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Short period-administration of myo-inositol and metformin on hormonal and glycolipid profiles in patients with polycystic ovary syndrome: a systematic review and updated meta-analysis of randomized controlled trials

J.-Q. ZHANG, C. XING, B. HE

Department of Endocrinology, Shengjing Hospital, China Medical University, Shenyang, Liaoning province, PR China

Abstract. – OBJECTIVE: This meta-analysis aims to perform an updated meta-analysis to evaluate myo-inositol (myo-ins) and the classical insulin sensitizer metformin in terms of efficacy and safety for treating women with polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS: A comprehensive literature search was performed using PubMed, Web of Science, EMBASE, Cochrane Library, PhRMA Clinical Study Results, Wan Fang, and CNKI databases; the database was searched from inception to June 2021. The random effects model was chosen to synthesize the effect sizes of individual trails. The registration number is CRD42021239786.

RESULTS: Nine randomized controlled trials (RCTs) and 612 patients were included in the analysis. Compared with metformin, myo-ins might be more effective in lowering triglycerides (TG) levels (SMD -0.49, 95% CI -0.74 to -0.24, p=0.0001, I^2 = 0%) and avoiding side effects (RR=0.14, 95% CI 0.08-0.24, p<0.00001, I^2 = 2%), while no significant differences were observed in other relevant indexes, such as total testosterone (TT) and sex-hormone binding globulin (SHBG).

CONCLUSIONS: Compared with metformin, the suitable supplemental dosage of myo-ins may be helpful in lowering levels of TG and avoiding adverse events (AEs).

Key Words:
Myo-inositol, Metformin, Polycystic ovary syndrome, Insulin resistance, Meta-analysis.

Introduction

Polycystic ovary syndrome (PCOS), which is associated with hyperinsulinemia, hyperandrogenemia, impaired glucose metabolism and aberrant adipokines production from the adipose tissue, is a heterogeneous reproductive and endocrine disorder[1-3]. The clear diagnosis of PCOS is challenging due to the heterogeneity and variability of clinical symptoms, since three diagnosis criteria have been proposed (i.e., Rotterdam's criteria in 2003, Androgen Excess Society in 2009, National Institute of Health consensus in 2012)[4,5]. According to those arrangements, the diagnosis should be based on a combination of at least two of the following three clinical features: chronic oligo-anovulation, hyperandrogenism (clinical and/or biochemical) and polycystic ovarian morphology[6]. Despite the diagnosis criteria do not include any metabolic parameters, insulin resistance, hyperinsulinemia and dyslipidemia are presented in a large number of PCOS women, leading to the rationale of using insulin sensitizers to treat the syndrome[5,7,8].

Currently, metformin, a classical and common insulin sensitizer that can reduce both hyperinsulinemia and hyperandrogenemia, is widely used for patients with PCOS[9]. Many studies[10,11] have suggested that metformin administration can have positive effects on peripheral insulin sensitivity in both normal-weight and overweight PCOS patients. Evidence[12-14] for improving lipid metabolism by metformin has been accumulated in the management of obesity and PCOS. Nevertheless, several adverse effects (AEs), such as gastrointestinal discomfort including nausea, bloating, and vomiting, cannot be ignored[15].

Inositol, particularly the most common one, myo-inositol (myo-ins), is effective in improving insulin resistance and hyperandrogenemia in PCOS patients[5]. It was found that myo-ins are

Corresponding Author: Bing He, MD; e-mail: hebing7557@163.com

able to ameliorate insulin resistance. Besides, the role they play in lipid metabolism *via* regulating various adipokine is predominant[16,17]. Moreover, some scholars[18] reported almost no AEs of inositol, especially myo-ins, rather than other isomers such as D-chiro-inositol (D-chiro-ins). Large doses of D-chiro-ins (>1200 mg/d) should be used with caution, since its toxicity for ovarian histology and function[19].

Hence, we performed a meta-analysis to compare myo-ins with metformin by reviewing the latest literature. The results may help physicians provide adequate treatment for patients with PCOS.

Materials and Methods

Search Strategy

We searched PubMed, Web of Science, EMBASE, the Cochrane Library, the PhRMA Clinical Study Results Database (www.clinicaltrials.gov), the Wan Fang database, and the China National Knowledge Infrastructure (CNKI) database, with time restrictions from the inception of these databases to June 2021. In addition, the search strategy also targeted unpublished studies to help minimize the risk of missing unpublished trials. We used different combinations of the following search terms: "polycystic ovary syndrome," "PCOS," "metformin," "inositol*," and "myo-inositol,". It was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021239786; https://www.crd.york.ac.uk/PROSPERO/).

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Research type: Randomized controlled trials (RCTs), regardless of whether the blind method is used.
2. Research object: Patients with PCOS, with no limits of ethnicity and duration, were diagnosed according to the Rotterdam criteria ["Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)," 2004][20] or the Androgen Excess Society (AES) criteria[21].
3. Intervention: Experimental group: given myo-ins; Control group: given metformin. Other adjunctive drugs (excluding folic acids) were maintained consistently between the two groups.

Exclusion Criteria

1. Women who give birth during the study period.
2. Duplicated studies.
3. Studies published in languages other than English or Chinese were excluded.
4. Outcomes include missing data or without outcomes of interest.

Outcomes of Interests

For each outcome variable, the comparisons were planned *a-priori*. Outcomes were divided into four groups: (1) androgen-associated outcomes, including total testosterone (TT), androstenedione (AND), dehydroepiandrosterone sulfate (DHEA-S) and sex hormone-binding globulin (SHBG); (2) body fat outcomes, including body mass index (BMI) and waist-hip ratio (WHR); (3) glucose metabolism and lipid metabolism outcomes, including fasting insulin level (FINS), fasting blood glucose levels (FBG), homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and (4) adverse effects (AEs).

Data Extraction

All the articles were downloaded into Endnote version 9 and independently screened and cross-checked by two investigators (Z.J.Q. and X.C.). The screening process were against the inclusion criteria initially by title and abstract, and subsequently by full text. If a consensus was not reached during these processes, a third investigator (H.B.) would arbitrate. Descriptive information was collected for each study, containing age, diagnostic criteria, BMI, intervention measures, experimental duration, and efficiency outcomes.

Assessment of Risk of Bias

Two researchers (Z.J.Q. and X.C.) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's "Risk of bias" tool[22] and extracted information with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Each dimension containing at least one item, was used to determine "low risk," "high risk," and "unclear risk" of bias. Where a difference of opinion arose between reviewers, they were resolved through discussion with a third author (H.B.).

Statistical Analysis

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23], a meta-analysis was designed. The present analysis was performed using Revman 5.3 software, Version 5.3. Continuous data were summarized as standardized mean differences (SMD) with 95% confidence intervals (CI), and dichotomous data as risk ratio (RR), with an α error of 0.05[24]. The random-effects method was applied to pool the data when heterogeneity existed. Meanwhile, if the number of included trials was greater than 10, funnel plots and Egger's test were employed for publication bias analysis.

Results

Literature Identification

The literature search yielded 111 publications, and 83 records left after removing duplicates. Immediately after, 11 records were included after screening title and abstract, and 72 records were filtered out for causes of unrelated studies (n=45), non-RCT trials (n=13), unable to meet the inclusion criteria (n=15). At last, totally 9 studies[25-33] and 612 PCOS patients involving 306 patients in experimental group and 306 patients in control group were included. The inclusion and exclusion criteria were strictly followed in the process of literature screening, and the flow of this screening process was presented in a PRISMA flow diagram (Figure 1). The basic clinical information containing diagnostic criteria, age, BMI, intervention measures, experimental duration and efficiency outcomes of patients were collected and summarized in Table I.

Quality Assessment

The random number table or the computer random number generator being used in most of the studies were clearly stated, but the concealment of allocation process was unclear for most of the studies included. Though four of the studies[26,30,32,33] were open-labeled without blinding,

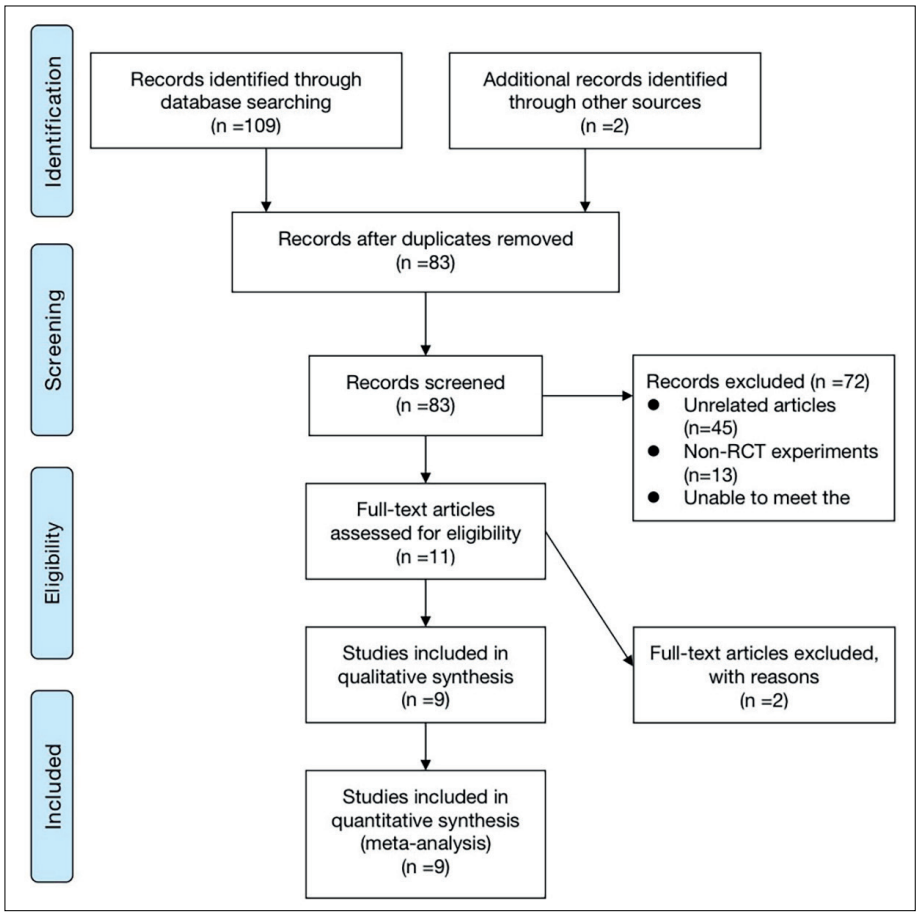

Figure 1. Flow diagram of searching and diagram selection.

Table I. The characteristics of the included studies.

Study	Country	Sample size		Intervention			Mean age (years)		Mean BMI (baseline)		
		Trial group	Control group	Trial group	Control group	Relevant outcomes	Trial group	Control group	Trial group	Control group	Duration
Fruzzetti et al[25]	Italy	24	22	myo-ins 4 g, Folic acid 40 mcg q.d.	Metformin 500 mg t.i.d	1, 13,1 6	21.6 ± 6.6	22.3 ± 6.0	27.3 ± 4.5	28.4 ± 5.2	6
Jamilian et al[26]	Iran	30	30	myo-ins 2 g, olic acid 200 µg b.i.d	Metformin 500 mg t.i.d	1, 4, 5, 6	27.7 ± 5.2	25.9 ± 4.8	27.1 ± 6.4	25.8 ± 3.8	3
Pourghasem et al[27]	Germany	50	50	myo-ins 2g, Folic acid 200 µg b.i.d	Metformin 1500 mg, Folic acid 200 µg q.d.	11, 14	31.08 ± 3.31	31.06 ± 1.11	29.79 ± 3.58	27.84 ± 3.68	3
Raffone et al[28]	Italy	60	60	myo-ins 4 g, Folic acid 400 µg q.d.	Metformin 1500 mg q.d.	14	29.1 ± 5.6	29.7 ± 6	25 ± 2.1	24.9 ± 2.7	6
Shokrpour et al[29]	Iran	26	27	myo-ins 2 g, Folic acid 200 µg b.i.d	Metformin 500 mg t.i.d	1, 7, 8, 9, 10, 11, 12, 13	28.3 ± 4.9	27.7 ± 3.2	28.1 ± 3.1	27.3 ± 3.3	3
Tagliaferri et al[30]	Italy	16	17	myo-ins 1000 mg b.i.d	Metformin 850 mg b.i.d	6, 14	25.62 ± 4.7	NA	32.55 ± 5.67	NA	6
Angik et al[31]	India	50	50	myo-ins 1 g b.i.d	Metformin 500 mg b.i.d	1, 3, 4, 11, 12, 13, 15, 1614	15-40	NA	24.1±4.13	23.23±2.65	6
Nehra et al[32]	India	30	30	myo-ins s 1 g b.i.d	Metformin 500 mg t.i.d	1, 4, 7, 8, 9, 10, 11, 12 ,13	23.8 ± 0.69	23.26 ± 1.03	26.45 ± 0.41	26.09 ± 0.76	6
Musacchio et al[33]	Italy	20	20	myo-ins 1.5 g b.i.d	Metformin 850 mg t.i.d	1, 3, 4, 6, 7, 8, 9, 10, 11, 12 ,13, 14	24-32	24-32	28.8 ± 0.7	26.2 ± 0.5	6

Outcomes of interest: 1. Body mass index (BMI); 2. Waist-Hip Ratio (WHR); 3. Androstenedione (AND; 4. Total Testosterone (TT); 5. Dehydroepiandrosterone sulfate (DHEA-S); 6. Sex-hormone binding globulin (SHBG); 7. Total cholesterol (TC); 8. Triglycerides (TG); 9. High-density lipoprotein cholesterol (HDL-C); 10. Low-density lipoprotein cholesterol (LDL-C); 11. Fasting blood glucose level (FBG); 12. Fasting insulin level (FINS); 13. Homeostatic model assessment of insulin resistance (HOMA-IR); 14. Adverse events (AEs).
Notes: myo-inositol (myo-ins); body mass index (BMI).

the laboratory results were objective and unlikely to be affected by the researcher's knowledge of the patients. The loss rate of the including studies ranged from 0% to 20%.

Impact on Androgen-Associated Hormones

TT was measured in five studies with 294 patients[26,30-33]. No significant differences were observed between myo-ins and metformin (SMD 0.16, 95% CI -0.56 to 0.88, p=0.66) (Figure 2).

SHBG production was observed in 133 patients from three studies[26,30,33]. No significant differences were observed between myo-ins and metformin (SMD -2.46, 95% CI -5.22 to 0.30, p=0.08) (Figure 2).

Impact on Body Fat

BMI was reported in seven studies[25,26,29-33] involving 393 participants. No significant differences were observed between myo-ins and metformin (SMD 0.43, 95% CI -0.19 to 1.05, p=0.17) (Figure 2).

WHR was calculated in three studies with 194 participants[30-32]. However, comparison with metformin resulted in no significant differences among groups (SMD 0.02, 95% CI -1.08 to 1.12, p =0.97) (Figure 2).

Impact on Glucose Metabolism and Lipid Metabolism Parameters

FINS was reported in four studies with 253 patients[29,31-33]. However, the forest plot showed no significant differences (SMD -0.07, 95% CI -0.37 to 0.24, p=0.66) (Figure 2).

FBG of 353 patients in five studies was recorded[27,29,31-33]. No significant differences were observed between myo-ins and metformin (SMD -0.06, 95% CI -0.53 to 0.41, p=0.80) (Figure 2).

Five studies[25,29,31-33] with 299 patients mentioned HOMA-IR. No significant differences were observed between myo-ins and metformin (SMD -0.03, 95% CI -0.54 to 0.48, p=0.90) (Figure 3).

TG was analyzed in 255 patients from four studies[27,29,32,33]. The results of the forest plot showed that myo-ins could lower the TG levels (SMD -0.49, 95% CI -0.74 to -0.24, p=0.0001) when compared with metformin (Figure 3).

TC measurements in 153 patients from three studies[29,32,33] were reported. No significant differences were observed between myo-ins and metformin (SMD 0.36, 95% CI -0.30 to 1.01, p=0.28) (Figure 3).

HDL-C was reported in 153 patients from three studies[29,32,33]. However, the forest plot showed no significant differences (SMD 0.33,95% CI -1.77 to 2.44, p=0.76) (Figure 3).

LDL-C was measured in 153 patients in three studies[29,32,33]. However, the forest plot showed no significant differences (SMD 0.34, 95% CI -0.26 to 0.94, p=0.26) (Figure 3).

Adverse Effects

AEs were noted in 439 patients in six studies[25,27,28,30,31,33]. Most people had no adverse reactions under the treatment of myo-ins; however, participants in the metformin group experienced several AEs, such as lactic acidosis, weakness, and gastrointestinal symptoms (RR=0.14, 95% CI 0.08–0.25, p<0.00001) (Figure 3).

Discussion

Metformin is one of the most widely used insulin sensitizers for regulating metabolic and endocrine disorders caused by PCOS. Inositol (known as the second messenger of insulin in human bodies) is presented in the form of phosphoinositol in cells. It plays a crucial role in maintaining cell shapes, regulating and controlling metabolism, and in signal transduction. Since inositol is endogenous, side effects are rarely reported[34].

Myo-ins (99%) forms the vast majority of inositol in cells, and D-chiro-ins is transformed from myo-ins through an epimerase, which is stimulated by insulin[35]. Each organ can regulate the intracellular balance of inositol levels and has a tissue-specific intracellular myo-ins to D-chiro-ins ratio that modulates metabolic processes; thus, disorders such as PCOS, obesity, and metabolic syndrome occur partly due to a ratio imbalance[5,36,37]. For instance, myo-ins has a relatively higher proportion in organs participating in cellular glucose uptake like the ovaries, normally at a physiological ratio of 40:1, and yet, the ratio in women with PCOS is only 0.2:1[38,39]. Once the balance is disturbed, the concentration of myo-ins in follicular fluid decreases and has detrimental effects on the content of myo-ins-inositolphosphoglycans, leading to a worse oocyte quality in PCOS patients[5,6,35,40]. Thus, exogenous supplementation of myo-ins in PCOS patients has attracted an increasing attention owing to its effectiveness against insulin resistance and dyslipidemia[41].

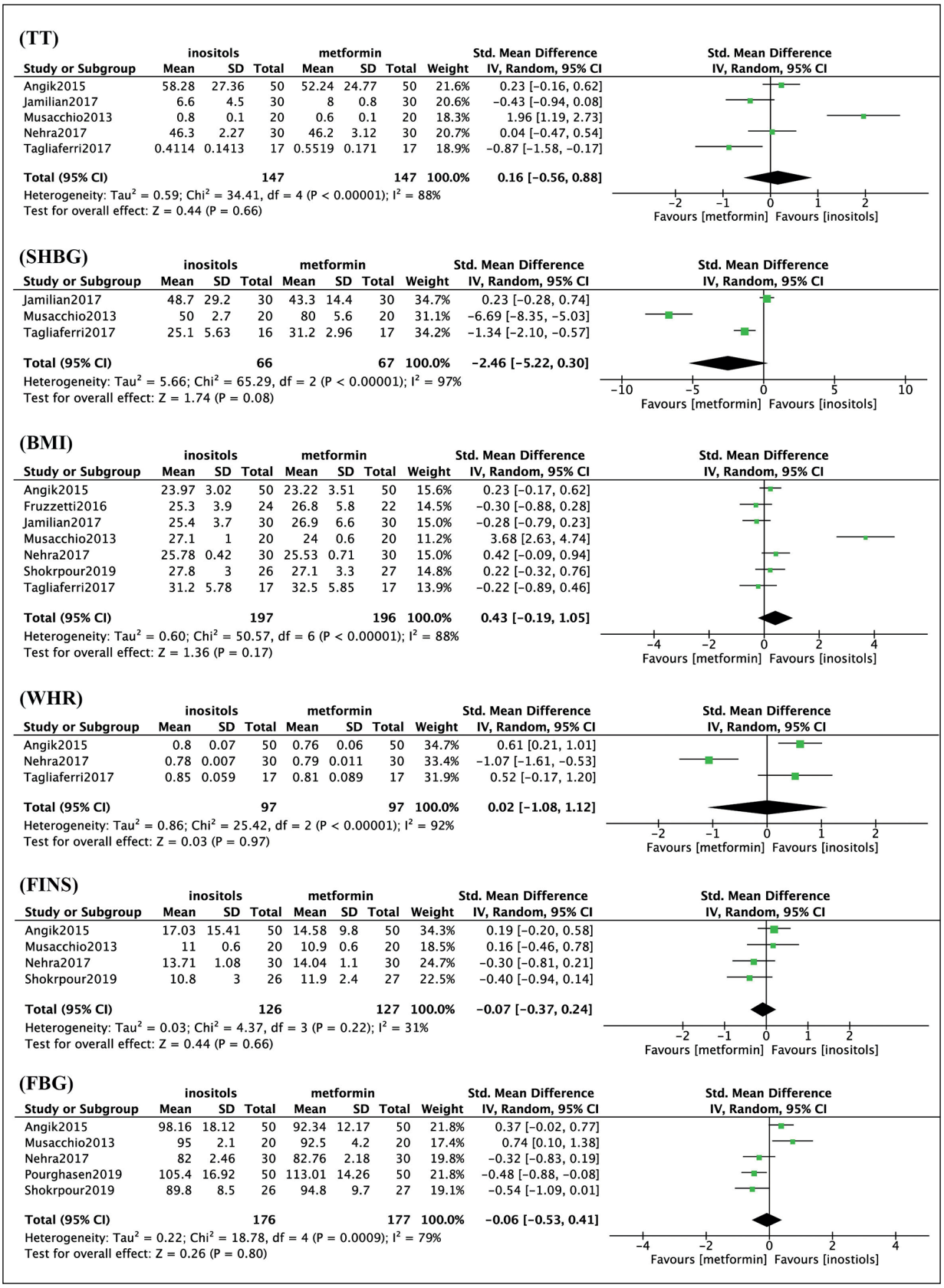

Figure 2. Results of meta-analysis.

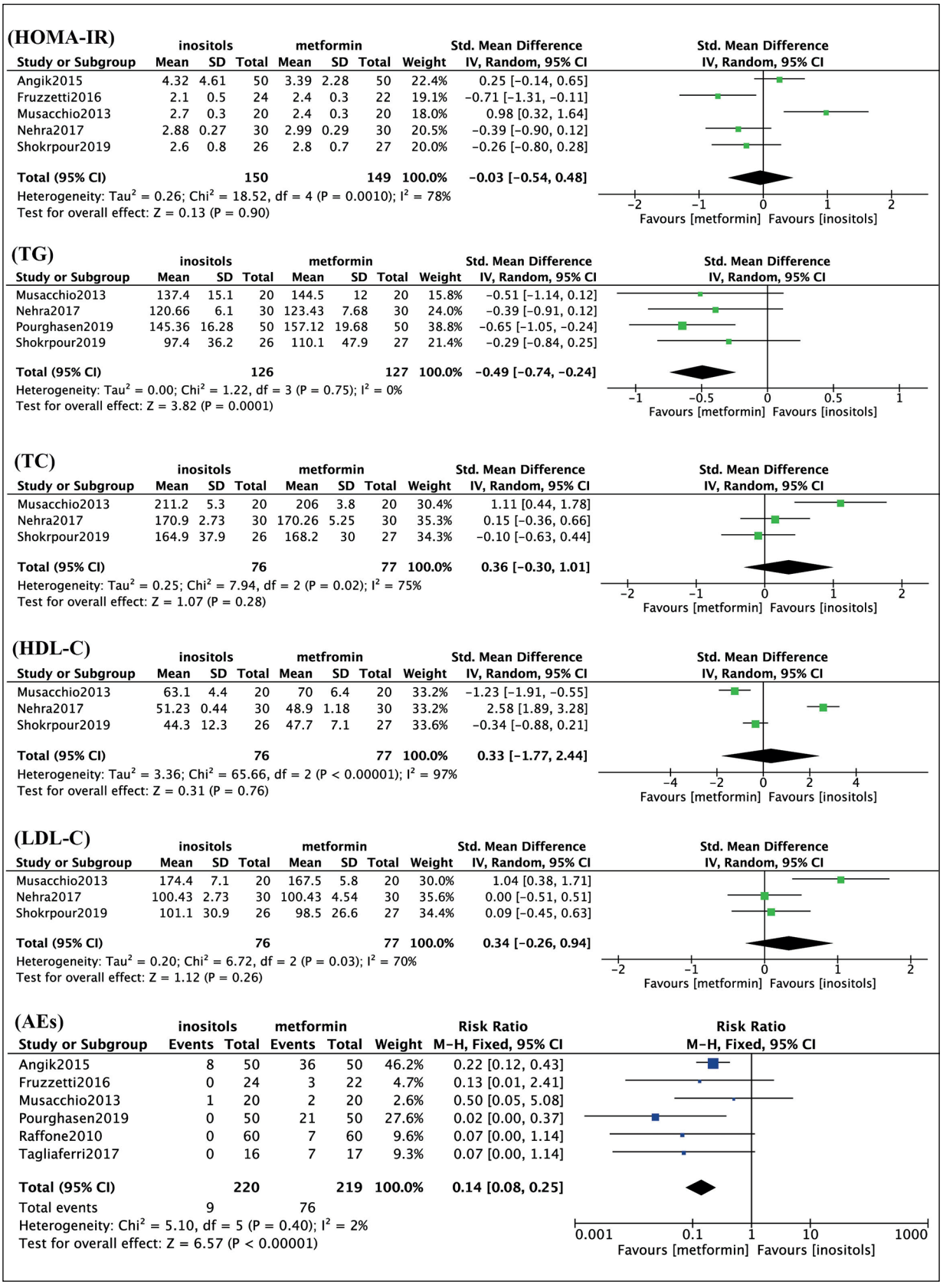

Figure 3. Results of meta-analysis.

We performed this meta-analysis to explore the endocrine metabolic differences between myo-ins and metformin of 9 studies involving 612 women with PCOS. Our results revealed that myo-ins may have more advantages on lowering TG when compared with metformin, and the side effects of metformin were also avoided. Other related indicators, such as TT, FBG, FINS and HOMA-IR, showed no significant differences in the present analysis. Facchinetti et al[18] compared myo-ins with metformin in 355 patients and reported seven parameters, nevertheless, despite AEs, no other significant differences were noted. Kutenaei et al[42] compared myo-ins with metformin in 638 patients and analyzed fourteen items, and it indicated that myo-ins may be beneficial in PCOS women with hyperandrogenism, as well as pregnancy outcomes. So far, no meta-analysis has focused on its efficacy in lipid metabolism.

Metformin can reduce androgen secretion from ovary and adrenal glands of PCOS women while stimulating SHBG production, modulating luteinizing hormone discharge, and attenuating the ovarian androgen response to gonadotropin stimulation by reducing circulating insulin and androgen levels[43,44]. Inositol can slow down the increased androgen concentrations in PCOS by balancing the myo-ins to D-chiro-ins ratio[45]. The ratio disturbances of myo-ins and D-chiro-ins in ovaries lead to an androgen-excess environment and insulin resistance, inhibiting the hepatic production of SHBG and increasing FT[46]. Regretfully, androgen-associated indexes like TT and SHBG could not be improved through myo-ins supplementation when compared to metformin in this analysis. Only two studies examined DHEA-S and AND, thus no synthesis or meta-analysis could be performed. Because of the limitation of measurement technology, it is often difficult to accurately determine the concentration of FT; therefore, the free testosterone index is often preferred to evaluate the level of active androgen production *in vivo*[47]. Unfortunately, only one of the included trials conducted investigations on it[31], and it showed the efficacy of myo-ins is better than metformin.

For the indicators related to body fat as well as glycolipid metabolism, myo-ins and metformin have the same effects on BMI and WHR. For the parameters related to glucose metabolism, none of the relevant outcomes showed significant differences between myo-ins and metformin, particularly HOMA-IR and FINS, two more accurate indexes of insulin resistance, with no significant differences appeared in this meta-analysis. For lipid metabolism parameters, such as TG, this is the first report on a significant difference observed when compared with metformin.

In terms of AEs, metformin can be associated with unwanted adverse effects like gastrointestinal disturbances, while most people had no adverse reactions after inositol administration, which was consistent with the meta-analysis by Facchinetti et al[18]. Nevertheless, in Angik et al[31] experiment, negative side effects were observed in eight patients who were under the intervention condition of myo-ins, with dosages of 1g twice daily; one had nausea, and the other seven had menorrhagia. In Musacchio et al[33] experiment, negative side effects were observed in only one patient with diarrhea by the use of myo-ins with dosages of 1.5 g twice daily.

Actually, in spite of myo-ins, D-chiro-ins has been proposed to correct defective insulin function in a variety of conditions characterized by metabolic dysfunction, such as PCOS[47]. Distinct from myo-ins, Unfer et al[6] demonstrated that supplementing high dosages of D-chiro-ins alone may be an unrecommendable choice for its toxicity on ovaries and may cause the deficiency of myo-ins. Exactly, the short-term administration (30 days) of 1200 mg/die D-chiro-ins in PCOS women should be avoided[48]. Consequently, treatment decisions of large amounts of D-chiro-ins have to be carefully evaluated in the clinic.

Heterogeneity, Study Strength and Limitations

There are multiple explanations for the high heterogeneity. First, the nationality, and the basic BMI of included patients were identified as the major factors resulting in heterogeneity. Second, the different duration of the treatment, the different dosages of myo-ins, potentially different phenotypes according to differ diagnosis criteria, leading to a heterogeneity of the partial results.

The study still had several bias and limitations. First, the trial sample size was relatively small, and the study treatment period was comparatively short. Second, some of these trials did not use double-blinding, thus causing an inevitable recall bias. Additionally, the criteria for various traits were not uniform meaning that different phenotypes (in this analysis, except for only one study[29] meet the AES criteria, all of the rest of

trials meet the Rotterdam criteria). Partial information was missed or recorded by the median and interquartile range in the process of collecting and extracting data.

With respect to clinical applications, either myo-ins supplementation alone or the synergistic activity of myo-ins and D-chiro-ins may be beneficial in ameliorating insulin resistance and hyperandrogenaemia for PCOS women. Regrettably, the adaptable duration of the treatment, the difference between inositol isoforms administered, the most appropriate dosages/ratio and the safety profile of inositols still lack of unified standards, hence, more high-quality prospective cohort studies and randomized controlled trials are needed. Besides, the potential underlying mechanisms of inositol in PCOS are not still fully delineated; thus, numerous basic experiments are urgently needed in this area as well.

Conclusions

To conclude, in comparison with metformin, it is the first meta-analysis to reveal that myo-ins might be more helpful on lowering TG of patients with PCOS. Furthermore, it can be confirmed that using myo-ins under a reasonable range of dosage could largely avoid the AEs of metformin supplementation. Regretfully, the available evidence is still not of high quality, therefore, more comprehensive RCTs are needed in the future for the management of PCOS using myo-ins.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

Zhang Jiaqi designed the research, collected data, analyzed data, and wrote the manuscript. Zhang Jiaqi and Xing Chuan screened and evaluated the literature. Zhang Jiaqi and Xing Chuan collected materials. He Bing reviewed and edited the manuscript. All the authors have read and approved the final manuscript.

Authors' Information

Department of Endocrinology, Shengjing Hospital, China Medical University, Shenyang, Liaoning province, PR China Jiaqi Zhang, Xing Chuan, Bing He.

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