REVIEW ARTICLE Agricultural Reviews, Volume 46 Issue 5: 796-801 (October 2025)

Investigating the Role of Inositol: Myo-inositol and D-Chiro-inositol in Diabetes: A Review

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10.18805/ag.R-2706

ABSTRACT

The sugar alcohol known as inositol and its derivatives are becoming more and more interesting in metabolism-related research studies due to its physiological roles. Inositol derivatives mainly myoinositol and d-chiroinositol have gained so much attention these days in the context of managing and treating metabolic issues such as diabetes and polycystic ovarian syndrome. For a long time, it was considered as the vitamin B, but later we got to know it is produced from glucose so considered non-essential. Nowadays rising rates of obesity which are further linked with diabetes and polycystic ovarian syndrome have fuelled demand for artificial sweeteners. Many people are searching for options to maintain their weight, which has led to the widespread usage of sucrose and fructose substitutes in the food industry. Sugar alcohols such as myo-inositol and d-chiro-inositol (which are not been commonly used) in particular can be metabolized without the need for insulin control and have little effect on blood sugar levels. These sugar substitutes have the potential to provide sweetness without raising blood sugar levels and adding calories. These have half of the sweetness of sucrose. This paper aims to thoroughly investigate and understand the various roles played by inositol in the complex field of managing metabolic diseases. To find out the eligible papers for review paper screening has been performed through PubMed, Science Direct, Web of Science and Google Scholar. Different sets of keywords such as inositol, d-chiro-inositol, myo-inositol, insulin-resistance, diabetes, insulin sensitivity, DCI and type 2 diabetes mellitus were used. Studies which full text article were present used for the review. Research articles have been included the studies specifically to find out the relation between myoinositol and diabetes or any metabolic disease. The development of many diseases, such as PCOS and diabetes, is linked with inositol deficiency. Myoinositol is derived from the food we eat as well as from within. The low levels of MI can be the result of several factors, including decreased dietary intake, increased catabolism, alterations in the gut and reduced biosynthesis. These two forms, myoinositol and d-chiroinositol play significant roles in regulating lipid metabolism and glycaemic control. glycaemic metabolism and this are also supported by many research studies. Therefore, it can be a possible treatment or management option for people suffering from metabolic issues such as diabetes and PCOS. Future studies should focus on how we can increase the intake of myo-inositol through diet and dietary food products.

Key words: Diabetes, Insulin sensitivity, Myoinositol, PCOS.

Diabetes is a very complicated disease and every possible treatment option should be explored and applied to control diabetes (Madhu *et al*., 2017). Sugar alcohols are molecules derived from sugars, with one hydroxyl group connected to each carbon atom (Awuchi *et al*., 2019). A form of sugar alcohol named inositol is naturally found in many foods. It is also generated by the human body as well. Myoinositol and D-chiroinositol are two common types of sugar alcohol which are having a positive impact on human health. Myoinositol for a long time considered vitamin B. Myoinositols produced from glucose so not considered an essential nutrient. Apart from this, it contains half the sweetness of sucrose which made it a point of attraction for the researchers as providing sweetness as well as health benefits too (Awuchi *et al*., 2019, DiNicolantonio, 2022). Myoinositol plays an important role in many physiological processes and has been researched for its possible health advantages, mainly in the context of insulin sensitivity improvement, hormone balance and mental wellness (DiNicolantonio *et al*., 2022; Özturan, 2019). In humans, myoinositol is generally produced from glucose and through different processes converted into free myoinositol. So myoinositol may found in free form or it can be attached to phospholipids or inositol phosphate derivatives. Each kidney also produces nearly 2 g of myoinositol per day which means in total approximately 4 g of myoinositol per day and other tissues synthesize it (DiNicolantonio *et al*., 2022). Aside from kidney organs such as the brain, testis and liver, also produces it inside the body which in comparison with the kidney quite low. This also shows the contribution of various organs to the endogenous production of inositol. The brain has the highest concentration of inositol and plays a significant

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How to cite this article: Chauhan, N. and Jogpal, V. (2025). Investigating the Role of Inositol: Myo-inositol and D-chiro-inositol in Diabetes: A Review. *Agricultural Reviews*. **46(5):** 796-801. doi: 10.18805/ag.R-2706.

Submitted: 12-03-2024 **Accepted:** 15-08-2024 **Online:** 13-11-2024

role in facilitating the binding of some steroid hormones and other neurotransmitters to their receptors (Bizzarri *et al*., 2016). Myo-inositol from the diet exists in a variety of phosphorylated forms as well which includes, forms (Ins-1-P, Ins-3-P, or Ins-4-P), forms [PP-InsP4, PP-InsP5, PP2-InsP3, or (PP) 2-InsP4] andinositol hexaphosphateform or phytic acid. In addition, regenratedinositoltriphosphate (IP3) and inositolbisphosphate (IP2) produce free inositol. As a result, consuming myo-inositol is expected to conserve both IP3 and IP2 (Greene *et al*., 1982). The production power of the body to produce myo-inositol is dependent on NAD+ and magnesium (Mg) therefore deficiency in any of these can result in a myoinositol deficiency (Chu *et al*., 1980, Bevilacqua *et al*., 2018). If caffeine intake is high in the diet this also increases the requirement of myoinositols. Myoinositol's requirements increase with age, antibiotics use, conditions like type 1 type 2 diabetes, refined carbohydrates intake and sodium deficiency (DiNicolantonio *et al*., 2022).

Inositol is naturally present in many food items such as brazil nuts, walnuts, beans, oats, citrus fruits and cantaloupe which includes melons. Oranges and cantaloupe are the rich sources of inositol. In plants, inositol is present as the phytic acid and its salts (phytates) which act as phosphate reserves and are present in wheat bran and seeds. Dietary inositol is indigestible and not properly absorbed but various food preparation processes partly degrade phytates to increase their availability. Inositols present in the form of glycerophospholipids, such as those found in plant-derived substances like lecithin, are efficiently absorbed and exhibit relatively high bioavailability (Awuchi *et al*., 2019, Chu *et al*., 1980). Insufficient food intake, increase in catabolism (substance breakdown), changes in the gut microbiota (microorganisms in the digestive system) and decrease in biosynthesis (the body's own production of inositol) can result in low levels of inositol (Chu *et al*., 1980).

Myo-inositol serve as a structural component for the cell membrane and is crucial for the synthesis of phospholipid. Which significantly contributes to insulin signalling by activating many secondary messengers in association to insulin (Anna *et al*., 2013, Giordano *et al*., 2011). Over the last decade, the combination of myoinositol and d chiroinositol has been significant in the treatment of PCOS due to its potency, accessibility and safety (Genazzani A.D., 2016). Inositol acts as a secondary messenger and engages in a variety of activities such as cell structure formation, nerve cell guidance, insulin function, calcium level regulation, fat breakdown and cell energy balancing. High glucose levels decrease myoinositol uptake and production while increasing breakdown and urine excretion. They also play important roles in several biological processes, such as (Croze *et al*., 2013).

- Assembly of the cytoskeleton.
- Guidance of nerve cells (epsin).
- Transduction of insulin signals.
- Regulation of intracellular calcium (Ca^{2+}) concentrations.
- Metabolism of fat.
- Maintenance of cell membrane potential.
- Gene expression.

Inositol has been investigated for its possible advantages in a variety of metabolic diseases. Specifically, Myo-inositol may help in the management of diabetes by boosting insulin sensitivity, decreasing high levels of glucose and lowering the risk of metabolic disorders. Increased level of blood sugar increases the urinary excretion and degradation of myoinositols. Aside from the increased level of blood sugar also decreases the absorption and production of myoinositol. Insulin resistance inhibits the conversion of myoinositol to d chiroinositols. In urinary excretion of myoinositol is prevalent in diabetic people (Kennington *et al*., 1990; DiNicolantonio *et al*., 2022). Myoinositol is converted into d chiroinositol through the insulin-dependent mechanism. Myoinositol and d chiroinositol are the two most important inositol stereoisomers in the human body (Genazzani, 2016). Once myoinositols enter the cell it helps in activating certain secondary messengers for insulin, FSH and TSH (Baillargeon *et al*., 2006). Myoinositols may help people with PCOS by enhancing ovarian function and regulating the menstrual cycle (Pizzo *et al*., 2014). It is beneficial in treating depression, but further proof is needed. According to research, inositol also helps preterm newborn's lung development, which highlights its significance in neonatal care (Burton *et al*., 1976; Matarrelli *et al*., 2013). Myo-inositol, particularly with the combination of folic acid, effectively prevents neural tube abnormalities (De Grazia *et al*., 2012).

Inositol is recommended as a risk-free and efficient therapy for polycystic ovarian syndrome (PCOS) and diabetes. The risk of getting metabolic disorders in PCOS patients also decreases with inositol use. Furthermore, myoinositol functions as an FSH second messenger, promoting menstrual cycle regularity and correcting the FSH/LH ratio (Unfer *et al*., 2012; Croze and Soulage, 2013). Myoinositol produced from glucose and subsequently transformed into free myoinositol. Recycling of conjugated forms of inositol, inositoltriphosphate (IP3) and inositolbisphosphate (IP2) formed free inositol (Bevilacqua and Bizzarri, 2018). Myo-inositol production requires NAD+ and magnesium. Thus, a shortage of either may result in a deficiency in myo-inositol (Eisenberg and Parthasarathy, 1987; DiNicolantonio *et al*., 2022).

Absorption, tissue transport and excretion of myo-inositol

In human approximately 99.8% of myo-inositol absorbed through the gastrointestinal tract (Clements and Reynerston, 1977). In the bloodstream, myoinositols enter through a NA+/K+ ATPase channel (Lewin *et al*., 1976; Eisenberg *et al*., 1987). Once it is absorbed, it reaches other tissues through the bloodstream only. So, sodium is responsible for the absorption from the intestine and reabsorption of myoinositol in the kidney. After intestinal absorption, myoinositol *via* the bloodstream reaches

various body tissues (Lahjouji *et al*., 2007). Some portion of this absorbed myo-inositol is metabolized in the liver (Lee *et al*., 2016). In male rats, it has been proved that organs like the kidneys, spleen, liver, reproductive tract, pituitary gland and prostrate actively accumulate myo-inositol. The organs like muscles and adipose tissues accumulate less amount of myoinositol due to their tendency to partial de novo synthesis capacity (Gonzalez-Uarquin, Rodehutscord *et al*., 2020). Myoinositols enter into cells *via* different transporters such as SMIT1 and SMIT2 these transporters are stimulated by an extracellular increase in osmotic pressure in kidney cells. This transporter system has been studied in tissues like brain, kidney and intestine. The transporter SMIT2 is located in the kidney cortex region where it supports in myoinositol reabsorption in the kidney (Aouameur *et al*., 2007; Bissonnette *et al*., 2008).

Cellular synthesis of myoinositol

The cell produces myoinositol endogenously in various organs including the kidneys, brain, testis and liver. For example, the kidneys create a substantial quantity of myoinositol, which contributes to the total cellular pool (Eisenberg *et al*., 1963). *Via* certain enzyme-mediated processes, myoinositol is synthesized within the cells. Several metabolic processes take place in order to synthesize myonositol through glucose. The conversion of glucose-6-phosphate to myoinisitol-1-phosphate catalysed by enzyme inositol-1-phosphate synthase and it is an essential route. After that Dephosphorylation of myoinositol-1-phosphate resulting in free Myoinositol. This biosynthesis route is dependent on the availability of key cofactors including nicotinamide adenine dinucleotide (NAD) and magnesium ions (Dinicola *et al*., 2017). Any deficits in these cofactors may have an influence on the cellular production of myoinositol.

Myoinositol mainly excreting by the kidney into the urine, with roughly 98% of it being reabsorbed into the circulation. To maintain myoinositol balance in the body myoinositol catabolism largely occur in kidney, this process is mediated by an enzyme myoinositol oxygenase. Enzyme myo-inositol oxygenasecontaining nonheme iron, generates D-glucuronic acid from myoinositol and the next metabolic processes include the conversion of D-glucuronic acid into D-xylulose-5-phosphate, which subsequently enters the pentose phosphate pathway. The end products of this process contribute to oxidative energy generation (DiNicolantonio *et al*., 2022).

The relationship between myoinositol and glucose metabolism

The association between myoinositol and glucose metabolism is complex, at both cellular and molecular levels. According to research, myoinositol and glucose transport pathways compete for salt availability. Elevated glucose levels have been shown to limit myo-inositol absorption in numerous tissues, demonstrating the interaction between these two molecules. Many research studies have also identified that increasing myo-inositol concentrations impact glucose absorption rate in the intestines. Dietary intake of MI has been reported to decrease thepost meal glucose levels and can enhance peripheral tissue insulin sensitivity among diabetic people. Inositol phosphoglycans, which are identified to act as insulin-like second messengers, may also play a role in these effects. A study in chickens showed, supplementation of MI to a diet deficient in calcium and phosphorus can increased blood glucose level, insulin and glucagon concentration as compared to a standard diet (Cowieson *et al*., 2013). This outcome is because of competition between myoinositol and glucose for sodium, enabling a co-transport mechanism system. The synthesis of protein kinase (PKB/Akt) and the transfer of GLUT4in the skeletal muscle of mice were also increased with dietary MI, especially in the presence of insulin (Croze and Soulage, 2013). This is coupled regulation of Phosphatidylinositol-3,4,5-trisphosphatethrough the activation of insulin receptor proteins. These results suggest that increasing circulating MI concentrations may cause a rise in insulin levels, activating the phosphatidylinositol (PI) pathway. Any abnormality in the plasma and urinary myoinositol and d-chiroinositol concentration are early signs and markers of insulin resistance and type 2 diabetes (Croze and Soulage, 2015). In addition, these low levels of inositol worsen the insulin resistance condition (Bevilacqua *et al*., 2018). Inositol also helps in managing elevated levels of blood glucose and promotes glycogen storage in muscles. An epimerase enzyme which converts myoinositol to d chiroinositol is insulin dependent so in insulin resistance conversion rate of myoinositol to d-chiroinositol gets highly impacted (Kennington *et al*., 1990; Ortmeyer, 1993). Therefore, low levels of myoinositols and DCI also represent insulin resistance (DiNicolantonio *et al*., 2022; Kennington *et al*., 1990).

In one longest study which was performed for 3 months, where effect of inositol derivatives supplementation assessed on HBA1C and fasting blood glucose as these are important markers of diabetes found that the both the marker improved (Pintaudi *et al*., 2016). Furthermore, in one study effect of myoinositol on insulin sensitivity, which is a condition related to diabetes found that myoinositols and d-chiroinositol improved insulin levels and increase subsequent glucose intake in children who have high insulin levels (Mancini *et al*., 2016).

An investigation on inositol property of glycaemic control and how inflammatory conditions affected by inositol have been examined in diabetic patients which found a beneficial effect in the prevention from atherosclerosis and cardiovascular associated complications separately from any antidiabetic treatment procedure given in diabetic person (Hernández-Mijares *et al*., 2015).

MI and PCOS

5% to 21% of women throughout their reproductive years face Polycystic ovary syndrome (PCOS) (Genazzani, 2016).

Insulin resistance condition is found in PCOS patients, regardless of their body mass index (BMI). So even if females have normal BMI, insulin resistance conditions may be present. This aspect highlights that PCOS is not just linked to body weight. Insulin resistance condition exist between seventy to eighty percent of women facing PCOS and abdominal obesity, as well as approximately 15%-30% of women who is having lean body type with PCOS (Croze *et al*., 2013). High insulin levels can trigger androgen production in ovaries by boosting luteinizing hormone (LH) release (DiNicolantonio *et al*., (2022) (Mohammed *et al*., 2020). Many recent studies indicate that polycystic ovary syndrome (PCOS) affects approximately 10% of women of reproductive age, particularly in developed countries. While it is a common condition, the exact cause of PCOS is not clear (Ebenezer *et al*., 2021).

Myoinositol and D-chiroinositol (DCI) participate in the intracellular transmission of insulin which are essential for process by which regulation of blood glucose take place includes glucose oxidation and storage as glycogen (Croze *et al*., 2013; Larner *et al*., 2010). An enzyme epimerase which converts Myoinositol to D-chiroinositol is also dependent on insulin, so epimerase enzyme decreased in insulin-resistant tissues (Kennington *et al.*, 1990; Ortmeyer, 1993). Therefore, Insulin resistance can also be caused by insufficiency of myo-inositol or a problem with the enzyme that converts myoinositol to DCI. Supplementation of DCI showed in individuals with PCOS that it significantly reduces insulin levels and free testosterone, as well as enhances blood pressure, triglyceride concentrations and ovulation. In many studies, it also has been seen that myo-inositol, regardless of the presence of d-chiroinositol, increases oocyte development, pregnancy rate and hormonal measures in PCOS patients. Additionally, myoinositol supplementation also improves insulin sensitivity, LH: FSH ratio and lipid profile. Myo-inositol treatment in overweight women with PCOS resulted in decreases in plasma Luteinizing Hormone, prolactin hormone, testosterone and insulin resistance (Le Donne *et al*., 2019).

In a 12-week study, in obese women facing PCOS found that Myoinositol treatment, in combination of folic acid, dramatically lowered hormonal parameters and increased insulin sensitivity (Artini *et al*., 2013). Myo-inositol monotherapy or the combination with DCI has been recognized to be beneficial in PCOS patients, as well as tolerated better than metformin, making it a more appealing therapeutic choice (Kutenaei *et al*., 2021).

This review has been written by PRISMA guidelines. The criteria for screening is the relevance to the topic not on which date those paper haven been published so publication date did not taken into consideration while screening for the articles. Screening was performed with Web of science, Science Direct, PubMed, Scopus and Google Scholar by manual search. Different keywords such as inositol, d-chiro inositol, myoinositol and diabetes insulin-sensitivity/resistance, diabetes and type 2 diabetes mellitus were used. Studies with full-text availability were used for the review. In the first search 1809 articles generated therefore, the titles examined. After that, 22 pieces of research were evaluated in detail. Research articles have been included which include the studies specifically to find out the relation between myoinositols and diabetes or any metabolic disease.

While exploring the deep interaction between Myo-inositol and diabetes management reveals that these chemicals play several functions in the complex landscape of insulin signalling and glucose metabolism. The sedentary lifestyle, rising demand for artificial sweeteners and calorie-conscious people fueled by the growing prevalence of diabetes and obesity have highlighted inositol as a feasible alternative (Awuchi *et al*., 2019). The widespread use of sugar substitutes, such as sucrose and fructose, highlights the critical need for solutions that give sweetness without increasing calorie intake or having a substantial impact on blood glucose levels (Awuchi *et al*., 2019); Greene and lattimer, 1982).

Sugar alcohols, which include inositol, have a low influence on blood sugar levels, providing a metabolic benefit since they are digested without the need for insulin control (Awuchi *et al*., 2019; Bevilacqua and Bizzarri, 2018; Özturan *et al*., 2019). Myoinositol and d-chiroinositol not only contribute to sweetness but also play an important function in blood sugar regulation (Awuchi *et al*., 2019; D'Anna *et al*., 2013; Baillargeon *et al*., 2006). Meanwhile, this review has highlighted the increased interest in research studies on inositol and its derivatives due to its critical function in a variety of physiological processes, including hormone control and insulin-mediated activities. The relationship between inositol deficit and the development of illnesses, particularly diabetes and PCOS, has been investigated. Inositol, which may be obtained from both dietary and internal sources, confronts problems that lead to low levels due to variables such as decreased nutritional intake, increased catabolism, changes in gut microbiota and decreased biosynthesis (Bevilacqua *et al*., 2018; Eisenberg *et al*., 1987). Myoinositol and d-chiroinositol playsessential role in lipid and glycaemic control as supported by extensive data (Chu *et al*., 1980; Croze *et al*., 2013; Burton *et al*., 1976; Kennington *et al*., 1990). In an investigation, a myoinositol-enriched liquid was given to individuals with diabetes and healthy individuals for 12 weeks which showed that this beverage improve of glycaemic control (Hernández-Mijares *et al*., 2015).

CONCLUSION

Myoinositol can be a possible treatment option for people suffering from illnesses such as diabetes, or at risk of getting diabetes, insulin resistance and PCOS. Many studies examined myoinositol for decades and it is completely safe to include. In all relevant studies effect of

inositol supplementation has been researched but, In the future, we need more studies that can find out how myoinositol should be taken through foods to have a positive effect on treating or preventing metabolic issues like diabetes and PCOS.

Conflict of interest

The author declares that there is no conflict of interest.

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