

## Inositols in Midlife

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ABSTRACT

This review describes the mechanistic, animal, and clinical data related to the use of inositols in midlife. It covers studies related to the mechanism of action of myo-inositol and D-chiro-inositol and randomized controlled trials conducted in postmenopausal women with metabolic syndrome and supports these data with the results of *in vitro* and animal studies on inositol in nephropathy and other related conditions. Recent advances related to biochemistry, pharmaceutical science, and genetics are discussed. It concludes that inositols have a potential role to play in maintaining metabolic health in postmenopausal women.

**KEYWORDS:** *Diabetes, D-chiro-inositol, myo-inositol, metabolic syndrome, postmenopausal*

### INTRODUCTION

The inositols, myo-inositol (MI) and D-chiro-inositol (DCI), have been studied extensively in endocrine as well as in metabolic disorders.<sup>[1]</sup> Less attention has been paid, however, to the potential effects of inositols in a midlife population. This is surprising because the prevalence of metabolic dysfunction and need for safe, well-tolerated metabolic modulation is greater in this age group. This review describes the rationale for the use of inositols in midlife individuals, the evidence related to its efficacy, possible pleiotropic benefits, and recent advances which may make their use a reality.

#### Inositol in nature

MI is commonly found in foodstuffs such as fruits, beans, grains, and nuts. Fresh vegetables and fruits contain more MI than frozen, canned, or salt-free preparations. A high MI diet may be said to contain 225–1500 mg/day/1800 cal.<sup>[2]</sup> Beans, cantaloupe, grapefruit, and whole grain bread are such sources of inositol. Phytic acid, a dietary nutrient, found in vegetables, grains, and legumes is also converted to inositol, but is not directly bioavailable to humans. Lecithins, however, are well absorbed and relatively bioavailable sources of inositol.

It is possible that change in dietary composition may mediate metabolic syndrome through MI deficiency. This is doubtful, however, as inositol can early be

produced by catabolism of glucose in the body. Inositol is not considered an essential nutrient or vitamin as it can be produced in the body. Most inositol is synthesized in the kidneys, in relatively large amounts (grams per day).

#### Inositol biology

Inositol biology is a relatively new but rapidly expanding field of endocrinology and metabolism. Earlier labeled as a Vitamin B, and as a pseudovitamin, this isomer of glucose is an active participant in multiple cellular processes and structures. In its free form, as isomers or as phosphate derivatives, it contributes to ion channel permeability, mRNA export and translation, cytoskeleton remodeling, stress response, metabolic homeostasis, oocyte maturation, sperm function, and cognitive function. As phosphatidylinositol, it is a prominent component of cytoplasmic membranes.<sup>[3]</sup>

Inositol dysregulation is associated with various acute and chronic diseases, though the mechanisms of action are not clear to researchers. Inositol supplementation, as MI, as DCI, or as a combination of both, has been tried in a diverse variety of disease states relevant to midlife, including diabetes, kidney failure, respiratory distress syndrome, Alzheimer's disease, and cancer.<sup>[1]</sup>

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### Inositol in insulin resistance states

Inositol is insulin mimetics which are able to reduce postprandial glycemia. Insulin resistance (IR) is associated with abnormalities in inositol metabolism and can be reversed or attenuated by inositol,<sup>[4]</sup> which is thought to be the second messenger of insulin.<sup>[5,6]</sup> Inositol supplementation can be used to manage disorders of IR and complications of diabetes (neuropathy, nephropathy, and cataract). It is suggested that inositols can be used as metabolic modifiers or metabolic modulators, in metabolic syndrome, to achieve a comprehensive metabolic health, without any side effects.<sup>[7]</sup>

Such a strategy is of special importance in vulnerable populations such as the elderly and those in midlife, as they are more prone to adverse effects of drugs, drug–drug interactions (due to polypharmacy), and hypoglycemia. It is possible that inositol supplementation inhibits inositol hexakisphosphate kinase 1 (IP6K1), thus reducing diphosphoinositol pentakisphosphate (IP7) production. This reduces the binding of IP7 with protein kinase B (Akt/PKB) (serine/threonine protein kinase), thus allowing Akt/PKB membrane translocation and insulin-stimulated glucose uptake.<sup>[8]</sup> This insulin-independent pathway circumvents IR in the AMPK pathway and opens the gates for a synergistic effect with metformin.

### Inositol in diabetes

In an animal study, DCI was administered to diabetes rats at two doses (30 and 60 mg/kg/day). The higher dose was found to reduce blood glucose while reducing serum insulin simultaneously. This was due to upregulation of glycogen synthase, protein glucose transporter-4 (GLUT-4), phosphatidylinositol-3-kinase (PI3K), P85, PI3KP110, and Akt, in the liver and skeletal muscle.<sup>[9]</sup>

Myo-inositol oxygenase (MIOX) is a tubular enzyme whose activity is upregulated in tubulointerstitial injury. MIOX catabolizes MI and its upregulation may reduce MI levels, while increasing reactive oxygen species generation, depleting reduced glutathione, and altering NAD<sup>+</sup>/NADH ratios. These changes may lead to progression of diabetic nephropathy.<sup>[10]</sup>

Such evidence is available from murine studies, in which high-fat diet-fed mice were found to have higher MIOX levels. Renal MI depletion in dietary-induced obesity (–19%) was less than that noted in diabetes mellitus (–35%) and hypertension (–51%). This raises the possibility of using inositol supplements to prevent and manage chronic kidney diseases of various etiologies.<sup>[11,12]</sup>

### Inositol in midlife

MI has been the focus of randomized controlled trials in postmenopausal women with metabolic syndrome. In a 6-month long study, 80 such women were treated with either diet +MI 2 g twice daily or diet + placebo, and MI improved diastolic blood pressure (–11%), homeostatic model assessment (HOMA) index (–75%), and serum high-density lipoprotein (HDL)-cholesterol (+22%) significantly.<sup>[13]</sup> In a 12-month study conducted in 80 postmenopausal women with metabolic syndrome, 2 g MI twice daily improved serum glucose, insulin, HOMA-IR, total cholesterol, HDL-cholesterol, and serum triglycerides, as compared to placebo, when administered in conjunction with dietary therapy. By the end of 1 year, 8 out of 40 women treated with MI did not meet the definition of metabolic syndrome. Such an improvement was noted in only 1 out of the 40 control participants.<sup>[14]</sup>

In another study of 60 postmenopausal women with metabolic syndrome, 2 g MI + 30 mg cocoa polyphenols + 80 mg isoflavones, was compared with placebo over 6 months. The combination of MI and nutraceutical improved glucose (–12 mg %), triglycerides (–20 mg %), visfatin (–0.9 ng/ml), resistin (–5 µg/l), and bone-specific alkaline phosphatase (+4ug/ml) as compared to placebo. No change was noted in HDL-cholesterol and adiponectin levels.<sup>[15]</sup>

### Recent advances

#### Genetics

Advances in genetics may contribute to greater use of inositols in therapeutics. Type 2 SH2 domain containing inositol 5-phosphatase (SHIP) is an important determinant of insulin sensitivity. Function-affecting mutations of SHIP have been detected in murine models of Type 2 diabetes and hypertension as well as in persons with type 2 diabetes. In a study of 1304 British individuals, from 424 families, single-nucleotide polymorphisms (SNPs) were found to correlate with hypertension and other components of metabolic syndrome. Similar SNP correlations were noted with hypertension in a cohort of 905 type 2 diabetes patients from France.<sup>[16]</sup> Such data may pave the way for individualized genotype-based therapy with inositols.

#### Biochemistry

Workers in biochemistry have also developed a gas chromatography–mass spectroscopy (GC-MS) method to detect MI in human plasma. This method is accurate and sensitive and can be used as marker to detect neural tube defects, especially spina bifida.<sup>[17]</sup> However, this method has not been used in routine clinical practice so far.

## Pharmaceuticals

Pharmaceutical researchers have identified various analogs of DCI and evaluated their ability to stimulate glucose transport. Based on positional analysis, the oxygen at positions 1 and 3 has minimal effect on activity. While the position 1 hydroxyl group can be modified with affecting glucose uptake, the position 3 hydroxyl is sensitive to modification. This shows a potential for the development and use of engineered DCI analogies with specific pharmacokinetic and dynamic properties.<sup>[18]</sup>

Currently, improved gel-capsule versions of MI and DCI are available which allow enhanced bioavailability as compared to powered formulations. The ratios of MI and DCI vary and are a subject of debate. It is thought, however, that absolute concentrations of MI and DCI are more important than their ratio.<sup>[19]</sup>

Researchers have also developed a novel C2-symmetrical chiral phosphoramidite, which allows bisphosphorylation and chiral resolution. This creates a concise synthetic route which can be used to prepare biologically relevant inositols in high optical purity.<sup>[20]</sup>

## CONCLUSION

This review highlights the potential for use of inositol supplementation in midlife. Robust data support the use of inositol in metabolic syndrome in postmenopausal women and suggest its use in related conditions such as thyroid disease and nephropathy. Further research and enhanced understanding of the mechanism of action of MI and DCI will encourage their use as nutraceutical supplements in maintaining optimal metabolism in midlife.

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## Conflicts of interest

There are no conflicts of interest.

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