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INOSITOLS AND PCO

# Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives

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**Abstract**

The incidence of metabolic syndrome (MetS), type II diabetes (T2D) and polycystic ovarian syndrome (PCOS) has been progressively increasing. Insulin resistance (InsR) seems to play a key role in a majority of phenotypes of these conditions, altering metabolic homeostasis, within muscle, liver, adipose and other tissues. Hyperinsulinemia is often associated with InsR and causes hormonal imbalances especially within ovaries and adrenals. Inositol is a polyalcohol, naturally occurring as nine stereoisomers, including D-chiro-inositol (DCI) and myo-inositol (MI), which have prominent roles in the metabolism of glucose and free fatty acids. MI and DCI have been classified as insulin-sensitizers and seem to adequately counteract several InsR-related metabolic alterations with a safe nutraceutical profile. Based on our analysis of selected studies that investigated MI and/or DCI, we conclude that supplementation with MI and/or DCI complement each other in their metabolic actions and act in synergy with other insulin sensitizing drugs and/or nutraceuticals. Nevertheless, considering the possible severe bias due to different methodologies across published studies, we conclude that there is a need for further studies on larger cohorts and with greater statistical power. These should further clarify outcomes and suitable therapeutic dosages of MI and DCI, possibly based on each patient's clinical status.

**Keywords**

Diabetes, insulin, insulin resistance, insulin sensitizer, polycystic ovary syndrome

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## Insulin resistance, polycystic ovarian syndrome, metabolic syndrome, and type II diabetes: master and minions

To date, the incidence of metabolic syndrome (MetS), type II diabetes (T2D), and polycystic ovarian syndrome (PCOS) is progressively increasing [1–3]. Insulin resistance (InsR) can be defined as a deregulation of glucose and insulin metabolism, and may display various degrees of elevated fasting and/or postprandial glucose and/or elevated insulin levels [4–6]. In particular, InsR plays a key role in the pathophysiology of MetS, T2D, gestational diabetes mellitus (GDM) and many PCOS phenotypes [1–13]. According to Reaven [9], values of insulin-mediated glucose disposal vary by a difference of $\geq 600\%$ between the most insulin-sensitive and the most insulin-resistant individuals. This variability has been attributed to differences in adiposity (25%), fitness (25%), and genetics (50%), although the dietary aspect may play an important role. Furthermore, the more insulin-resistant a person is, the more insulin must be secreted to support glucose disposal [10].

InsR seems to alter several cellular events within liver, muscle, and adipose tissue [11,12] as follows: 1) impaired glucose transported type 4 (GLUT4) receptor translocation to the cell membranes, where GLUT4 is responsible for intracellular glucose transport; 2) reduced activity of pyruvate dehydrogenase (PDH), where PDH enables glucose entry in the Krebs' cycle for conversion to ATP; 3) reduced activity of glycogen synthase (GS), where GS catalyzes glucose conversion to glycogen; 4) impaired insulin inhibition of adenylate cyclase enzyme (ADC), which controls free fatty acid (FFA) release from fat stores [4,11,12]. This results in elevated plasma FFAs, which are further increased by excess body fat and/or excess intake of fat.

InsR-related cellular events affect metabolic homeostasis, causing several detrimental effects [13]: 1) less glucose is taken up and used inside muscle cells, leading to hyperglycemia; 2) more glucose is directed to the liver, which converts it into excess triglycerides in addition to those synthesized from elevated plasma FFAs; 3) hyperglycemia stimulates excess insulin production, which in turn causes excessive triglyceride and cholesterol synthesis; 4) subsequently, blood triglycerides are elevated leading to fat storage, especially in the liver and adipose tissue.

To date, several insulin sensitizing drugs have been used to alleviate InsR and many symptoms of InsR-related conditions. Inositol is a polyalcohol classified as an insulin sensitizer and it is naturally occurring as nine stereoisomers, two of which, D-chiro-inositol (DCI) and myo-inositol (MI) showed a safe nutraceutical profile and seem to significantly alleviate InsR and several InsR-related metabolic alterations [14]. Inositol is synthesized by both prokaryotic and eukaryotic cells, while in mammals, it is obtained

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from dietary sources (as free inositols, phosphatidyl-inositol or inositol-6-phospahte), and endogenous synthesis from glucose. The MI derivative inositol triphosphate (ins-1,4,5P3, insP3) acts as an intracellular second messenger, regulating the activities of several hormones such as insulin, follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH) [15]. MI, which is the most abundant form of inositol in humans, is converted to DCI by an epimerase enzyme [16]. These two stereoisomers showed an insulin-like action in vivo through their respective derivatives inositolphosphoglycans (IPGs) MI-IPG and DCI-IPG, which act as insulin mediators [17,18]. In particular, accumulating evidence [17,18] suggests that MI and DCI metabolic derivatives work in synergy with each other, as illustrated in Figure 1 [8]: (1) MI induces GLUT translocation to the cell membrane, thus enhancing cellular uptake of glucose; (2) DCI stimulates PDH thus supporting ATP production through the Krebs' cycle; (3) both MI and DCI stimulate GS, thus supporting glucose conversion to glycogen stored inside cells, and (4) MI derivatives inhibits ADC enzyme, thus reducing FFAs release from adipose tissues. This particular effect is beneficial because elevated concentrations of FFAs cause impairment of intracellular insulin signaling and support increased triglycerides synthesis [4,11,12].

Since MI to DCI conversion by epimerase has been found to be impaired in insulin-resistant tissues (e.g. 1% versus the normal of 8% in muscle tissue), it makes sense to add DCI to MI supplementation. Epimerase activity and its metabolic down regulation may be determined by the genetics relevant to InsR [17]. Thus, ingested DCI will compensate for low endogenous DCI synthesis and its excessive urinary excretion [17,19–21] and will ensure an adequate tissue content of DCI derivatives, which have distinct mechanisms of action from MI derivatives in support of glucose disposal (Figure 1). Furthermore, DCI supplementation by itself would not be recommended because: (a) DCI does not convert to MI, thus it would not provide the mechanisms of action that are unique to MI, such as those described in the previous paragraph under items (1) and (4); (b) evidence of systemic MI

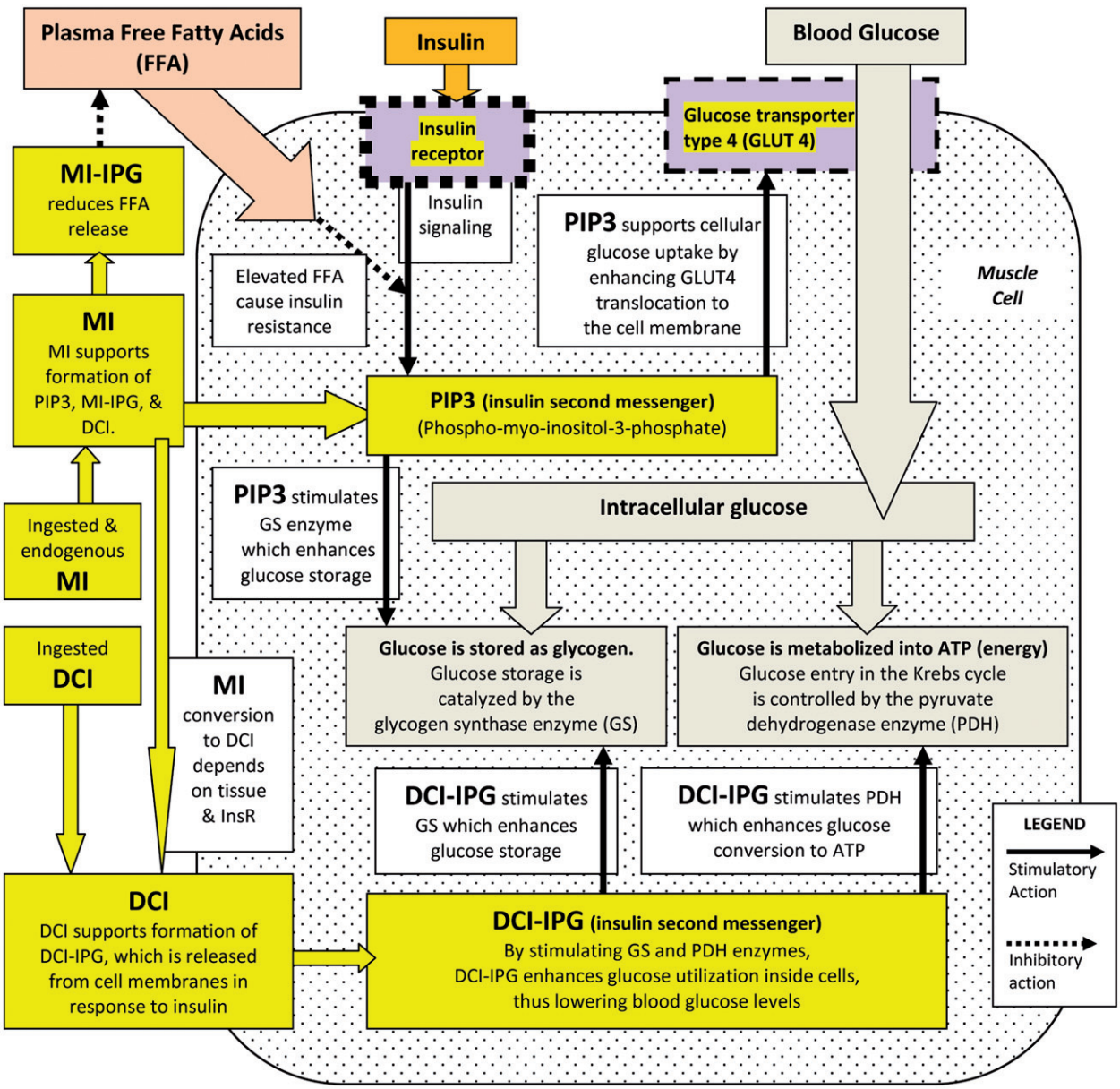


Figure 1. Roles of myo-inositol and d-chiro-inositol in supporting insulin-stimulated glucose entry and its utilization inside cells with detailed biochemical mediators and the involved enzymes. Adapted from Paul & Brady, *''Inositol Modulation of Essential Metabolic Pathways of Insulin Resistance in Metabolic Syndrome, Polycystic Ovarian Syndrome, and Type 2 Diabetes''* (Townsend Letter, August/September 2015). MI: Myo-Inositol. DCI: D-Chiro-Inositol. FFA: Free Fatty Acids. ATP: Adenosine Triphosphate.

and MI-IPG deficiency was shown for many InsR-related conditions. This may be due to a number of factors including poor MI intracellular uptake combined with excess urinary loss of MI. In turn, these may due to elevated blood glucose levels since MI competes with glucose for cellular transporters [17,19–21]; (c) since epimerase is typically down regulated in these conditions, in insulin sensitive tissues, we hypothesize that higher than normal MI intake and MI body stores may work by ''pushing'' the epimerase by substrate mass action, thus increasing synthesis of DCI.

To date, several intervention studies seem to confirm that inositols may play a key role in improving hormonal and metabolic homeostasis in PCOS [1,22–27], assisted reproductive technology (ART) [28–31], and even in GDM [32–35]. InsR is involved in a majority of PCOS phenotypes, MetS, T2D, and GDM, thus the aim of this article is to summarize the current knowledge regarding the mechanisms of action of MI and DCI metabolic derivatives on insulin signaling and the results obtained from the most significant intervention studies for these conditions to date.

## Inositol's effects in polycystic ovarian syndrome

PCOS, in particular, is defined by the presence of two out of the following clinical features: oligo-anovulation; hyperandrogenism (clinical or biochemical); presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or an increased ovarian volume (> 10 ml) [36,37]. It affects about 4–8% of the women in reproductive age [38–40]. As previously stated [8,41,42], PCOS in our opinion can be considered the result of inter-related endocrine alterations, resulting from various lifestyle, genetic, and fat mass related factors. Current evidence suggests that InsR and compensatory hyperinsulinemia play an important pathogenic role in the hyperandrogenism of many PCOS phenotypes, which in turn causes anovulation in both obese and lean women with PCOS [43,44]. Specifically, hyperinsulinemia acts synergistically with LH to enhance androgen production of theca and adrenal cells [45]. Hyperglycemia and hyperinsulinemia have different effects depending on the target organ. Muscles are typically responsible for about 85% of glucose disposal and when this is diminished by InsR, it causes hyperglycemia, which in turn triggers hyperinsulinemia. On the other hand, ovaries, adrenals, and the brain remain sensitive to insulin and in the setting of InsR they end up being excessively stimulated by abnormally high levels of insulin.

Overall, the MI doses used in most published studies ranged from 2 to 4 gr/day, while a meta-analysis [27] study of MI for PCOS treatment concluded that the higher dose of 4 gr MI/day seems to achieve better results. Based on this, we left out of our analysis studies that used doses of 2 gr of MI or smaller, unless it was combined with other nutraceuticals or pharmaceuticals. Table 1 reports the main results reported from our study selection [41,46–54], which investigated the effects of MI and/or DCI supplementation on oligomenorrhea, elevated androgens, markers of InsR and of MetS. Most of these studies reported that MI and/or DCI interventions were able to significantly restore regular menstrual periods and ovulation compared to control groups and decrease biochemical and clinical hyperandrogenism. Eight of these studies [41,47,49–54] reported significant and dramatic improvements in homeostatic model assessment (HOMA) and/or Glu/IRI, while seven of them [46,48,49–51,53,54] also reported significant improvements for insulin [fasting and/or area under the curve (AUC) post glucose tolerance test) and for glucose (fasting and/or AUC post glucose tolerance test)]. Regarding dyslipidemia markers, four of these studies [46,47,49,51] showed significant lowering of blood triglycerides and total cholesterol. Notable increases in high density lipoproteins (HDL) were reported in three of these studies.

One study by Nordio et al. [50] and one by Minozzi [51] investigated a combination of MI plus DCI in a softgel form with doses equivalent in bioavailability with powder dosages of 3300 mg MI plus 84 mg DCI/day. This study by Nordio et al. [50] compared the effects of MI plus DCI treatment with that of a dose of 4 g MI/day in powder form. They found that, after six months of treatment, both MI and MI plus DCI groups showed improvements in various metabolic markers of PCOS and MetS, but the combined MI plus DCI supplementation seemed twice as effective in reducing HOMA-IR, compared to that of MI alone. Furthermore, all the rest of the results reported for the MI plus DCI group were also better than those for the MI alone group (Table 1). In addition, we previously evidenced [41,52,55] that an intervention with 4 gr MI alone seems to have the most marked effect on the metabolic profile, whereas that with 1 gr DCI alone reduces hyperandrogenism better. However, it is interesting to remark that the metabolic improvements reported for the group treated with 1 gr DCI were fairly similar to those obtained for the group treated with 4 gr MI, thus implying that a lower dose of DCI may achieve similar benefits for some aspects of PCOS than a four times higher dose of MI [41]. This similarity in results may be explained by the fact that relatively high doses of MI, such as 4 gr, may significantly increase the MI to DCI conversion through substrate mass action on the epimerase enzyme. However, lower doses of MI may be just as efficacious when DCI is supplemented at the same time, as demonstrated in the study by Nordio et al. [50], which used for treatment the equivalent of 3300 mg MI plus 80 mg DCI, as discussed above.

Based on all available data, it is currently widely accepted that both MI alone, DCI alone, and their combination may alleviate many of the metabolic deregulations typical of PCOS. In spite of all current evidence, to date there is no robust consensus on the ideal dose of MI and/or DCI for PCOS treatment, nor which MI/DCI ratio may be ideal for inositol supplements. However, based on the known mechanisms of action of MI and DCI derivatives and promising results from studies with their combination [50,51], it makes sense to always recommend using MI plus DCI when treating PCOS. MI seems effective for PCOS in doses of 3–4 gr/day. The DCI dose may be close to but not higher than 300 mg/day. This is based on results of one study showing that supplementing with doses higher than 300 mg DCI may impair oocyte quality, probably due to lowering of MI/DCI ratio in the ovary [16]. However, the upper limit for DCI may prove to be higher in future studies if MI is supplemented simultaneously with DCI.

For example, the combined therapy with a softgel containing 550 mg MI + 13.8 mg DCI (equivalent to 3300 mg MI + 84 mg DCI in powder format), showed to retain the beneficial effects of MI treatment alone on oocyte and embryo quality in PCOS patients enrolled in IVF program, regardless of their age [57].

The conclusions of the ''International Consensus Conference on myo-inositol and D-chiro-inositol in Obstetrics and Gynecology'' [56], also emphasized the negative effect of increasing doses of DCI on the ovary (the so-called ''DCI paradox'') and suggested that administering MI and DCI in a proposed ''physiological ratio'', of (40:1) may be ideal. This opinion is based on the assumption that plasma ratio of MI/DCI in normal subjects is 40:1. However, the data substantiating this value has not been published yet, while a study by Baillargeon [19] found that plasma MI/DCI ratio in normal individuals was 111, while that of PCOS patients was 206.

In addition, it has not been demonstrated that a MI/DCI ratio in a supplement matching that of plasma MI/DCI in normal individuals is better than any other possible ratios obtained from combining DCI doses of less than 300 mg (to preserve oocyte quality) with MI doses of 2–4 g (proven effective with MI alone).

Table 1. Summary of most relevant intervention studies with myo-inositol and/or d-chiro-inositol for women with polycystic ovarian syndrome.

| | | Markers of insulin resistance or sensitivity | | | | | | Cardiovascular markers | | | | | Weight | | Androgens | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author(s), patients and length of the study | Daily dose | Gluc/IRI | HOMA-IR | AUC insulin | Fasting insulin | AUC glucose | Fasting glucose | Triglycerides | HDL | Total cholesterol | DBP | SBP | BMI | WHR | Total testosterone | Free testosterone |
| Nestler et al., 1999.<br>Obese PCOS, 8 weeks. | 1200 mg DCI<br>placebo | –<br>– | – | –62%<br>NS | –37% but NS<br>NS | –8% but NS<br>NS | NS<br>NS | –40%<br>NS | NS<br>NS | –8%<br>NS | –4%<br>NS | –3%<br>NS | NS | –2%<br>NS | –32%<br>NS | –55%<br>NS |
| Iuorno et al., 2002.<br>Lean PCOS, 8 weeks. | 600 mg DCI | +84% insulin sensitivity | – | –36% | – | –17% | –7% | –52% | – | –19% | –7% | –3% | – | – | –66% | –73% |
| Gerli et al., 2007.<br>PCOS, 14 weeks. | 4 gr MI + 400 mcg FA | – | – | – | – | – | – | – | +5% | – | – | – | –2% | | – | – |
| Constantino et al., 2009.<br>PCOS, 12 weeks. | 4 gr MI + 400 mcg FA | – | –80% | –35% | NS | –16% | NS | –51% | – | –19% | –3% | –7% | NS | – | –72% | –72% |
| | placebo + 400 mcg FA | – | –13% | –2% | NS | no chg. | NS | –11% | – | +5% | +2% | +5% | NS | – | –6% | –4% |
| Nordio & Proietti, 2012.<br>PCOS, 6 months. | equiv. to 3300 mg MI + 84 mg DCI | | –44% | –38% | –28% | –38% | –12% | – | – | – | –9% | –2% | –2% | –2% | –66% | –73% |
| | 4 gr MI | – | –21% | –36% | –22% | –32% | –11% | – | – | – | –6% | –2% | –1% | –1% | –59% | –72% |
| Minozzi et al., 2013.<br>PCOS, 6 months. | equiv. to 3300 mg MI + 84 mg DCI | – | –40% | – | –18% | – | –16% | –13% | +8% | –14% | – | – | – | – | – | – |
| Pizzo et al., 2014.<br>PCOS, 6 months. | 4 gr MI + 400 mcg FA | +76% | –50% | – | – | – | – | – | – | – | NS | –8% | NS | | –36% | –22% |
| | 1 gr DCI + 400 mcg FA | +81% | –49% | – | – | – | – | – | – | – | NS | –7% | NS | | –33% | –23% |
| Laganà et al., 2015.<br>PCOS, 6 months. | 1 gr DCI + 400 mcg FA | +80% | –49% | – | – | – | – | – | – | – | NS | –7% | NS | | –33% | –24% |
| Genazzani et al., 2014.<br>PCOS, 12 weeks. | 0.5 gr DCI and no diet | +43% | | | –23% | | –11% | | | | | | –5% | | –38% | |
| Sacchinelli et al., 2014.<br>PCOS, 12 months. | 4 gr MI + NAC + 400 mcg FA | – | –51% | | –45% | | –12% | | | | | | | | | |

MI: Myo-Inositol. DCI: D-Chiro-Inositol. Gluc/IRI: Glucose/Insulin ratio. HOMA-IR: Homeostatic Model Assessment – Insulin Resistance. AUC: Area under the Curve. HDL: High Density Lipoprotein. DBP: Diastolic Blood Pressure. SBP: Systolic Blood Pressure. BMI: Body Mass Index. WHR: Waist to Hip Ratio. FA: Folic Acid. NAC: N-AcetylCysteine.

Adapted from Paul & Brady, *''inositol modulation of essential metabolic pathways of insulin resistance in metabolic syndrome, polycystic ovarian syndrome, and type 2 diabetes''* (Townsend letter, August/September 2015).

Table 2. Effects of Myo-inositol for metabolic syndrome in postmenopausal and pregnant women.

| Author(s), patients and length of the study | | Markers of insulin resistance | | | Cardiovascular markers | | | | Weight | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Daily dose | HOMA-IR | Fasting insulin | Fasting glucose | Triglycerides | HDL | Total chol. | DBP | SBP | BMI | waist | WHR |
| Giordano et al., 2011. | 4 gr MI + diet | –77% | –69% | –17% | –21% | +28% | –20% | –12% | –4% | –3% | –6 cm | – |
| Postmenopausal women, six months. | placebo + diet | –25% | NS | –4% | NS | NS | –7% | no chg. | NS | –1% | –1 cm | – |
| Santamaria et al., 2012. | 4 gr MI + diet | –78% | –70% | –15% | –34% | +21% | –22% | –16% | –7% | –5% | –7 cm | – |
| Postmenopausal women, 12 months. | placebo + diet | –42% | –33% | –6% | –9% | +5% | –10% | –9% | –1% | –2% | –1 cm | – |
| Capasso et al., 2013. Postmenopausal women, six months. | 4 gr MI + Lipoic Acid + diet | –33% | –45% | –10% | –19% | +15% | –5% | – | – | –5% | –2 cm | –9% |
| | placebo + diet | –1% | no chg. | –5% | no chg. | no chg. | no chg. | – | – | –3% | –1 cm | –9% |
| Malvasi et al., 2014. Healthy pregnant women with metabolic syndrome. | 2 gr MI+ 800 mg DCI + 10 mg Mn + 400 mcg FA | – | – | –4% | –24% | +10% | –20% | NS | –5% | – | – | – |

MI: Myo-Inositol. DCI: D-Chiro-Inositol. HOMA-IR: Homeostatic Model Assessment – Insulin Resistance. HDL: High Density Lipoprotein. DBP: Diastolic Blood Pressure. SBP: Systolic Blood Pressure. BMI: Body Mass Index. WHR: Waist to Hip Ratio. Mn: Manganese. FA: Folic Acid.
Adapted from Paul & Brady, ''*inositol modulation of essential metabolic pathways of insulin resistance in metabolic syndrome, polycystic ovarian syndrome, and type 2 diabetes*'' (Townsend letter, August/September 2015).

The research for optimal doses of MI and DCI needs to be pursued further in PCOS women that are pregnant or in menopause.

## Inositol's effects in metabolic syndrome

MetS is defined by a set of related clinical features, most of them attributed to InsR, including some but not all of the following: hyperinsulinemia, abnormal glucose tolerance, increased plasma triglyceride, decreased high-density-lipoprotein cholesterol concentrations, smaller/denser low-density-lipoprotein particles, hypertension, and abnormalities of fibrinolysis [10]. Often, MetS leads to the development of T2D and insulin-dependent diabetes.

The studies summarized in Table 2 investigated the role of MI or MI plus DCI in ameliorating the InsR-related features of MetS [58–61]. Three studies [58–60] used as an intervention 4 gr MI/day, one of them included additional lipoic acid [60], while another study [61] used the combination of 2 gr MI with 800 mg of DCI plus 10 mg of manganese (Mn) and 400 mcg of folic acid (FA). All studies included a placebo group, and three of them had all groups on a hypocaloric diet. The first three studies [58–60] showed a significant reduction of HOMA-IR, fasting insulin, and fasting glucose compared to controls (placebo plus diet). Furthermore, there was a significant improvement in the level of triglycerides, HDL, total cholesterol, and a reduction of diastolic blood pressure in all these studies [60–61]. Three studies [58–60] reported significant weight loss (as shown by a reduction in body mass index (BMI) and waist circumference) in the group treated with MI. The combination of lipoic acid and MI may be justified as follows: 1) supplementation with lipoic acid by itself was found to increase insulin sensitivity by about 20–30% [62,63]; 2) lipoic acid and inositol-derived second messenger DCI-IPG are both cofactors for the PDH enzyme, thus may act in synergy to maximize PDH activity, which supports glucose entry into the Krebs cycle.

## MI, DCI, lipoic acid and n-acetyl cysteine may complement or outperform insulin-sensitizing pharmaceuticals

Santamaria et al. [59] compared the results of their intervention study with 4 gr MI and a hypocaloric diet, with results from other intervention studies, where pharmaceutical insulin-sensitizers metformin and glitazones were used. They concluded the following regarding the potential benefits of MI interventions: 1) MI may improve HOMA better than glitazones; 2) MI may reduce triglycerides better than glitazones and metformin; 3) MI may increase HDL better than glitazones and metformin; 4) MI may reduce systolic and diastolic blood pressure similarly to metformin; 5) MI may reduce waist circumference and waist to hip ratio (WHR), while glitazones have been shown to support weight gain in some cases.

Since InsR is a common denominator among MetS, T2D,GDM, and certain PCOS phenotypes several insulin-sensitizers have been used to treat them, while a healthy lifestyle (diet and physical activity) is always recommended [23,24,26,53,64]. Although all insulin-sensitizers share similar therapeutic goals, each of them has specific cellular targets, mechanisms of action, and side effects. In this section, we will summarize the current evidence for the synergistic effects of MI and/or DCI used in conjunction with pharmaceuticals and/or other nutraceuticals that are insulin-sensitizing. The synergy of lipoic acid with MI was discussed in the previous section in relation to the study by Capasso et al. [60], and we note here two more studies that have shown benefits in PCOS from the combination of lipoic acid with MI [65] or with DCI [66].

One of the most prescribed (and more studied) pharmaceutical for InsR is metformin, and its insulin sensitizing effects may be in

part due to increasing the release of DCI-IPGs from cell membranes, thus triggering their participation in intracellular insulin signaling [17]. Considering that patients with InsR have insufficient DCI-IPG tissue stores [17,19–21], supplementation with DCI and/or MI (since MI is the precursor to DCI) would likely enhance body stores of their metabolic derivatives. Thus we could expect a synergistic effect from combining metformin treatment with MI and DCI supplementation, as is shown in the studies discussed below.

A study by Le Donne et al. [67] showed that the combination treatment of 500 mg metformin with 4 gr MI/day caused more fat loss and better restoration of regular menstrual cycles in obese PCOS patients than the treatment that involved only diet and metformin.

Raffone et al. [68] studied PCOS infertile patients who received 1500 mg metformin/day or 4 gr MI/day plus folic acid (400 mcg/day): according to their data, both metformin and MI can be considered as first line treatment for restoring normal menstrual cycles in most patients with PCOS, although the MI treatment seemed to be more effective than metformin (higher restoration of spontaneous ovulation and pregnancy rate). A study by Cappelli et al. [69] compared the effects of the combination of 2 gr MI plus 800 mg of lipoic acid plus 1700 mg metformin per day, to those of the treatment with 3000 mg metformin/day for PCOS. This study showed that the addition of MI and lipoic acid to the 1700 mg dose of metformin produced a better improvement in the metabolic profile of PCOS patients than the 3000 mg dose of metformin in regards to: weight loss (decreased BMI), InsR (decreased HOMA), and hyperandrogenism (decreased free testosterone).

Another nutraceutical that may benefit InsR-related conditions is N-Acetylcysteine (NAC), a precursor to glutathione. Studies suggest that NAC has an insulin sensitizing effect, with one of them showing that a dose of 600 mg of NAC produced similar improvements in PCOS symptoms as 500 mg metformin [70]. NAC's mechanism of action may be related to mitigating the effects of elevated FFAs on insulin signaling.

Based on the studies discussed, we conclude that the combination of metformin with MI or with MI plus lipoic acid may have improved outcomes over metformin treatment alone. We hypothesize that the addition of DCI and NAC to MI and lipoic acid may further improve outcomes of InsR treatment with metformin for InsR-related conditions, which remains to be investigated. Minozzi et al. [71] showed that the addition of MI to the oral estro-progestin (EPs) treatment was more effective in improving endocrine, metabolic, and clinical profile in patients with PCOS than EPs alone. While MI is likely improving insulin sensitivity, EPs are typically known to only affect the sex hormones. Finally, Kamenov et al. [72] showed that the addition of MI to clomiphene citrate improved induction of ovulation and pregnancy rate in anovulatory women with PCOS and InsR.

## Conclusion

Based on our analysis in this article, we conclude that treatment with either or both isoforms of inositol (MI and/or DCI) seem to alleviate InsR acting in synergy with each other and/or, in conjunction with insulin sensitizing pharmaceuticals drugs and/or other nutraceuticals. Based on the rationale presented here, it makes sense to recommend the initiation of treatment for MetS, T2D and insulin-resistant PCOS phenotype conditions with lifestyle interventions and nutraceuticals that may include MI plus DCI, lipoic acid, and NAC. Then, upon evaluation of the results of such combined interventions, pharmaceutical drugs such as metformin may be added, as needed. It is important to note that inositols should not be ingested at the same time with carbohydrate meals due to their competition with glucose for intestinal absorption and intracellular uptake. Patients should also have adequate nutritional status of magnesium (Mg), Mn, zinc (Zn) and B vitamins for optimization of inositol derivatives formation and their actions.

In spite of accumulating evidence, it is currently not possible to draw firm conclusion(s) about the efficacy of these interventions for several reasons: 1) the severe bias due to different samples size, dose, and duration of intervention among the published studies on this topic; 2) the enrolled patients may differ from one study to another regarding biophysical characteristics; 3) our analysis was not derived from a systematic meta-analysis, which should be considered a limitation of our work. Thus, we strongly emphasize the need of additional studies on larger cohorts and with greater statistical power, which may further clarify the outcomes of MI and DCI treatment, establishing the most suitable therapeutic strategies based on patient's clinical condition, and exploring the possibility of individually tailored dosages of MI and DCI.

## Declaration of interest

All the authors have no proprietary, financial, professional or other personal interest of any nature in any product, service, or company other than what is declared for each author under credentials. C. Paul provides research consulting services to Designs For Health, Inc but has no particular financial interest in any product containing ingredients mentioned in this article. The authors alone are responsible for the content and writing of this article. No specific funding was obtained.

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