Sensitol™

Supports normal insulin function and cellular metabolism

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Sensitol™ is a unique formulation comprised of two naturally occurring isomers of inositol – myo-inositol (MI) and D-chiro-inositol (DCI) – along with alpha lipoic acid, designed to modulate the metabolic pathways involved in insulin resistance. Insulin resistance (InsR) is a syndrome involving a dysregulation of insulin and glucose metabolism that has been implicated as a causative and/or aggravating factor in many pathological conditions and diseases such as:[39,40,41]

- Metabolic Syndrome (MetS) and Obesity
- Type II Diabetes (T2D)
- Gestational Diabetes
- Polycystic Ovarian Syndrome (PCOS)
- Gout
- Cancer
- Various inflammatory conditions
- Brain degenerative conditions

Genetics seem to play a role in the risk of developing all these conditions, along with lifestyle and diet, while supplementation with specific nutrients or herbal extracts can help reduce this risk.[2,8-13]

Highlights

Inositol

Inositol occurs naturally as nine isomers in a variety of vegetable and animal foods as well as in the human body. Two of the isomers, myo-inositol (MI) and D-chiro-inositol (DCI), have been recognized to be the most predominant and have important functions in human physiology, such as mediating cell signaling from insulin and from sex and thyroid hormones. The average adult consumes approximately 900mg/day of myo-inositol. However, it is not clear how much dietary inositol is actually absorbed.

Inositol Supplementation

Inositols are not considered essential nutrients since they can be synthesized in the body from glucose at the rate of 2-4g MI/day. However, MI and DCI may be considered conditionally essential nutrients for conditions where dysglycemia and InsR play critical roles, and for which dietary inositol intake and endogenous production are not adequate, such as MetS, gestational diabetes, T2D and PCOS. Thus, MI and DCI supplementation with InsR may help bring insulin signaling and glucose metabolism closer to homeostasis.

Combining Alpha Lipoic Acid (ALA) with MI:[3,4,5,44,66]

- ALA has been shown to increase insulin sensitivity by approximately 20-30%.[46,47]
- ALA is a cofactor for the pyruvate dehydrogenase (PDH) enzyme.[46] Since DCI-IPG (DCI-inositol phosphoglycan) is also a cofactor of the PDH enzyme, these two endogenous metabolites may act in synergy to boost PDH activity, which in turn supports the conversion of glucose to energy.

MI and DCI Derivatives and Insulin Signaling

MI and DCI are components and precursors of intracellular signaling mediators of insulin action (see Figure 1). MI and DCI derivatives include phosphoinositol phosphates (PIPs) and inositol phosphoglycans (IPGs): MI-IPG and DCI-IPG. DCI-IPG contains a methylated form of DCI and galactosamine, while MI-IPG contains MI and glucosamine; both contain zinc and manganese.[6,15]

Figure 1 illustrates the specific intracellular roles of MI- and DCI-derived mediators which affect glucose-related metabolic pathways.[1,2, 6,15,16,17,18] Inositols and their derivatives support improved glucose metabolism as follows:

1. MI-derived phosphoinositol-3-phosphate (PIP3) up-regulates glucose transport inside the cells by stimulating GLUT4 translocation to the cell membrane.[15]
2. DCI-IPG stimulates the PDH enzyme, facilitating the conversion of glucose to ATP.[15,16]
3. PIP3 and DCI-IPG increase glucose storage as glycogen inside cells through the stimulation of the glycogen synthase enzyme.[7,15,16]
4. MI-IPG down-regulates the release of free fatty acids (FFAs) from adipose tissues,[16] which is beneficial because elevated FFAs have been shown to impair glucose disposal, causing InsR and increased triglyceride synthesis.[19]

These four inositol mechanisms of action tend to counteract important metabolic dysregulations occurring in InsR syndromes, such as impaired glucose transport and reduced cellular disposal along with elevated plasma fatty acids.[19,20] Supplementation with MI and/or DCI seems to help up-regulate the production of MI-IPG, DCI-IPG and PIPs in the body,[6,18] and by doing so may partially counteract some of the main metabolic dysregulations specifically occurring in InsR. There may be evolutionary adaptations that involve inositol-related pathways which explains why their supplementation is so effective in alleviating InsR.

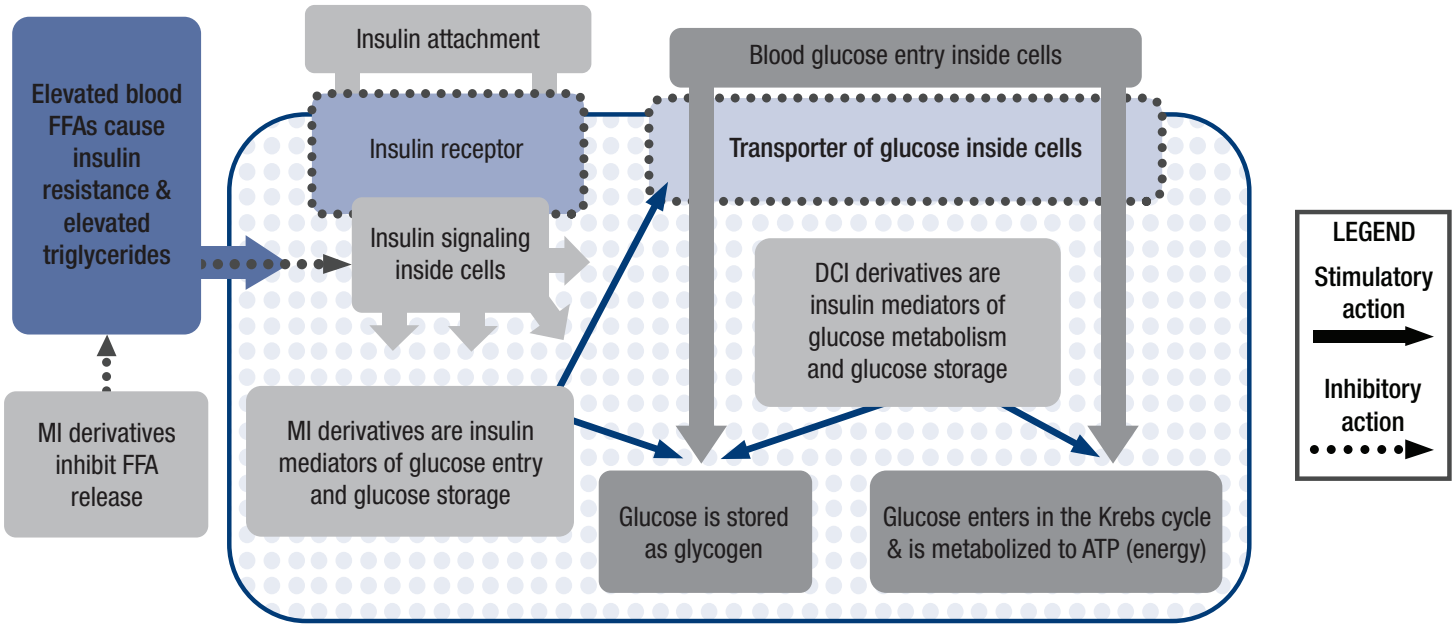

FIGURE 1. ROLES OF MI AND DCI DERIVATIVES IN SUPPORTING INSULIN-STIMULATED GLUCOSE ENTRY AND ITS UTILIZATION INSIDE CELLS

Increased nutritional demand for MI and DCI may be due to:

1. ***Impaired conversion*** – The conversion of MI to DCI is achieved by an epimerase enzyme whose activity inversely correlates with the degree of insulin resistance in various tissues.[6,7] MI to DCI conversion is about 8% in muscle cells but its activity is tissue-specific and may be reduced in insulin resistance to as low as 1%. Tissues such as brain, heart and ovaries contain higher amounts of MI than other tissues, whereas liver, muscle and fat tissues, which have significant glycogen storage, contain higher amounts of DCI than other tissues. However, the overall content of MI is much higher than DCI in all tissues and their ratios are tissue- and metabolic state-dependent.[1,14,21,28]

> Since MI to DCI conversion is impaired in individuals with InsR, it is important to include DCI when supplementing with MI. Conversely, supplementing with DCI alone cannot fulfill the MI roles that are distinct from DCI, since DCI does not convert to MI.

2. ***Excess urinary loss*** – Individuals with PCOS or diabetes were found to have elevated urinary excretion of MI and DCI.[6,21,22] This excess urinary loss may be due to a combination of genetics and elevated blood glucose, the latter of which outcompetes MI and DCI for reabsorption in the kidneys.[22]

Studies have also found elevated MI/DCI ratios in plasma or urine of individuals with InsR or in relatives with diabetes (pointing to the condition's genetic component),[32] as well as in those with PCOS.[21] These elevated MI/DCI ratios are attributed to an impaired conversion of MI to DCI. This is a reflection of reduced activity of the epimerase enzyme, which may be caused by genetics and/or glucose intolerance.[1,14] In fact, many research groups have suggested using the urinary MI/DCI ratios as an index of InsR.[59-63]

Myo-Inositol and Metformin

Metformin is a pharmaceutical drug often prescribed for conditions that involve InsR. One of its mechanisms of action involves the release of DCI-IPGs from cell membranes, which enhances insulin sensitivity. However, the efficiency of metformin's actions may be dependent on having adequate DCI-IPG stores in the body, which were shown to be inadequate with InsR.[21,22,23] Thus, supplementation with MI and DCI may be warranted in patients who are taking metformin. One study with PCOS subjects showed that the addition of 2g MI and 800mg alpha lipoic acid to 1700mg metformin achieved better results in lowering weight, HOMA (homeostatic model assessment for quantifying insulin resistance), and testosterone than the 3000mg dose of metformin alone (see Table 1).[66] This approach may be especially useful for patients who cannot tolerate the side effects of higher doses of metformin.

TABLE 1. EFFECTS OF ADDING MI AND ALPHA LIPOIC ACID TO METFORMIN WITH PCOS-RELATED SYMPTOMS

	Treatment	BMI	HOMA	Total Testosterone
Study for PCOS, BMI >40, 6 mo, 2013[66]	3000mg metformin	-15%	-13%	-33%
	1700mg metformin + 2g MI + 800mg lipoic acid	-28%	-33%	-75%

Inositols and Metabolic Syndrome

Supplementation with MI, or MI + DCI, has been shown to alleviate many aspects of MetS in postmenopausal and pregnant women. Table 2 displays the ranges of results from four studies that tested the effects of MI[42,43,44] or MI + DCI[45] supplementation on improving various metabolic markers of MetS. Three of the studies reported dramatic decreases in HOMA-IR, fasting insulin, and fasting glucose, which were much more pronounced than in the placebo + diet group.[42,43,44] Cardiovascular risk markers improved dramatically in all four studies.[42-45]

TABLE 2. SUMMARY OF INTERVENTION STUDIES WITH MI AND/OR DCI FOR METABOLIC SYNDROME

		Markers of Insulin Resistance or Sensitivity			Markers of CVD Health				
Study Purpose	Daily Dose	HOMA-IR	Fasting Insulin	Fasting Glucose	Triglycerides	High Density Lipoprotein	Total Cholesterol	Diastolic Blood Pressure	Systolic Blood Pressure
MI for MetS in menopause[42,43,44]	4g MI[42,43] 4g MI + 400mg lipoic acid[44]	-33% to -78%	-45% to -70%	-4% to -17%	-19% to -34%	+10% to +28%	-5% to -22%	-12% to -16%	-4% to -7%
MI + DCI for MetS in pregnancy[45]	2g MI + 800mg DCI	-	-	-4%	-24%	+10%	-20%	NS	-5%

Inositols and Gestational Diabetes

Supplementation with 4g MI was shown to reduce the risk of developing gestational diabetes in women with PCOS.[48,49,50] In one study where pregnant PCOS women were given 4g MI, the incidence of gestational diabetes in the MI group was 17.4% versus 54% in the control group.[48] In a different study, where MI + diet was used to treat gestational diabetes, there was a significant improvement in HOMA-IR of -50% versus the -29% achieved in the placebo + diet group.[50]

In an animal study, DCI was shown to decrease hyperglycemia and enhance glucose disposal regardless of gender.[18] Excess urinary loss of MI and DCI was observed in diabetics, which may likely be responsible for worsening insulin signaling and sensitivity. This in turn may create a vicious cycle that progressively increases MI and DCI deficiencies in a majority of body tissues.[14,28]

Inositols for PCOS

PCOS is characterized by hyperandrogenism, oligoanovulation and oligomenorrhea.[24-28] Many researchers consider PCOS to be a subset of MetS with exaggerated InsR and additional dysregulation of sex hormones affecting 5-10% of women.[8-11]

Women with hyperinsulinemia are at higher risk for PCOS, MetS, and associated comorbidities.[27,28] Approximately 80% of obese PCOS women are hyperinsulinemic, as are 30-40% of lean PCOS women.[1,29] Women with PCOS tend to have 30-40% lower glucose disposal than weight-matched normal controls.[28] One cause of the exacerbated InsR is believed to be due, at least in part, to a number of post-insulin receptor signaling alterations which affect glucose transport and its cellular metabolism.[30,31,32] Since PCOS often involves genetic polymorphisms on insulin signaling pathways, it will likely manifest with InsR in all phases of a woman's life.

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

TABLE 3. SUMMARY OF INTERVENTION STUDIES WITH MI AND/OR DCI FOR PCOS

		Markers of Insulin Resistance or Sensitivity						Markers of CVD Health					Androgens	
Study Purpose	Daily Dose	Gluc/IRI	HOMA-IR	AUCi	FI	AUCg	FBG	TG	HDL	TCH	DBP	SBP	TT	FT
MI and/or DCI for PCOS[27, 36-38,53-58]	4g MI and/or 500-1200mg DCI	+43% to +84%	-49% to -80%	-35% to -62%	-23% to -45%	-16% to -17%	-7% to -12%	-40% to -52%	+5%	-8% to -19%	-3% to -7%	-3% to -8%	-32% to -72%	-22% to -72%
MI + DCI for PCOS 6 mo, 2012[9]	3300mg MI +84mg DCI		-44%	-38%	-28%	-38%	-12%	-	-	-	-9%	-2%	-66%	-73%
	4g MI	-	-21%	-36%	-22%	-32%	-11%	-	-	-	-6%	-2%	-59%	-72%
MI + DCI for PCOS 6 mo, 2013[10]	3300mg MI +84mg DCI	-	-40%	-	-18%	-	-16%	-13%	+8%	-14%	-	-	-	-

AUCg: Area Under the Curve Glucose
AUCi: Area Under the Curve Insulin
DBP: Diastolic Blood Pressure
FBG: Fasting Blood Glucose
FI: Fasting Insulin
FT: Free Testosterone
Gluc/IRI: Glucose immunoreactive insulin*
HDL: High-Density Lipoprotein
HOMA-IR: Homeostatic Model Assessment for Quantifying Insulin Resistance*
SBP: Systolic Blood Pressure
TCH: Total Cholesterol
TG: Triglycerides
TT: Total Testosterone

***HOMA-IR** = Homeostatic model assessment of insulin resistance = Venous plasma glucose (mmol/l) x plasma insulin (mU/l) / 22.5
***Gluc/IRI** = Ratio of fasting glucose (mmol/l) /fasting immunoreactive insulin (mU/l)

Numerous studies have investigated the potential for MI and/or DCI to alleviate the main physiological imbalances of PCOS, including infrequent ovulation, oligomenorrhea, elevated androgens and hyperinsulinemia (see Table 3). All MI and/or DCI interventions achieved significant improvements in the dysregulations characteristic of PCOS. Ovulation and menstrual regularity were restored in a significantly higher percentage of women in the treatment groups, while total and free testosterone levels were significantly lowered closer to normal.

Combined MI + DCI for PCOS

Research shows that supplementation with DCI alone may impair oocyte quality and cause physiological imbalances in the ovaries and possibly other tissues. Supplementation with a combination of MI + DCI appears to be a more effective and appropriate approach.[27,37] The rationale is 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 implies that MI has molecular actions on pathways other than those related to its conversion to DCI.

Supplement Facts

Serving Size 2 capsules
Servings Per Container 60

Amount Per Serving	% Daily Value
Inositol (as myo and D-chiro) 1.6 g	*
Alpha Lipoic Acid 100 mg	*

*Daily Value not established.

Other Ingredients: Microcrystalline cellulose, vegetable sterate, silicon dioxide.

MADE WITH GMO-FREE INGREDIENTS

How to Take

- Take two capsules, two times per day, ideally 12 hours apart, or as directed by a health care practitioner.
- Best taken on an empty stomach, especially away from meals high in carbohydrates.[21,22] Inositol absorption is also impaired by compounds in coffee.

For a list of references cited in this document,
please visit the product landing page at catalog.designsforhealth.com