Inositol Modulation of Essential Metabolic Pathways of Insulin Resistance in Metabolic Syndrome, Polycystic Ovarian Syndrome, and Type 2 Diabetes

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This article will review the evidence for the abilities of myo-inositol (MI) and D-*chiro*-inositol (DCI) to improve dysglycemia and related characteristics of metabolic syndrome (MetS), type 2 diabetes (T2D), gestational diabetes, and polycystic ovarian syndrome (PCOS) by acting in critical metabolic pathways of insulin resistance (InsR).

1. Basic Facts About Inositols

Inositol occurs naturally as nine isomers in a variety of vegetarian and animal foods as well as in the human body. The two isomers MI and DCI have been recognized to be the most predominant and with important functions in human physiology. D-pinitol (a methylated form of DCI) also occurs in human tissues and in certain foods. See Figure 1 (p. 102) for details.

MI and DCI are components of intracellular signaling mediators of insulin action (see details in Figure 2, p. 102).[1,2] Most compelling research to date has been performed with the MI and DCI forms of inositol.

Only a few human studies have used the D-pinitol form and had mixed results. Orally administered D-pinitol was shown to be partially (approximately 33%) converted to DCI in the human body, but no clinical studies are available to date to show how its effects compare with those of MI and/or DCI supplementation.[2–5]

Inositol is not considered an essential nutrient in human nutrition, since MI and DCI can be synthesized in the human physiology from glucose. MI converts into DCI at rates that are specific for various types of tissues.[6] However, MI to DCI conversion has been found to be much lower than normal in patients with T2D or PCOS, as evidenced by their measurement in blood, tissues and urine. For example, one study assessed the urinary ratio of MI/DCI in various populations and the results were as follows[6]:

- 2.5 for control subjects;
- 20.4 for type 2 diabetic patients which may include PCOS patients;
- 13.2 for nondiabetic relatives of type 2 diabetes patients;
- 13.6 for type 2 diabetic patients.

The conversion of MI to DCI is achieved by an epimerase enzyme and its activity was observed to correlate inversely with the degree of insulin resistance.[6,7] Some researchers have categorized this epimerase downregulation as an "enzyme defect" associated with syndromes that display InsR. However, there are reasons to believe that this so-called defect may not simply represent a random genetic mutation but may be the result of evolutionary pressures for adaptation to variable food intake and survival, which selected genetic types more susceptible to developing InsR.[8–14] Thus, the downregulation of epimerase may be viewed instead as a genetically programmed metabolic switch meant to downregulate glucose utilization, thus favoring metabolism of fat for fuel. Specifically, epimerase inhibition results in the reduction of DCI produced from MI in various tissues, while intracellular glucose disposal is influenced by DCI derived cellular mediator DCI-IPG. Figure 2 depicts the intracellular roles of DCI-IPG. Thus, when DCI levels are lowered, glucose metabolism is impaired and this explains in part the state of InsR.[6]

Some researchers hypothesize that this adaptation may have occurred during an "evolutionary type of InsR" triggered by famine, in which case body fat stores release more free fatty acids (FFA). In contrast, the "modern type of InsR" often occurs in the setting of excess caloric intake, especially from fat and high body fat. However, these two distinct metabolic states are similar in the sense that they both display elevated plasma free fatty acids. Excess fatty acids have been shown to impair glucose disposal through well known metabolic switches, which can cause or aggravate InsR.[13,14]

2. MI and DCI Derivatives Alleviate Insulin Resistance

MI and DCI were revealed to be components of a large family of intracellular insulin-signaling mediators. These include phosphoinositol phosphates (PIPs) and inositol

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Inositol Modulation

Figure 1: Dietary sources and supplement forms available for inositols. Relevant inositol forms in human physiology and their interconversions.

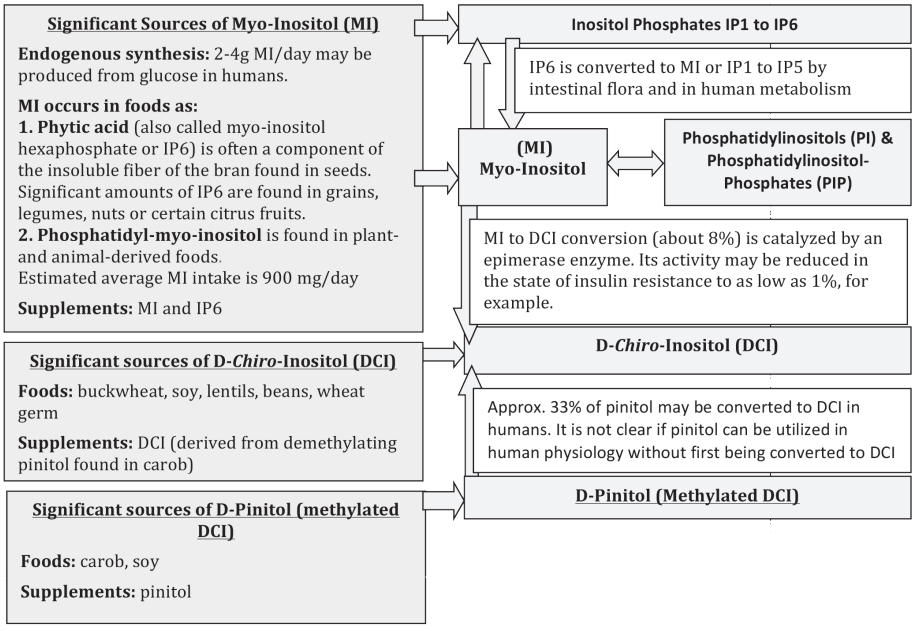
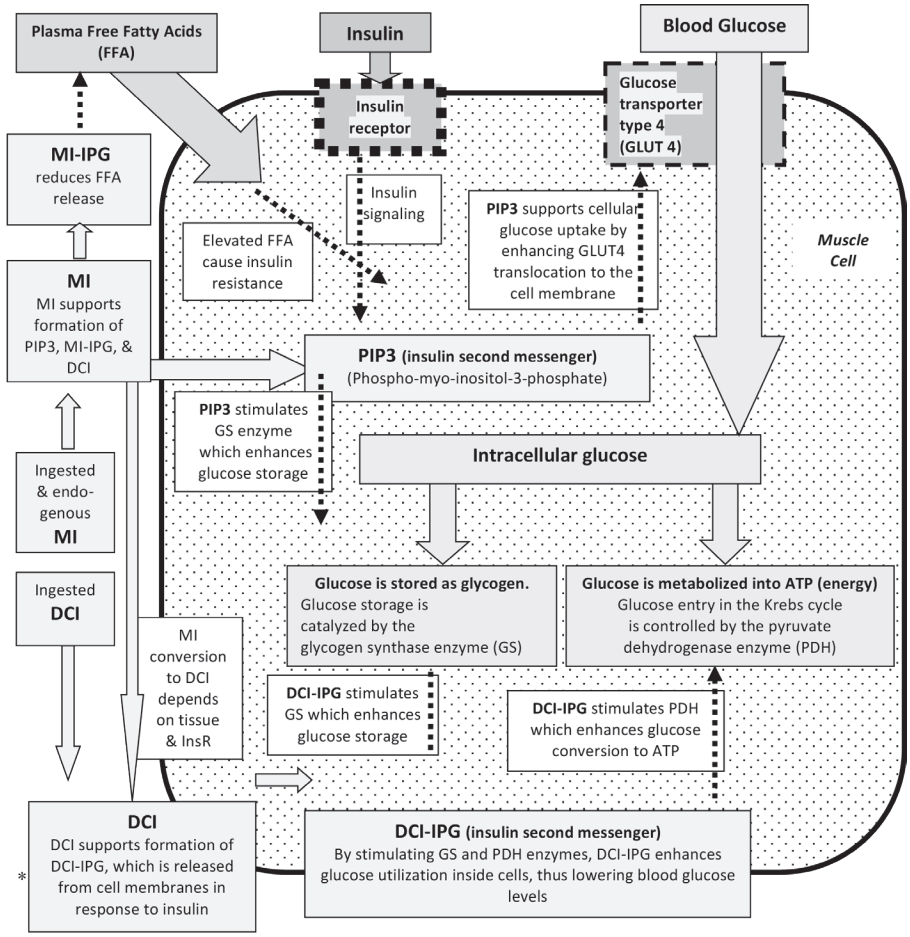


Figure 2: Roles of MI and DCI in supporting insulin stimulated glucose entry and its utilization inside cells.



phosphoglycans (IPGs; MI-IPG and DCI-IPG). The structure of DCI-IPG contains a methylated form of DCI and galactosamine, while that of MI-IPG contains MI and glucosamine and both types of IPGs contain Zn and Mn.[6,15]

Figure 2 illustrates the intracellular roles of MI and DCI derived mediators of insulin signaling for glucose disposal.[6,15–18]

Inositols and their derivatives support an improvement of glucose metabolism, as follows:

1. MI derived phosphoinositol-3-phosphate (PIP3) upregulates glucose transport inside the cells by stimulating GLUT4 translocation to the cell membrane.[15]
2. DCI derived DCI-IPG supports enhancement of glucose conversion to ATP by increasing its transport in the Krebs cycle. This is achieved by the stimulation of the pyruvate dehydrogenase (PDH) enzyme.[15,16]
3. MI and DCI derivatives PIP3 and DCI-IPG, respectively, increase glucose storage as glycogen inside cells. This is achieved by the stimulation of the glycogen synthase enzyme (GS).[7,15,16]
4. MI derivative MI-IPG supports downregulation of free fatty acids (FFA) release from adipose tissues by inhibiting the enzyme adenylate cyclase.[16] This effect is beneficial because FFA have been shown to impair glucose disposal, thus causing InsR and increased triglycerides synthesis.[19]

The four inositol mechanisms of action listed above tend to counteract some of the important metabolic deregulations occurring in InsR syndromes such as impaired glucose transport and insufficient cellular disposal along with elevated plasma fatty acids.[19,20]

In conclusion, researchers hypothesize that supplementation with MI and/or DCI is likely upregulating the production of MI-IPG, DCI-IPG, and PIPs in the body, and by doing so it is at least partially counteracting some of the metabolic deregulation specific to the state of InsR.[6,18]

Also, since MI to DCI conversion is impaired in individuals with InsR, it is important to always include DCI along

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- Supports glucose transport inside the cells
- Supports glucose conversion to ATP by increasing its transport in the Krebs cycle
- Supports glucose storage as glycogen inside cells
- Supports down-regulation of free fatty acids (FFAs) release from adipose tissues, which is beneficial because elevated FFAs have been shown to impair glucose disposal and increase triglycerides synthesis)

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with supplemental MI. Conversely, supplementing with DCI (or D-pinitol) alone cannot not fulfill the MI roles that are distinct from DCI, since DCI does not convert to MI.

Metformin is an insulin-sensitizing pharmaceutical drug and it is important to remark here that one of its mechanisms of actions involves the release of DCI-IPGs from cell membranes, making them available to participate as secondary messengers in insulin signaling. However, the efficiency of metformin's action may be dependent on having adequate DCI-IPG stores in the body, which were shown to be inadequate when InsR was present.[21–23] Thus, we hypothesize that supplementation with MI and DCI may be warranted in most patients that are prescribed metformin for glucose control.

3. Supplementation with Inositols Forms MI and/or DCI Alleviates InsR and Related Abnormalities of PCOS

Polycystic ovary syndrome and its characteristic physiological imbalances. PCOS is characterized by hyperandrogenism, oligoanovulation, and oligomenorrhea and has been reviewed extensively by P. W. Smith in the May 2014 issue of the *Townsend letter* and by Saha, Marshall, and Murray.[24–26] Many researchers consider PCOS a subset of MetS with exaggerated InsR and additional dysregulation of sex hormones affecting 5% to 10% of women.[8–11] PCOS was also referred to as "Syndrome XX," since it is a more severe form of Syndrome X or a phenotypical subset of T2D.[1,24,25,27,28]

Women with PCOS are more susceptible to display elevated insulin levels and to develop MetS with its associated comorbidities.[27,28] Hyperinsulinemia occurs in approximately 80% of obese PCOS women, as well as in 30% to 40% of lean PCOS women.[1,29] PCOS women tend to have 30% to 40% lower glucose disposal than weight-matched normal controls.[28] One cause of the exacerbated InsR in PCOS is believed to be due, at least in part, to a number of postinsulin receptor signaling alterations which affect glucose transport and its cellular metabolism.[30–32]

Since PCOS often involves genetic polymorphisms on insulin signaling pathways, it will likely manifest with InsR in all phases of a woman's life. For example, for PCOS women in menopause the syndrome manifests as an exacerbated state of InsR and displays an above average risk of obesity, metabolic syndrome, diabetes, and cardiovascular disease.[33]

A syndrome similar to PCOS is believed to affect men who are relatives of women with PCOS with the same 5% to 10% incidence as in women. PCOS-specific genes are inherited as an autosomal inherited trait (not related to the sex chromosomes). Men with PCOS genetics have similar hormonal patterns as PCOS women (elevated androgens and low SHBG) and – more importantly – a similar exaggerated state of insulin resistance and risk of cardiovascular diseases. This type of male syndrome is often associated with early onset baldness in the 20s.[34,35]

Summary of Studies that Used MI and/or DCI for PCOS.

Since 1998 numerous studies have been published which investigated the potential for MI and DCI to alleviate the main physiological imbalances of PCOS: infrequent ovulation, oligomenorrhea, elevated androgens, and hyperinsulinemia, a manifestation of InsR.

Table 1 includes a listing of the results from the most relevant studies that used either MI or DCI alone, or a combination of both for alleviating PCOS. All MI and/or DCI interventions achieved significant improvements in the PCOS characteristic deregulations. Ovulation and menstrual regularity were restored in a significantly higher percentage of women in the treatment groups. Total and free testosterone levels were significantly lowered in all studies that measured it (see Table 1). One study also showed improvement in LH and LH/FSH ratio.[36]

All 10 inositol interventions summarized in Table 1 achieved dramatic reductions in homeostatic model assessment of insulin resistance (HOMA-IR), while 5 studies reported impressive lowering of insulin (area under the curve [AUC] post glucose load) and glucose (fasting and/or AUC post a glucose tolerance test).

The dyslipidemia markers (triglycerides, HDL, total cholesterol) were reported in 6 of the studies listed in Table 1 and all show statistically significant improvements. Most dramatic changes were observed in triglyceride lowering, while notable improvements were also seen for HDL, total cholesterol and blood pressure.

Most studies have investigated either DCI or MI for PCOS interventions, but it is not clear why researchers chose one form over the other in any particular study. Two studies tested a combination of MI + DCI (the equivalent of 3300 mg MI + 84 mg DCI in powder form), while 1 of them compared the effects of this combination with that of 4g MI alone (see results in Table 1).[27,37] After 6 months of treatment, both MI and MI+DCI groups showed improvement in all the measured metabolic parameters. However, the MI + DCI combination reduced HOMA-IR twice as much with the rest of the results also superior to those obtained in the MI alone group. It is interesting to note that the results obtained at the end of the study (after 6 months) were significantly better than at midpoint (after 3 months), which implies that MI and/or DCI interventions needed some time to realize their full potential.

The rationale for using the MI + DCI combination was stated by the study authors as follows: "Both myo-inositol (MI) and D-chiro inositol (DCI) glycans administration has been reported to exert beneficial effects at metabolic, hormonal and ovarian level. Beside these common features, MI and DCI are indeed different molecules: they belong to two different signal cascades and regulate different biological processes."[37] This concept is also substantiated by the distinct metabolic roles of MI versus those of DCI and their respective derivatives as outlined in Section 2 and Figure 2.

One recent study showed that interventions with 4 g/d MI or 1 g/d DCI yielded very similar results in parameters measured such as improved ovulation, HOMA-IR, androgen levels, and blood pressure (see Table 1).[38] This may be explained by the fact that the 4 g/d doses of MI could possibly push the conversion of MI to DCI to an extent that may correct the DCI deficiency, at least in part. So, from this study alone one could conclude that DCI is 4 times more potent than MI in alleviating certain PCOS symptoms.

Larner authored many studies investigating and reviewing DCI, and he proposes that this is the more potent form of inositol for alleviating InsR.[6,16,18] On the other hand, MI is needed for oocyte quality and maturation. Concerns have been expressed by some researchers regarding supplementation with DCI without MI, since it may cause an MI deficit in the ovary.[7]

Overall, the MI doses used in studies ranged from 2 to 4 g/day, while a meta-analysis study of MI for PCOS concluded that the higher dose of 4 g/d seems to achieve much better results than lower doses in a higher percentage of subjects. Also, the benefits of inositol supplementation seem to correlate inversely with body fat, prompting researchers to speculate that obese patients may need and benefit from higher doses than 4 g/d.[29] Inositols compete with glucose for entry in the cells, so high blood glucose levels may require increased amounts of inositol.

Many of the MI, DCI, and MI + DCI interventions presented in Table 1 showed a trend for enhancing weight loss as evidenced by small but statistically significant reductions in BMI, while some also showed a reduced waist/hip ratio, an indication of reducing abdominal fat. Intra-abdominal fat generates inflammatory cytokines and contributes more to plasma free fatty acids than subcutaneous fat stored in the rest of the body. Plasma free fatty acids and inflammation are contributing factors to insulin resistance.

4. Supplementation with Inositols Alleviates Characteristic Abnormalities of MetS

The metabolic syndrome has been defined by "resistance to insulin-stimulated glucose uptake occurring in approximately 25% of the population at large" and association with a number of conditions known to be risk factors for coronary heart disease and diabetes.[39–41]

Supplementation with MI, or a combination of MI + DCI, has been proved to alleviate many aspects of MetS in postmenopausal and pregnant women. See Table 2 (p. 106) with results from four studies that have tested the effects of MI or MI + DCI supplementation on improving various metabolic markers of MetS.[42–45] Three of the studies described in Table 2 have reported dramatic drops in HOMA-IR, fasting insulin, ➤

Table 1: Summary of Main Intervention Studies with MI and/or DCI for Women with PCOS

		Markers of insulin resistance or sensitivity						Markers of CVD health					Weight		Androgens	
	Daily Dose	Gluc /IRI	HOMA-IR	AuC Insulin	Fasting Insulin	AUC Glucose	Fasting Glucose	Trigly-cerides	HDL	Total Chol.	DBP	SBP	BMI	WHR	Total Test	Free Test
PCOS Obese, 8 wks[53]	1200 mg DCI	–	–	–62%	–37% but NS	–8% but NS	NS	–40%	NS	–8%	–4%	–3%		–2%	–32%	–55%
	Placebo	–	–	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
PCOS lean, 8 wks[54]	600 mg DCI	+84% Insulin Sensitivity	–	–36%	–	–17%	–7%	–52%	–	–19%	–7%	–3%	–	–	–66%	–73%
PCOS, 14 wks[55]	4g MI + 400 mcg FA	–	–	–	–	–	–	–	+5%	–	–	–	–2%	–	–	–
PCOS, 12 wks[56]	4g MI + 400 mcg FA	–	–80%	–35%	NS	–16%	NS	–5%	–	–19%	–3%	–7%	NS	–	–72%	–72%
	Placebo +400 mcg FA	–	–13%	–2%	NS	no change	NS	–1%	–	+5%	+2%	+5%	NS	–	–6%	–4%
PCOS, 6 mo[37]	equivalent to 3300 mg MI + 84 mg DCI		–44%	–38%	–28%	–38%	–12%	–	–	–	–9%	–2%	–2%	–2%	–66%	–73%
	4g MI	–	–21%	–36%	–22%	–32%	–11%	–	–	–	–6%	–2%	–1%	–1%	–59%	–72%
PCOS, 6 mo[27]	equivalent to 3300 mg MI + 84 mg DCI	–	–40%	–	–18%	–	–16%	–13%	+8%	–14%	–	–	–	–	–	–
PCOS, 6 mo[38]	4g MI + 400 mcg FA	+76%	–50%	–	–	–	–	–	–	–	NS	–8%	NS		–36%	–22%
	1g DCI + 400 mcg FA	+81%	–49%	–	–	–	–	–	–	–	NS	–7%	nS		–33%	–23%
PCOS, 6 mo[57]	1g DCI + 400 mcg FA	+80%	–49%	–	–	–	–	–	–	–	NS	–7%	NS		–33%	–24%
PCOS, 12 wks[36]	0.5g DCI and no diet	+43%			–23%		–11%						–5%		–38%	
PCOS, 12 mo[58]	4gMI + NAC + 400 mcg FA	–	–51%		–45%		–12%									

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and fasting glucose, which were more pronounced than in the "placebo + diet" group.[42–44] The fourth study reported only improvement in fasting glucose.[45] Cardiovascular risk markers improved dramatically as well in all four studies. Also to be noted in the MI intervention groups is the enhanced weight loss versus the diet-only groups.[42–44]

The addition of lipoic acid in the study by Capasso may be justified by the following facts[44]:

- Lipoic acid supplementation has been found to increase the insulin sensitivity by about 20% to 30%.[46,47]
- Lipoic acid is a cofactor for the PDH enzyme.[46] Since DCI-IPG is also a cofactor of the PDH enzyme, this further supports the possibility that these two endogenous metabolites may act in synergy and in a complementary way to boost the activity of PDH, which in turn supports the conversion of glucose to energy.

Supplementation with 4 g MI was also shown to reduce the risk of developing gestational diabetes in PCOS women in three studies.[48–50] For example, D'Anna et al. supplemented pregnant PCOS women with 4 g MI and found that the incidence of gestational diabetes in the MI group was 17.4% versus 54% in the control group.[18] In another study, where MI + diet was used to treat gestational diabetes, there was a significant improvement in HOMA-IR of −50% versus −29% achieved in the placebo + diet group.[50]

D-*chiro*-inositol was administered to STZ diabetic rats and rhesus monkeys and shown to decrease hyperglycemia and enhance glucose disposal regardless of sex.[18] No human studies have been published so far to investigate MI or DCI for benefiting T2D, but all the evidence presented in this review supports the idea that MI and DCI supplementation may be beneficial for these patients by improving insulin sensitivity.

Pinitol, the methylated form of DCI, was tested in a few human studies using participants with T2D. The results are inconsistent and especially disappointing for obese diabetic participants.[2–5] It seems that approximately 33% of pinitol is converted to DCI in the human body, and it is not clear whether it needs to be in order to be beneficial or utilized in human metabolism. It is difficult to compare the effectiveness of pinitol with MI and/or DCI because these have been tested in different types of populations and not side by side in comparative studies.

5. Considerations for Optimal Dosing of MI and or DCI for Alleviating InsR in PCOS and MetS

Based on the studies reviewed above the 4 g MI dose, and doses ranging from 500 mg to 1200 mg of DCI, seem to be effective in alleviating InsR and the related metabolic derangements in PCOS, MetS, and gestational diabetes.

Individuals with PCOS or diabetes have a significant DCI deficiency in various tissues (liver, muscle, kidney, blood) compared with normal individuals, so it makes sense to supplement them with a dose of DCI comparable to the ones used in studies so far. However, one study showed that a safety threshold for DCI supplementation in PCOS patients may be set at 300 mg DCI/day, the highest dose that will not reduce oocyte maturation.[64]

Based on the pharmacokinetics of supplemental inositol, it makes sense to split the daily dose and provide half of it, every 12 hours, in order to maintain continuous therapeutic levels of inositols. It is best to take inositols on an empty stomach, especially away from meals high in carbohydrates, since inositol competes with glucose for absorption in the gut and uptake from the bloodstream into cells.[21,22]

Patients should make sure that they have adequate intake of zinc, manganese, and magnesium, as these minerals have an important role in inositol transport and metabolism. Other supplements, such as lipoic acid and NAC, may have additive synergistic effects in improving glucose metabolism.[44,46,47,51,52]

In conclusion, MI and DCI may be deemed conditionally essential nutrients for conditions such as MetS, T2D, and PCOS wherein dysglycemia and InsR play critical roles. The results of the clinical studies discussed in this review show that average dietary inositol intake and endogenous inositol production need to be supplemented with additional MI and DCI in order to bring their glucose metabolism closer to homeostasis.[27,36–38,53–58] This concept is also supported by the excess urinary loss of MI observed in these conditions. Thus, MI and DCI qualify as ingredients for medical foods in support of PCOS, MetS, gestational diabetes, and possibly also T2D.

For example, a dietary supplement is offered commercially by Designs for Health Inc., under the name Sensitol, which provides an inositol supplement composed of MI, DCI, and lipoic acid.

Table 2: Summary of Studies with MI for Metabolic Syndrome in Postmenopausal and Pregnant Women

		Markers of insulin resistance			Markers of CVD health					Weight loss		
	Daily Dose	HOMA-IR	Fasting Insulin	Fasting Glucose	Tri-glycerides	HDL	Total Cholesterol	DBP	SBP	BMI	Waist Circumference	WHR
Women postmenopausal n = 80, 6 mo[42]	4 g MI + diet	–77%	–69%	–17%	–21%	+28%	–20%	–12%	–4%	–3%	–6cm	–
	placebo + diet	–25%	NS	–4%	NS	NS	–7%	no chg	NS	–1%	–1cm	–
Women postmenopausal n = 80, 12 mo[43]	4 g MI + diet	–78%	–70%	–15%	–34%	+21%	–22%	–16%	–7%	–5%	–7cm	–
	placebo + diet	–42%	–33%	–6%	–9%	+5%	–10%	–9%	–1%	–2%	–1cm	–
Women postmenopausal n = 155, 6 mo[44]	4 g MI + lipoic acid + low-cal diet	–33%	–45%	–10%	–19%	+15%	–5%	–	–5%	–2cm	–9%	
	placebo + diet	–1%	no change	–5%	no chg	no chg	no chg	–	–	–3%	–1cm	–9%
Healthy pregnant women with MetS, n = 65, 60 days[45]	2 g MI + 800 mg DCI +10 mg Mn + 400 mcg FA	–	–	–4%	–24%	–10%	–20%	ns	–5%	–	–	–

In conclusion, human clinical trials using MI and/or DCI supplementation have only employed menopausal women with InsR, women of reproductive age with PCOS, and pregnant women at risk of gestational diabetes or those who have already developed it.

However, based on all the evidence available and mechanisms of action, it is reasonable to believe that MI and DCI may also improve glucose metabolism in most women with InsR or T2D of reproductive age regardless of PCOS status. The same rationale leads us to believe that most men with InsR as part of MetS or T2D may similarly benefit from MI and/or DCI supplementation. Men related to women with PCOS, who are likely to have PCOS type genetics, may benefit from these interventions even more so.

Individuals with dysglycemia, InsR, and diabetes tend to have elevated urinary excretion of MI, while that of DCI is typically reduced.[6,21,22] Excessive urinary loss of inositols may be due to elevated blood glucose which competes with inositols for reabsorption in the kidneys.[22] All studies report consistently that these individuals have an elevated urinary MI/DCI ratio, which may be due in part to a poor MI to DCI conversion. Each patient may have a different genetic and metabolic situation, while their diet and degree of obesity also influence their degree of InsR and thus MI/DCI ratios in various tissues. If the measurement of plasma and urinary MI and DCI become commercially available, it may be then feasible to optimize MI + DCI supplementation based on the ongoing needs of individual patients and on objective testing in the clinical setting. In fact, the urinary MI/DCI ratio has been proposed as an index of InsR by many research groups.[59–63]

Notes

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