 3 mo followed by metformin 1500 mg daily for 3 mo	placebo for 3 mo followed by metformin 1500 mg daily for 3 mo	6	fasting glucose, fasting insulin, HOMA-IR	7
Sun DW et al, 2013 d1	27/27	26.6 ± 1.2/28.8 ± 1.8	the Rotterdam consensus	81.3 ± 3.4/83.1 ± 4.8	29.2 ± 1.4/29.9 ± 1.5	90.1 ± 3.2/90.3 ± 2.4	atorvastatin 20 mg daily for 3 mo	placebo for 3 mo	3	fasting glucose, fasting insulin, HOMA-IR, BMI	6
Sun DW et al, 2013 d2	27/27	26.6 ± 1.2/28.8 ± 1.8	the Rotterdam consensus	81.3 ± 3.4/83.1 ± 4.8	29.2 ± 1.4/29.9 ± 1.5	90.1 ± 3.2/90.3 ± 2.4	atorvastatin 20 mg daily for 3 months followed by metformin 1500 mg daily for 3 m	placebo for 3 mo followed by metformin 1500 mg daily for 3 mo	6	fasting glucose, fasting insulin, HOMA-IR, BMI	6
Wang R et al, 2019	30/30	29.9 ± 4.9/29.8 ± 4.6	the Rotterdam consensus	81.4 ± 3.3/82.1 ± 3.4	29.1 ± 1.8/29.2 ± 1.7	90.3 ± 2.6/90.3 ± 2.5	atorvastatin 20 mg daily for 3 months followed by metformin 1500 mg daily for 3 mo	placebo for 3 mo followed by metformin 1500 mg daily for 3 mo	6	fasting glucose, fasting insulin, HOMA-IR, BMI	6
Zhao CE et al, 2019	40/40	29.1 ± 3.3/28.8 ± 3.1	the Rotterdam consensus	NR	29.5 ± 1.1/29.8 ± 1.2	NR	atorvastatin 20 mg daily for 3 mo	placebo for 3 mo	3	fasting glucose, fasting insulin, HOMA-IR, BMI	6

BMI = body mass index, d1, d2 = different study duration, HOMA-IR = homeostasis model assessment of insulin resistance, NR = not report.
Quality was assessed by the established Jadad scale and 4–7 points implied high-quality trials.
Data are presented as mean ± SD.

and exclusion criteria were selected for this systematic review and meta-analysis. The key characteristics of the nine RCTs and Jadad scores were given in Table 1. Two hundred four PCOS patients were included in the atorvastatin therapy group and 202 PCOS patients were included in the placebo group. The diagnosis of PCOS was based on criteria of the Rotterdam consensus except 1 study.[19] The maintenance doses of atorvastatin were 20 or 40 mg/day. PCOS patients in 2 studies[19,31] received atorvastatin 40 mg/day for 6 weeks. The treatment durations varied from 6 weeks to 6 months. Only 4 studies[15,28,29,32] reported the waist circumference. The weight value was not available in 4 studies.[19,20,27,30] All studies with 5 or larger points were of high quality.

3.2. Risk of bias

The risk of individual study bias was presented in Figure 2, 4 articles showed low risk of bias,[15,19,20,32] and 5 articles showed unclear risk of bias.[27–31] As shown in Figure 3, the funnel shape according to the fasting glucose concentration was almost symmetrical, which also indicated that there was no potential publication bias.

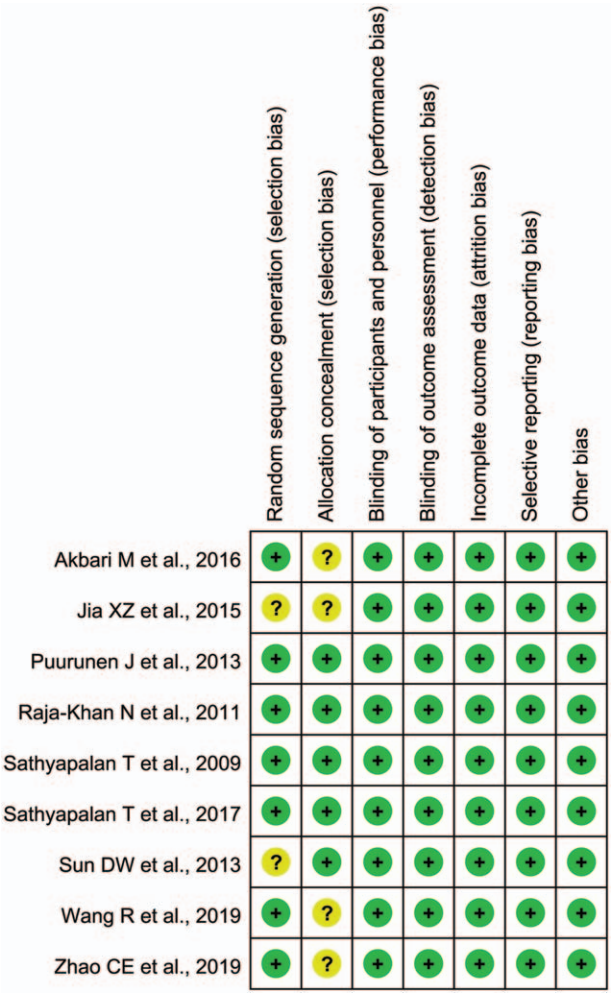

Figure 2. Risk of bias within included studies.

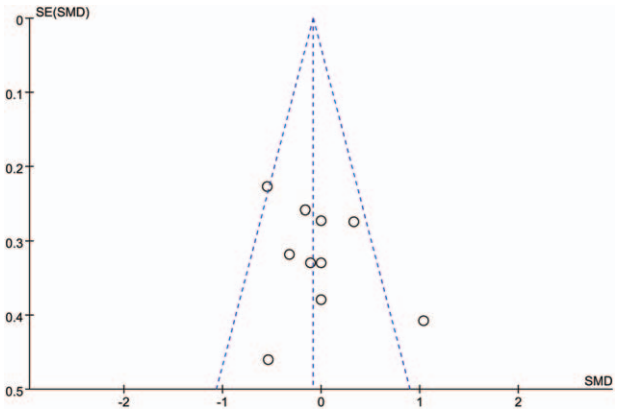

Figure 3. Funnel plot for estimation of potential publication bias.

3.3. Fasting glucose concentration

Eight trials[15,19,20,27–29,31,32] involving a total of 356 patients measured the fasting glucose concentration (179 receiving atorvastatin therapy and 177 receiving placebo). As shown in Figure 4A, the RE model was used because significant heterogeneity between studies for the 2 groups was observed ($P = .07$, $I^2 = 43\%$). Compared with placebo, atorvastatin therapy did not reduce the fasting glucose concentration in PCOS patients dramatically (SMD -0.06, 95% CI -0.31 to 0.20, $P = .66$). On sensitivity analyses, we found the I^2 value ranged from 0% to 50% and the Z value for overall effect ranged from 0.16 to 1.53, which indicated the result was not robust.

3.4. Fasting insulin level

Seven trials[15,19,20,27–29,32] involving 316 patients evaluated the fasting insulin level. As shown in Figure 4B, the RE model was used because statistical heterogeneity for this variable was significant ($P < .00001$, $I^2 = 96\%$). Compared with placebo, atorvastatin therapy decreased fasting insulin level obviously (SMD -1.84, 95% CI -3.06 to -0.62, $P = .003$). On sensitivity analyses, we found the I^2 value ranged from 95% to 96%, and the Z value for overall effect ranged from 2.43 to 3.19, which implied the result was very stable.

3.5. HOMA-IR

Six trials[15,27–30,32] involving 318 patients assessed the HOMA-IR. As shown in Figure 5A, the RE model was used because significant heterogeneity between studies for the 2 groups was observed ($P < .00001$, $I^2 = 97\%$). PCOS patients in atorvastatin therapy group had lower HOMA-IR value than those in placebo group (SMD −4.12, 95% CI −6.00 to -2.23, $P < .0001$). The sensitivity analyses showed that the I^2 value was 97% unchangeably and the Z value for overall effect ranged from 3.97 to 4.27, which suggested the result was very robust.

3.6. BMI value

Seven trials[19,20,27–31] involving 332 patients measured the BMI. As shown in Figure 5B, the fixed-effect model was used because insignificant heterogeneity between studies for the two groups

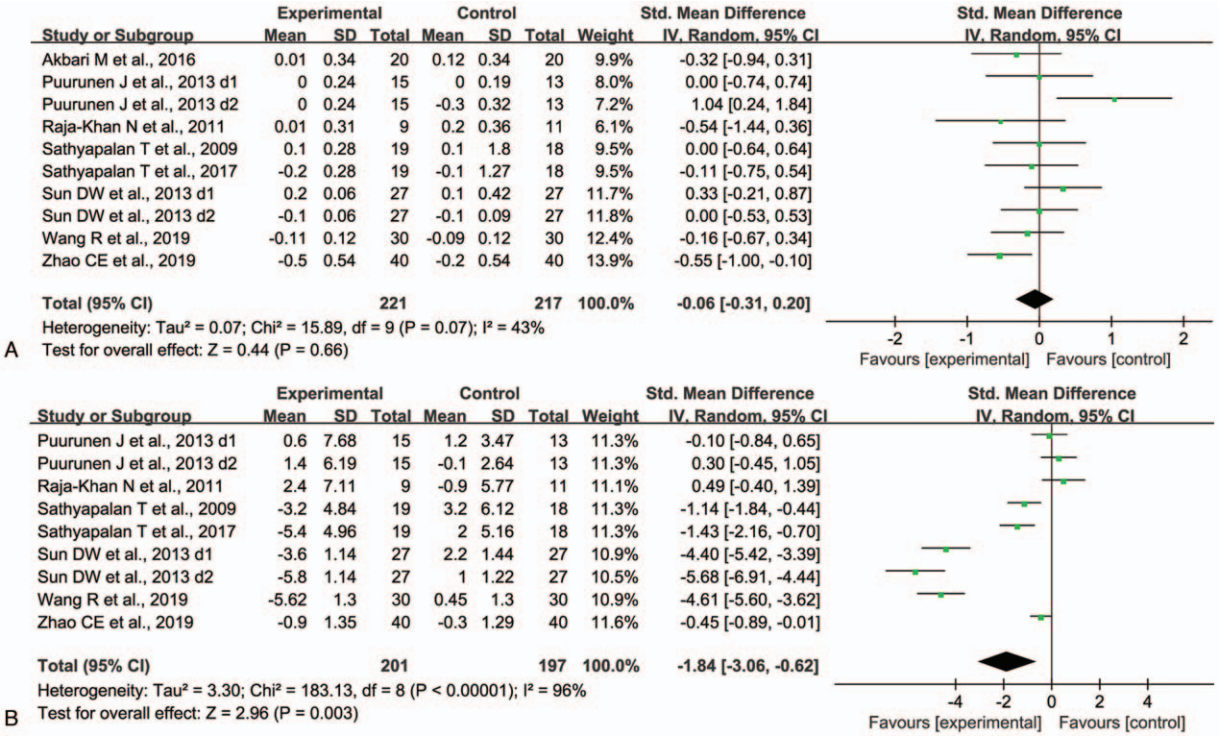

Figure 4. Comparison of atorvastatin therapy and placebo in the fasting glucose concentration (A) and fasting insulin level (B) for women with polycystic ovary syndrome.

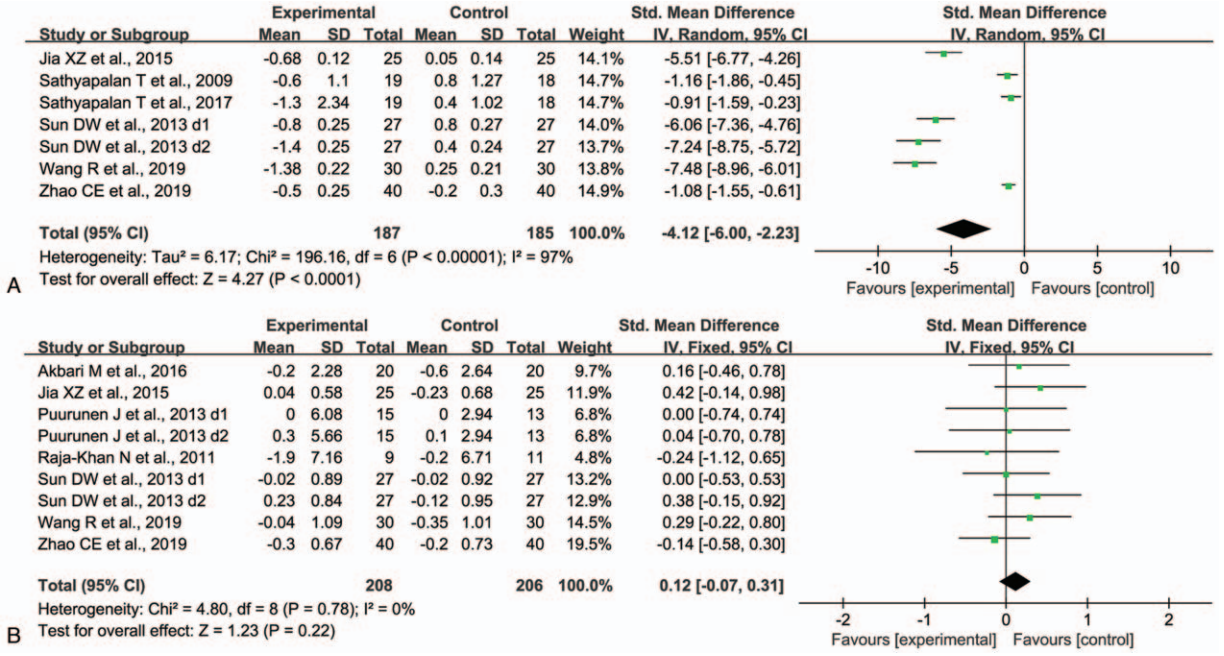

Figure 5. Comparison of atorvastatin therapy and placebo in the HOMA-IR (A) and BMI value (B) for women with polycystic ovary syndrome. BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance.

Table 2

Subgroup analyses according to the study duration by meta-analysis.

Study duration	No. of patients				SMD (95% CI)				I^2 (%)				*P* value			
	①	②	③	④	①	②	③	④	①	②	③	④	①	②	③	④
≤3 mo	259	219	221	272	−0.19 (−0.43, 0.06)	−1.08 (−2.35, 0.18)	−3.37 (−5.59, −1.16)	0.04 (−0.20, 0.28)	32	94	97	0	0.14	0.09	0.003	0.74
6 mo	179	179	151	142	0.12 (−0.33, 0.58)	−2.82 (−5.38, −0.26)	−5.18 (−10.10, −0.25)	0.28 (−0.05, 0.61)	56	97	98	0	0.59	0.03	0.04	0.10

BMI = body mass index, CI = confidence interval, ① = fasting glucose, ② = fasting insulin, ③ = HOMA-IR, ④ = BMI, HOMA-IR = homeostasis model assessment of insulin resistance, SMD = standardized mean difference.

was observed ($P=.78$, $I^2=0\%$). The BMI value showed insignificant decrease in the atorvastatin group compared to placebo group (SMD 0.12, 95% CI −0.07 to 0.31, $P=.22$). On sensitivity analyses, we found that the I^2 value remained constant at 0% and the Z value for overall effect ranged from 0.77 to 1.68, which indicated the result was very robust.

3.7. Subgroup analyses

As shown in Table 2, the differences of fasting glucose concentration or BMI value between atorvastatin group and placebo group in 2 subgroups were all insignificant ($P>.05$). Atorvastatin therapy decreased fasting insulin level significantly in 6 months subgroup ($P=.03$), but not in ≤3 months subgroup ($P=.09$). The HOMA-IR benefits were observed in 2 subgroups ($P<.05$).

4. Discussion

Typical characteristics of PCOS include elevated androgen levels, anovulation, irregular menstruation, insulin resistance, dyslipidemia, vascular endothelial dysfunction, and polycystic ovary morphology. It has been reported that the risk of type 2 diabetes, metabolic syndrome and cardiovascular diseases in PCOS patients is significantly higher than that of healthy people. Abnormal increase in androgen levels is not the main cause of insulin resistance. Insulin resistance may be correlated with the oxidative stress-mediated serine phosphorylation of the insulin receptor and its substrate protein. Insulin receptors are difficult to bind to the serine-phosphorylated substrate molecule, which hinders the transmission of insulin receptor signaling. The targeted physiological activity cannot be initiated, and glucose transport is inhibited, thereby leading to the occurrence of insulin resistance.[33]

In the current work, we revealed that atorvastatin therapy had no dominant effects on fasting glucose level and BMI value, but it could dramatically lower fasting insulin level and HOMA-IR value in women with PCOS. In the case of constant fasting blood glucose level, insulin sensitivity increased with the decrease of fasting insulin level. The results of this study suggested that atorvastatin could significantly improve insulin sensitivity or reduce insulin resistance in PCOS patients. This may be due to the fact that atorvastatin can selectively inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase and down-regulate the mevalonate pathway, which is closely associated with insulin resistance. In regard to risk of bias, 2 trials did not describe a specific method of random sequence generation, including random number table, computer random number generator or coin toss random sampling. Four trials did not illuminate an adequate method of allocation concealment, such as sequentially opaque, sealed envelopes, serially-numbered identical drug containers, centralized or pharmacy-controlled randomization. In addition, we executed subgroup and sensitivity analyses in order to minimize the influence of a particular study or an inferior study design. Study duration was not the influencing factor of HOMA-IR, fasting glucose concentration and BMI in the atorvastatin treatment of PCOS patients.

The age of onset of PCOS is early. Obesity and glycolipid metabolism disorder can appear in the early stages of this disease. Measures to protect pancreatic β cells and cardiovascular function by inhibiting the development of inflammatory and oxidative stress in the body should be initiated as soon as possible. Patients with indications of statin therapy, such as high low-density lipoprotein, obesity, cardiovascular or cerebrovascular diseases, especially need to receive statins treatment in time regardless of the patient's age after the failure of lifestyle intervention.

In conclusion, atorvastatin therapy can significantly reduce the fasting insulin level and HOMA-IR value of PCOS patients, indicating that atorvastatin has the effect of ameliorating insulin resistance in women with PCOS. However, the shortcomings of this meta-analysis mainly include the small sample size of trials, and the failure to conduct long-term follow-up. Therefore, more large-sample, multi-center, well-designed RCTs are needed to implement to further ascertain this conclusion.

Author contributions

Investigation: Lin-Lin Chen, Jian-hong Zheng.
Methodology: Lin-Lin Chen, Jian-Hong Zheng.
Writing – original draft: Lin-Lin Chen.
Writing – review & editing: Jian-Hong Zheng.

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