Effects of Inositol in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Kohsuke Hayamizu¹, Yui Kuramochi¹, Akihide Sumino¹, Nobuo Izumo¹, Megumi Furukawa², Makoto Nakano³

¹Laboratory of Food Chemistry, Yokohama University of Pharmacy, Yokohama, Japan
²Laboratory of Pharmacotherapy, Yokohama University of Pharmacy, Yokohama, Japan
³Pharmaceutical Education Center, Yokohama University of Pharmacy, Yokohama, Japan

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*Corresponding author: Laboratory of Food Chemistry, Yokohama University of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama, Kanagawa 245-0066, Japan, Fax : +81-45-585-913-01; Tel: +81-45-585-913-00; E-mail: k.hayamizu@hamayaku.ac.jp

Abstract

Background & Aims: To clarify the effects of treatment with inositol’s, D-chiro-inositol, myo-inositol, and pinitol, on hormonal and metabolic parameters in women with Polycystic Ovary Syndrome (PCOS), we conducted a systematic review and meta-analysis of recent randomized clinical trials of inositol’s in PCOS.

Methods: The systematic review was conducted using data obtained from randomized controlled trials performed to assess the effects of inositol’s compared with placebo (UMIN000025843). The primary outcomes included serum insulin, HOMA index, sex hormones, and ovulation rate.

Results: Eight studies involving 577 patients were eligible for systematic review. The meta-analysis results showed that compared with the control group, inositol’s may improve fasting insulin (Standardized Mean Difference (SMD) −1.06, 95% CI −1.83 to −0.29, p = 0.007), area under the curve (AUC) of Oral Glucose Tolerance Test (insulin SMD −0.76, 95% CI −1.20 to −0.32, p = 0.0008; glucose SMD −0.55, 95% CI −0.88 to −0.17, p = 0.004), free testosterone (SMD −1.94, 95% CI −3.28 to −0.61, p = 0.004), sex hormone binding globulin (SMD 1.10, 95% CI 0.37 to 1.82, p = 0.004), and ovulation rate (Risk Ratio 1.42, 95% CI −1.00 to 2.02, p = 0.05).

Conclusions: Inositol’s may be effective for PCOS by improving insulin resistance.

Keywords: Inositol, Polycystic ovary syndrome, Systematic review, Meta-analysis

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, occurring in 4%–8% of this population [1, 2]. It is associated with a wide range of maladies, such as hormonal and metabolic impairments, ovarian dysfunction, and menstrual irregularity. According to the Rotterdam criteria developed in 2003, PCOS is diagnosed if two out of the three following features are recognized: chronic oligo- or anovulation, anatomically polycystic ovaries on ultrasonography, and clinical and/or biochemical hyperandrogenism [3]. Although not included as criteria, insulin resistance and hyperinsulinemia are important etiologic factors associated with the typical clinical signs and hormonal disorders of PCOS. Indeed, insulin resistance along with hyperinsulinemia affects approximately 40%–50% of PCOS patients, both lean and obese [4–9]; however, in obese women with PCOS, the prevalence of insulin resistance accompanied by compensatory hyperinsulinemia approaches 80% [10]. Treatment of PCOS with insulin-sensitizing drugs, such as metformin, troglitazone, and pioglitazone, has been shown to improve ovulatory function and reduce circulating androgens, collaborating the critical link between insulin resistance and the pathogenesis of this syndrome. Among these insulin-sensitizing agents, metformin is most commonly used in the treatment of PCOS, although it has no official indication outside of type 2 diabetes in many countries and therefore is considered as an off-label product when used in nondiabetic women with PCOS. Nevertheless, nausea, diarrhea, and weight increase are side effects of metformin, which reduce patient compliance and the suitability of its use [6,11,12].

Recent studies suggest that some abnormal activities of insulin might be dependent on Inositol phosphoglycan (IPG) mediators of insulin signaling [13,14]. It was also suggested that deficiency in a specific D-chiro-inositol (DI)-containing IPG might underlie the insulin resistance, similarly to the case in type 2 diabetes [15,16]. DI intake has been shown to reduce insulin resistance in PCOS patients, as well as to improve ovarian function and decrease hyperandrogenism [17,18]. These studies have suggested the putative presence of defect in the insulin-signaling pathway in which DI-IPG is a mediator of insulin activity, thus contributing to the pathophysiology of the insulin resistance of PCOS [19]. Myo-inositol (MI), a kind of stereoisomer of DI, has been reported to be correlated with ovarian function [20] and with oocyte quality in patients undergoing In vitro fertilization (IVF), independently of the circulating plasma level of MI [21]. Against this background...
and based on clinical studies, it has been reported that inositol has beneficial effects on PCOS [18,20,22]. Unfer, et al. published a review of the effect of inositol [23], but they did not conduct a meta-analysis. In the present systematic review, we present updated information about DI and MI treatment for women with PCOS and clarify their effects. To clarify the effects of treatment with inositol, DI, MI on hormonal and metabolic parameters in women with PCOS, we conducted a systematic review and meta-analysis of recent randomized clinical trials of inositol in PCOS.

**Methods**

**Design**

We followed the Cochrane Handbook for Systematic Reviews of Interventions in conducting this meta-analysis [24]. The results are reported according to the Preferred Reporting Items for Systematic Review [25]. The protocol was registered at UMIN (identifier: UMIN000025843).

**Data source and search strategy**

We searched the PubMed, Cochrane, MEDLINE, and Ichushi-Web databases for intervention studies published between 1970 and December 2021 investigating the effects of inositol on insulin sensitivity, serum sex hormones, and ovarian function in PCOS. Search terms included “inositol,” “pinitol,” “polycystic ovary syndrome,” and “PCOS.” No language restrictions were applied. Additional trials were identified by scanning the reference lists of the identified publications. The electronic search was performed by AS, MF and YK.

**Study selection**

Two authors (KH and MN) independently screened the titles and abstracts to identify studies according to the following inclusion criteria: (i) patient: PCOS; (ii) intervention: inositol; (iii) comparator: placebo or folic acid; (iv) outcome measure: symptoms related to PCOS, namely, insulin sensitivity, glucose metabolism, serum hormones, and ovarian function; (v) study design: prospective, parallel group, or cross-over and randomized controlled clinical trial (RCT); and (vi) intervention period: ≥2 weeks.

**Data extraction**

Data were extracted and quality was assessed independently by two investigators (KH, YK and MN), using guidelines published by the Cochrane Collaboration [24]. Any disagreement was resolved by discussion and in consultation with a statistician, if required. We extracted data on study design, form of treatment, daily dosage of inositol, duration of the active treatment phase, age, sample size, mean ± SD of blood insulin, glucose, sex hormone, HOMA-R before (or at baseline) and after treatment, and number of ovulations after treatment.

**Statistical analysis**

Meta-analysis was conducted using Cochrane Program Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and R 3.3.1 and using the RcmdrPlugin EZR package [26,27]. A random effect model and the generic inverse variance method were performed to accommodate the heterogeneity of study designs. We calculated pooled Standardized mean difference (SMD) with the 95% Confidence interval (CI) for continuous outcomes of changes from baseline, and the Risk ratio (RR) with the 95% CI for categorical outcomes between two direct comparisons with the DerSimonian and Laird random effects [24]. Interstudy heterogeneity was assessed using the Cochrane Q (χ²) statistic at α < 0.10 and quantified by I² statistics, where I² ≥ 50% represented considerable heterogeneity [24]. For continuous outcomes, Standard deviation (SD) at one time point was calculated using the following formula: SD = SE × n⁰.5 (SE = standard error, n = number of participants). As a countermeasure to deal with missing values of SD of change from baseline, we used SD imputation with the following formula: SDchange = (SDtime1−SDtime2) / 2 − 2R × SDtime1 × SDtime2) / 2 [24].

Subgroup meta-analyses were conducted to explore whether the effect of treatment on each outcome was associated with the chemical structure of inositol’s and/or with the duration of intervention. Publication bias or small-study effect was assessed with the funnel plot method and using Egger’s test [28,29]. Sensitivity analyses, in which each study was systematically removed and the effect size was recalculated for the remaining studies, were carried out to explore the impact of individual studies on the pooled risk.

**Results**

**Study selection and characteristics**

Of the 162 records retrieved through electronic and reference searches, 143 were excluded after evaluation of the title and abstract, and 11 were excluded after a full text review (Figure 1). Eight studies met the inclusion criteria, the characteristics of which are summarized in Table 1 [20, 30-35, 36]. The largest number of subjects in an individual study was 283, which was almost 14-fold greater than the smallest number. Of the eight included studies, six reported the effect of MI and two reported the effect of DI on PCOS. The studies that involved MI and DI interventions were conducted in Italy and the US, respectively. There were no reports of studies using pinitol for PCOS. Four studies used folic acid as a placebo because the inositol samples used in these studies were commercial products containing folic acid. Among the included studies, six were conducted in a double-blind manner with adequate blindness, but for two trials relevant information on the blindness was not included in the paper. The risk of bias in the included studies is summarized in Table 2, which was assessed by the methods recommended in the Cochrane Handbook [24].
Fasting insulin, fasting glucose, and HOMA index (metabolic outcomes)

Six studies involving 202 participants reported the fasting insulin. These studies were highly heterogeneous ($I^2 = 83\%$). In the random effects model, there was a statistically significant difference in fasting insulin between the inositol-treated group and the control group (SMD $-1.06$, 95% CI $-1.83$ to $-0.29$, $p = 0.007$; Figure 2A). In terms of fasting glucose, in four studies, data synthesis was conducted by a random effects model; this revealed no statistically significant difference between the inositol-treated group and the control group (SMD $-0.27$, 95% CI $-0.66$ to $0.13$, $p = 0.19$; Figure 2B). Only two studies reported the HOMA index. In the random effects model, there was a statistically significant difference in HOMA index between the two groups (SMD $-1.30$, 95% CI $-1.61$ to $-0.99$, $p < 0.00001$; Figure 2C).

Oral Glucose Tolerance Test (OGTT)

In terms of the area under the curve (AUC) of insulin and glucose in the oral glucose tolerance test (OGTT), four studies analyzed this under a random effects model. There were statistically significant differences between the two groups (insulin: SMD $-0.76$, 95% CI $-1.20$ to $-0.32$, $p = 0.0008$, Figure 3A; glucose: SMD $-0.52$, 95% CI $-0.88$ to $-0.17$, $p = 0.004$, Figure 3B).

Hormonal and related parameters (endocrine outcomes)

In terms of serum testosterone, no statistically significant difference was found between the inositol and control groups by meta-analysis (SMD $-0.27$, 95% CI $-0.66$ to $0.13$, $p = 0.19$; Figure 4A). However, in terms of serum free testosterone, there was a
Effects of Inositol in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Table 1: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study type</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Intervention (g / day)</th>
<th>Duration (weeks)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artini et al, 2013 [30]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 25 Control 25</td>
<td>34.9 ± 2.1</td>
<td>26.5 ± 6.1</td>
<td>Treatment 2.0g MI + 0.2μg FA (n=25) Control 0.4g FA (n=25)</td>
<td>12</td>
<td>Women who were 1. Presence of micro polycystic ovaries at ultrasonography 2. Mild to severe hirsutism and /or acne 3. Oligomenorrhea or amenorrhea 4. Absence of adrenal deficiency and /or other endocrine disease* 5. normal PRL levels</td>
<td>Other than inclusion criteria</td>
</tr>
<tr>
<td>Dona et al, 2012 [31]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 18 ControlB</td>
<td>23.5 ± 2.1</td>
<td>21.6 ± 1.9</td>
<td>Treatment 1.2g MI (n=18) Control placebo (n=8)</td>
<td>12</td>
<td>Women who were 1. Age 22-30 2. PCOS (oligo-and /or anovulation, biochemical sign of hyperandrogenism) 3. Heigh serum free testosterone and/or hirsutism</td>
<td>Women who were 1. BMI&gt;25 2. Hyperandrogenism 3. Thyroid dysfunction 4. Cushing’s syndrome 5. Late- onset adrenal hyperplasia</td>
</tr>
<tr>
<td>Costantino et al, 2009 [32]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 23 Control19</td>
<td>28.8 ± 4.8</td>
<td>22.8 ± 0.5</td>
<td>Treatment 4.0g MI + 0.4μg FA (n=23) Control 0.4g FA (n=19)</td>
<td>12-16</td>
<td>Women who were 1. Diagnosed PCOS by ultrasound 2. Oligomenorrhea 3. Heigh serum free testosterone and/or hirsutism</td>
<td>Other than inclusion criteria</td>
</tr>
<tr>
<td>Genazzani et al, 2008 [33]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 10 Control10</td>
<td>not available</td>
<td>not available</td>
<td>Treatment 2.0g MI + 0.2μg FA (n=10) Control 0.2μg FA (n=10)</td>
<td>12</td>
<td>Women who were 1. Presence of micro polycystic ovaries at ultrasonography 2. Mild to severe hirsutism and /or acne 3. Oligomenorrhea or amenorrhea 4. Absence of adrenal deficiency and /or other endocrine disease* 5. Normal PRL levels</td>
<td>Other than inclusion criteria</td>
</tr>
<tr>
<td>Gerli et al, 2007 [34]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 45 Control47</td>
<td>29.0 ± 6.5</td>
<td>34.0 ± 8.5</td>
<td>Treatment 4.0g MI + 0.4μg FA (n=23) Control 0.4g FA (n=19)</td>
<td>14</td>
<td>Women who were 1. Age&lt;35 2. Oligomenorrhea or amenorrhea 3. Diagnosis PCOS by ultrasound</td>
<td>Women who were 1. Hyper PRL 2. Abnormal thyroid function 3. Received medications likely to influence hormonal profile</td>
</tr>
<tr>
<td>Gerli et al, 2003 [35]</td>
<td>Italy</td>
<td>RCT</td>
<td>Treatment 136 Control147</td>
<td>28.6 ± 10.1</td>
<td>34.0 ± 13.6</td>
<td>Treatment 0.2g MI (n=136) Control placebo (n=147)</td>
<td>14</td>
<td>Women who were 1. Age&lt;35 2. Oligomenorrhea or amenorrhea 3. Diagnosis PCOS by ultrasound</td>
<td>Women who were 1. Hyper PRL 2. Abnormal thyroid function 3. Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Isorno et al, 2002 [20]</td>
<td>US</td>
<td>RCT</td>
<td>Treatment 10 Control10</td>
<td>28.2 ± 4.7</td>
<td>22.4 ± 0.9</td>
<td>Treatment 0.6g DI (n=10) Control placebo (n=10)</td>
<td>6-8</td>
<td>Women who were 1. Oligomenorrhea 2. Hyperandrogenism 3. Normal thyroid-function test 4. Normal serum PRL</td>
<td>Women who were 1. Diabetes mellitus 2. Received medications during 2 months before the study</td>
</tr>
<tr>
<td>Nestler et al, 1999 [36]</td>
<td>US</td>
<td>RCT</td>
<td>Treatment 22 Control22</td>
<td>29.6 ± 6</td>
<td>31.3 ± 2.4</td>
<td>Treatment 1.2g DI (n=22) Control placebo (n=22)</td>
<td>6-8</td>
<td>Women who were 1. Oligomenorrhea 2. Hyperandrogenism 3. Normal thyroid-function test 5. Normal serum PRL</td>
<td>Women who were 1. Diabetes mellitus 2. Received medications for at least two months</td>
</tr>
</tbody>
</table>

Mean±SD  
MI: Myoinositol  DI: D-Chiro-inositol  PRL: Prolactin

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Table 2: Assessment of risk bias based on the evaluation domains listed in the Cochrane Collaboration Risk Bias Tool

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artini, et al 2013 [30]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dona, et al 2012 [31]</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Costantino, et al 2009 [32]</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Genazzani, et al 2008 [33]</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gerli, et al 2007 [34]</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Iuorno, et al 2002 [20]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nestler, et al 1999 [36]</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 2: Meta-analysis of fasting insulin, fasting glucose and HOMA-index

A: Fasting insulin level, B: Fasting glucose level, C: HOMA-index
Effects of Inositol in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials


statistically significant difference between the two groups (SMD −0.76, 95% CI −1.20 to −0.32; p = 0.001; Figure 4B).

In terms of androstenediol, a precursor of testosterone, three studies showed that inositol decreased its serum concentration (SMD −1.94, 95% CI −3.28 to −0.61, p = 0.004; Figure 4C).

Regarding Sex hormone binding globulin (SHBG), a glycoprotein that binds with high affinity to 17 beta-hydroxysteroid hormones such as testosterone and estradiol, it was shown that inositol increased serum SHBG compared with that in the control group (SMD 1.10, 95% CI 0.37 to 1.82, p = 0.003; Figure 4D).

For other hormones, such as Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Prolactin (PRL), Estradiol (E2), and 17-hydroxyprogesterone (17-OHP), these were reported in only two studies (Table 3). LH and FSH were shown to decrease, and estradiol and 17-OHP were shown to increase significantly. On the other hand, no change of LH/FSH ratio was observed.

Ovulation rate

A random effects model was employed in the analysis of ovulation rate as the overall heterogeneity was considerably high (I² = 84%). Inositol showed a tendency to improve the ovulation rate (RR 1.42, 95% CI 1.00 to 2.02, p = 0.05; Figure 5).

Publication bias

According to the Cochrane Collaboration, the test for funnel plot asymmetry for the assessment of publication bias should be used only in cases with at least 10 studies [24]. In this study, the maximum number of studies for use in the meta-analysis was only six, fasting insulin and androstenediol, so we used the results of Egger’s test only as a reference. Funnel plots and Egger’s test of studies investigating the effect of inositol on fasting insulin and androstenediol indicated no publication bias (Figure 6). However, it was not meaningful to assess the publication bias of fewer than six studies reporting the effect of inositol.

Discussion

PCOS is a common endocrine disorder in women of reproductive age and is associated with ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology, as well as metabolic disorders, including hypertension and dyslipidemia [1-9,37]. It has been reported that the primary pathogenesis of PCOS is associated with increased insulin resistance. Therefore, in the pharmaceutical treatment of PCOS, insulin sensitizers, such as metformin, may be useful [38-42].

Inositol’s belong to the sugar alcohol family comprising nine cyclohexane-1,2,3,4,5,6-hexol stereoisomers. These molecules provide the structural basis for inositol phosphates, important secondary messengers in eukaryotic cells, and serve as critical components of the structural lipids, phosphatidylinositol and phosphatidylinositol phosphate [43]. Myo-inositol (cis-1,2,3,5-trans-4,6-cyclohexanehexol, MI) and D-chiro-inositol (cis-1,2,4-
Figure 4: Meta-analysis of serum testosterone, free testosterone, androstenediol and sex hormone binding globulin (SHBG) A: Testosterone, B: Free testosterone, C: Androstenediol, D: SHBG

trans-3,5,6-cyclohexanehexol, DI) represent a promising treatment for PCOS, having shown some therapeutic benefit [44]. Notably, no substantial side effects have been reported for them [44], although this issue probably warrants more attention. In fact, as these compounds are marketed as dietary supplements, it is not easy to reveal their adverse effects. Moreover, in the controlled studies that have been carried out, as also discussed below, the populations that were enrolled were typically too small to achieve significant findings regarding the occurrence of side effects. Furthermore, not being pharmaceuticals, inositol compounds can be included in many formulations that differ among countries or regions, making comparison between clinical trials conducted in different locations difficult.
Table 3: Meta-analysis of change of serum female hormone status

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of studies*</th>
<th>No. of subjects</th>
<th>WMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>2</td>
<td>70</td>
<td>-2.90 (-4.22, -1.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FSH</td>
<td>2</td>
<td>70</td>
<td>-3.00 (-3.24, -2.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>2</td>
<td>70</td>
<td>-0.37 (-0.37, 0.16)</td>
<td>0.42</td>
</tr>
<tr>
<td>PRL</td>
<td>2</td>
<td>70</td>
<td>-0.63 (-1.76, 0.51)</td>
<td>0.28</td>
</tr>
<tr>
<td>E2</td>
<td>2</td>
<td>70</td>
<td>14.67 (5.78, 23.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>17-OHP</td>
<td>2</td>
<td>70</td>
<td>0.50 (0.02, 0.98)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*: Artini 2013[30] and Genazzani 2008[33]
17-OHP: 17-hydroxy-progesterone

In this study, an increase of the ovulation rate was observed in PCOS patients upon inositol intervention (Figure 5). To explain this, the following speculation can be proffered. It is known that serum testosterone is high in PCOS patients, and a decrease in serum SHBG level and an increase in free testosterone have been reported[45]. Since SHBG has been reported to exhibit a decrease in its expression due to insulin resistance [46-48], insulin resistance may be involved in the hyperandrogenism in PCOS [49,50]. In present study, decreases in serum androstenedione and free testosterone along with an increase in SHBG were identified (Figure 4). Furthermore, an improvement of insulin resistance was observed (Figure 2, 3). These results suggest that...
insulin resistance was improved by inositol intervention, and free testosterone decreased via increasing SHBG; this resulted in an increase in the ovulation rate in PCOS. The efficacy of inositol for glucose metabolism has also been reported in clinical trials on patients with gestational diabetes [51,52]. However, its efficacy for glucose metabolism in type 2 diabetic patients or those with impaired glucose tolerance has not been shown clearly [53-56]. From these findings, no definitive conclusions can yet be drawn about the effect of inositol administration on improving insulin.

Our searches identified only two reports in which female hormones were assessed (Table 3). Although the blood estradiol (E2) level was also shown to be significantly elevated upon treatment with inositol compared with that upon administration of a placebo, this may also have been an effect of the rise in SHBG. Significant decreases in both LH and FSH were also observed when inositol was administered. However, because there was no significant change in the LH/FSH ratio, it seems that this is not a physiologically meaningful change in PCOS.

By the way, in vivo, MI is converted to DI by epimerase, but the rate of conversion is tissue-specific; the ratio of MI to DI has been reported to be insulin-dependent, with a lower DI / MI ratio and reduced DI synthesis in patients with type 2 diabetes due to reduced epimerase activity [57-60]. Unlike tissues such as muscle and liver, the ovary does not become insulin resistant [61-63]. Therefore, in hyperinsulinemia PCOS patients, epimerization of MI to DI is expected to be enhanced in the ovary, leading to MI deficiency. As a direct correlation between MI concentration in follicular fluid and oocyte quality has been reported [21], MI deficiency is thought to be responsible for the poor quality of oocytes in PCOS patients. In other words, a DI paradox is assumed, in which DI improves insulin resistance in PCOS but has no effect at the ovarian level [64]. Although the study investigated ovulation rates after the intervention, no information on the DI paradox is available because oocyte quality was not included as an outcome in our study. This remained an issue for future work.

Evidence has shown that chromium and vitamin D are other food components besides inositol that can be effective for PCOS [57-59]. Chromium is a trace element related to glucose metabolism and lipid metabolism, and it has been reported to be useful for body weight maintenance and the management of fasting glucose level in type 2 diabetic patients [65].

Heshmati et al. [65] and Tang et al. [66] reported the influence of chromium supplementation on PCOS patients as revealed by meta-analyses, with improvement of HOMA-IR being observed. However, serum total testosterone and serum free testosterone were found to be significantly elevated upon chromium supplementation, so no definitive conclusions about the usefulness of this approach for PCOS could be drawn [68]. Moreover, Akbari et al. reported on a meta-analysis of the effects of vitamin D supplementation on oxidative stress and inflammatory markers in PCOS patients [67]. Their results revealed decreases in high-sensitivity C-reactive protein and malondialdehyde and an increase in total antioxidant capacity. However, the authors did not confirm any effects of vitamin D supplementation on insulin resistance, high androgen, and amenorrhea, which are common in patients with PCOS.

In this study, the effect of inositol's in Assisted reproduction technologies (ART) has not been verified. Infertility treatment can be considered as one of the therapeutic objectives of PCOS, but the published papers are actually rather scarce to perform a meta-analysis, so this is a task for future work. In addition, most of the papers for the meta-analysis were on studies conducted in Italy, so there is little evidence about this issue from other regions.

The treatment for PCOS differs depending on whether the patient’s goal is to become pregnant. In the case of infertility treatment, hormone therapy, traditional Chinese medicine, laparoscopic ovarian drilling, and ART, among others, are carried out [68]. It is anticipated that PCOS therapy involving the improvement of insulin resistance will be developed not only for care in the field of obstetrics and gynecology but also for the prevention of metabolic diseases. None the less, further progress in clinical research is necessary for the prevention of PCOS, which is also a high-risk group of metabolic abnormalities in the middle-aged and elderly.

The finding of this meta-analysis study is that the effect of inositol in patients with PCOS is suggested that mediated by an improvement in sex hormones via an improvement in insulin sensitivity.

Conclusion

Although the pathology of PCOS has not been clarified, evidence suggests that inositols may be effective against this condition by improving insulin resistance. However, the RCTs performed to date have limitations, especially regarding insufficiency in the evidence for assessing FSH, LH, and estradiol. More large and long-term RCTs of inositols are needed to confirm or refine the results of this study.

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Author contributions

Kohsuke Hayamizu and Makoto Nakano designed the research and wrote the article; Kohsuke Hayamizu, Nobuo Izumo and Makoto Nakano analyzed and interpreted data; Kohsuke Hayamizu and Makoto Nakano revised the article critically; Akihide Sumino, Yui Kuramochi and Megumi Furukawa conducted database search, data management. Kohsuke Hayamizu, Yui Kuramochi and Makoto Nakano judged risk bias; Kohsuke Hayamizu had primary response for final contents. All authors read and approved the final manuscript.
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