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Role of Dietary Myo-Inositol in Diabetes and Diabetic Complications

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KEYWORDS

Inositol, Diabetes, Diabetic complications

ABSTRACT:

Inositol, a sugar produced in the body and found in various foods, exists in different forms, with Myo-inositol and D-chiro-inositol (DCI) being the most prevalent in dietary supplements. These forms are recognized for their insulin-mimetic properties, aiding in the regulation and stabilization of postprandial blood sugar levels. Imbalances in inositol metabolism are linked to insulin resistance and microvascular complications in diabetes, suggesting that adequate inositol levels are crucial for optimal metabolic health.

This study explores the potential benefits of Myo-inositol supplements in managing or preventing complications associated with diabetes and polycystic ovarian syndrome (PCOS), as well as other insulin resistance-related conditions like neuropathy, nephropathy, and cataracts. It assesses the effectiveness of Myo-inositol in clinical and animal studies, tracing its dietary origins and excretion. The review also examines how inositol impacts insulin sensitivity, highlighting the role of inositol glycans as signaling molecules in insulin activity, with the goal of understanding Myo-inositol's therapeutic potential in metabolic health.

1. Introduction

Myo-inositol was an innately occurring cyclitol that could be found in phospholipids, inositol phosphate analogues, and in free form in both animal and plant cells [1].

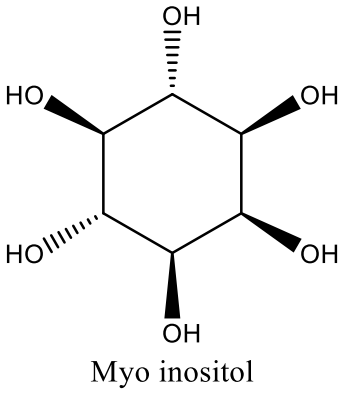

Figure 1: Myo-inositol

Inositol, serving as the structural foundation, is utilized by secondary messengers such as Inositol triphosphate (IP3), Phosphatidylinositol phosphate (PIP2 and PIP3), and inositol glycans. As a result, myo-inositol was essential for various cellular functions, including but not limited to survival, cell proliferation, reproduction, osteogenesis, and maintenance of the peripheral nervous system's functioning [2–6] (Figure 1). Anomalies in the metabolism of two different isomers of the inositol molecule, myo-inositol and DCI, were linked to diabetes microvascular complications and insulin resistance. Myo-inositol was more readily achievable through dietary means when myo- and DCI were given as dietary supplements. In insulin-resistant animal models, insulin-mimicking effects were observed, and in humans, similar effects were exhibited in cases of PCOS, an endocrine metabolic disorder.

The objective of this review was to summarize the findings of randomized controlled studies that assessed the advantages of dietary inositol supplements in relation to insulin resistance or the prolonged effects of diabetes. To understand the therapeutic efficacy of supplements like myo-inositol sourced from various origins for individuals with insulin resistance, a variety of dietary sources of myo-inositol were explored, as well as its renal metabolism.

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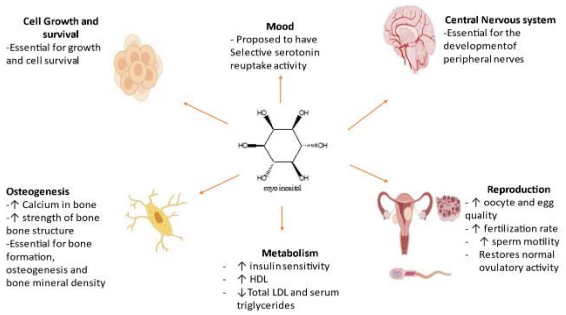

Figure 2: Myo-inositol Supplementation: Roles and Advantages in Promoting Human Health.

Finally, the aggregated data were examined to gain a comprehensive understanding, drawing insights from research conducted on both animals and humans to understand the potential and unclear mechanisms of action underlying the insulin-sensitizing effects of inositol derivatives.

2. Myo-inositol content in common foods: myo-inositol's nutritional sources

With its six hydroxy groups arranged in various orientations, cyclohexane-1,2,3,4,5,6-hexol exists in nine stereoisomeric forms. Cyclohexahexanehexol (cis-1,2,3,5) was the most commonly found in nature and became known as the most common isomeric form of inositol. Myo-inositol, a member of the Vitamin B family, was originally thought to be an essential nutrient. However, it was later understood that it was not necessary, as the human body could produce sufficient amounts from D-glucose. In the diet, myo-inositol was found in a variety of foods. It existed in free form and was also present as part of complex molecules like phytic acid (inositol hexaphosphate), especially in plants. Phytic acid functions as a primary reservoir of phosphorus in numerous plant tissues, notably prevalent in nuts, seeds, and grains [7]. Inositol phospholipids were found in the membranes of both plant and animal cells. Phytic acid primarily serves as the main reservoir of phosphorus across various plant tissues, with notable concentrations found in seeds and bran. As a result, fresh vegetables, fruits and seed-containing foods emerge as significant dietary sources of myo-inositol, boasting the highest levels among commonly consumed foods. (beans, grains, and nuts). In comparison to cereals derived from other grains, oat and bran cereals had higher myo-inositol content, while Brazil nuts (9.4%), almonds (6.7%), and walnuts (6.3%) had the highest phytic acid concentrations [8]. Regarding dietary fibre levels, beans and peas topped the list, with leafy greens ranking at the bottom. For example, a serving of fresh grapefruit juice (120 ml) had a myo-inositol content as high as 470 mg, which was more than double the recommended daily intake. The average American consumed 900 mg of myo-inositol daily, with lipids accounting for 56% of this amount. It was possible to obtain 225 to 1500 mg/day of myo-inositol per 1800 calories from typical meals, depending on their composition [9].

3. The absorption and metabolism of dietary myo-inositol

Digestion and absorption

In monogastric animals, phytase enzymes found in the intestinal mucosa released inositol stored within phytic acid in the stomach. Plants, microbes, and animal tissues all contained Myo-inositol hexaphosphate phosphohydrolase (EC 3.1.3.26 and EC 3.1.3.8) [8]. These enzymes, involved in inositol metabolism, produced orthophosphate and a series of intermediate products, including free inositol and its phosphate derivatives: mono-phosphate inositol, di-phosphate inositol, tri-phosphate inositol, tetra-phosphate inositol, and penta-phosphate inositol. A substantial portion of ingested inositol hexaphosphate was metabolized to inositol. Phosphatidylinositol (lysoPI), a key form of myo-inositol in cell membranes, underwent degradation in the intestinal lumen. This degradation was primarily facilitated by pancreatic phospholipase A, an enzyme that hydrolysed phosphatidylinositol to produce lyso-phosphatidylinositol and free fatty acids. Once lysoPI entered an intestinal cell, it could follow one of two metabolic pathways: one by further digestion to produce glyceryl phosphoryl inositol, a compound that then participated in various cellular processes or metabolic pathways within the cell. Another pathway involved reacylation via acyltransferase activity. The reacylation effectively converted lysoPI back into phosphatidylinositol. This reformed phosphatidylinositol was crucial for cell membrane integrity and function, as well as in various signalling pathways within the cell [7].

The human gastrointestinal tract absorbed nearly every free myo-inositol consumed (99.8%), attributing to a Na+/K+-ATPase-containing active transport mechanism [7]. It was found that the half-life of myo-inositol was 22

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minutes, and a fasting plasma concentration in healthy and normal persons was about 30 mM [7,9]. Small but considerable levels of myo-inositol could also be found in phospholipids associated with serum lipoproteins in circulation and phytic acid at 0.1–0.4 mM concentration [10].

Organ and tissue incorporation

Research conducted by Lewin et al., the focus was on understanding the behaviour of radioactively labelled myo-inositol after it was injected intraperitoneally into male rats. Lewin et al. (1976) investigated the distribution of radioactively labelled myo-inositol in male rats following intraperitoneal injection. Within an hour, radio-labelled myo-inositol was deposited in significant concentrations in the seminal vesicles, thyroid, and coagulating glands. Myo-inositol also concentrated in major organs like the liver, pituitary gland, spleen, and prostate glands. Among the male reproductive organs, only the coagulating gland, epididymis, seminal vesicle, vas deferens, and prostate did not show radioactivity values 10–30 times higher than those observed in the serum. The tissues of the heart, examined as muscle tissues, concentrated little inositol. However, the brain and testis, which have considerable quantities of endogenous inositol, were unable to concentrate it from the blood. Approximately 60% of the radio-labelled myo-inositol was detected in the liver, which has a higher accumulation of lipids. In contrast, in most other organs, myo-inositol predominantly existed in its free form.

Myo-inositol catabolism did not take place in bilaterally nephrectomised rats, indicating that the primary site of inositol catabolism in rats is the nephrons [11]. As expected, rats that underwent nephrectomy still exhibited an inability to convert inositol to carbon dioxide. In contrast, animals that underwent a sham operation metabolized around 16% of myo-inositol into CO2. Animals that underwent nephrectomy showed higher deposits of radioactivity myo-inositol levels across most examined organs, likely because the kidneys were responsible for processing or eliminating significant quantities of the supplied inositol.

A notable deviation from this pattern was noted in the brain, where radioactivity increased to a greater extent in sham-operated animals compared to animals that underwent nephrectomy. This occurrence might suggest that some inositol metabolites, which are produced in the kidneys, have a higher propensity to cross the blood-brain barrier (BBB) compared to inositol itself. This increased ability to traverse the BBB could lead to higher levels of radioactivity (indicative of these metabolites) in the brains of sham-operated animals [7].

Cellular uptake

Three primary pathways contribute to the cellular acquisition of inositol:

De novo biosynthesis: This pathway involves the synthesis of inositol from glucose-6-phosphate catalysed by the enzyme inositol monophosphatase (IMPase). Through this process, inositol monophosphate is converted into free myo-inositol.

Maintenance via 1-D-myo-inositol phosphate synthase (MIPS): MIPS is another essential enzyme involved in maintaining the cellular pool of myo-inositol. This enzyme plays a crucial role in synthesizing phosphatidylinositol and other inositol-containing phospholipids.

Degradation of membrane phospholipids: In addition to de novo biosynthesis, inositol can also be obtained through the degradation of membrane phospholipids that contain inositol. When these phospholipids undergo hydrolysis, they release inositol phosphates, which are subsequently dephosphorylated to yield free inositol.

These processes were connected to the degradation of membrane phospholipids containing inositol and the absorption of inositol from the extracellular fluid [12]. Figure 3 illustrated how specialized myo-inositol transporters transferred inositol from extracellular fluid. The coordinated action of H-Myo-inositol transporter and Sodium-dependent myo-inositol transporters exist as SMIT1 and SMIT2ensured efficient and regulated uptake of inositol from the extracellular environment, adapting to the cell's metabolic needs [13]. SMIT1 and SMIT2 were transporters that enabled the uptake of inositol into cells in a sodium-dependent manner. These transporters worked by co-transporting sodium ions (Na+) along with inositol, utilizing the sodium gradient across the cell membrane to drive the transport process. The co-transport mechanism of SMIT1 and SMIT2 was crucial for inositol uptake, especially in tissues where the sodium gradient was a significant driving force for transport processes. The active transport of myo-inositol

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relies on the coordinated action of SMIT1 and SMIT2, which effectively co-transport a pair of two ions against their concentration gradient. This mechanism generates essential energy required for the uptake process. Found in the brain, SMIT1 and SMIT2 likely played a role in regulating the brain's myo-inositol content, which was 100 times greater than that of the rest of the body. Even with the presence of SMIT, SMIT2 facilitated myo-inositol uptake in the rat intestinal tract and oversaw myo-inositol reabsorption in the kidneys of rabbits [14,15]. The inosituria associated with diabetes mellitus was caused by the interference of D-glucose and phlorizin with this active transport. It was significant to emphasize that D-chiroinositol was transported specifically through SMIT2 and not SMIT1.

4. Results Metabolism

Myo-inositol de novo biosynthesis

In certain emphasized organs, namely the rat brain, liver, testis, and kidneys, the endogenous synthesis of myo-inositol from glucose took place in three stages: In the initial stage, hexokinase phosphorylated glucose; the second stage was where MIPS transformed glucose-6-phosphate into myo-inositol-1-phosphate; and in the final stage, IMPase dephosphorylated myo-inositol-1-phosphate to produce free inositol (See Figure. 3). The formation of myo-inositol-1-phosphate in myo-inositol biosynthesis was the limiting step in the majority of species [16]. The essential endogenous production of inositol in the kidney, yielding approximately 2 g per day, contributed to a total daily production of around 4 g in a bi-nephric individual. This held great significance for humans, particularly noteworthy as it surpassed the daily intake of inositol through food, which was about 1 g/day. It also contributed to the fact that extra-renal tissues in both humans and animals possessed the capability for inositol production endogenously. The rabbit brain acquired half of its free inositol through on-site endogenous synthesis, with the remaining half sourced from circulation.

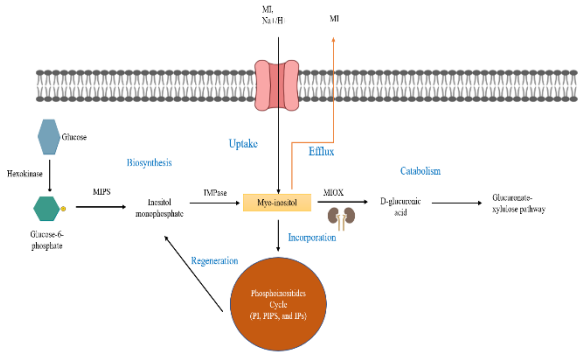

Figure 3: Myo-inositol is taken up from the extracellular space through a specific H-Myo-inositol transporter. It can be synthesized de novo from glucose, regenerated, incorporated into the phosphoinositide cycle, effluxed, and catabolized by MIOX enzyme in the nephrons.

Myo-inositol transformation into isomers, derivatives, or incorporation into phospholipids

One or more of the groups on myo-hydroxyl inositol could be epimerized, phosphorylated, or methylated to produce a variety of derivatives. However, myo-inositol could not be used to make several of these molecules in animal cells. Epi-inositol, allo-inositol, and cis-inositol were synthetically created compounds that are isomers of inositol. Sequoyitol, quebrachitol, and pinitol are methylated inositol derivatives (5-O-methyl-myo-inositol, 2-O-methyl-chiro-inositol, and 3-O-methyl-chiro-inositol, respectively), synthesized by some plant species, yet it was doubtful that myo-inositol would be the source of these chemicals in the human body. Various phosphorylated forms of myo-inositol existed within cells, encompassing monophosphorylated forms. These included inositol monophosphate isomers such as Ins-1-P (inositol 1-phosphate), Ins-3-P (inositol 3-phosphate), and Ins-4-P (inositol 4-phosphate). Hexaphosphorylated inositol hexakisphosphate, commonly known as IP6 or phytic acid, was a molecule where all six hydroxyl groups of inositol were phosphorylated. Additionally, pyrophosphate types were more complex phosphorylated forms of inositol, such as PP-InsP4 (diphosphoinositol pentakisphosphate), PP-InsP5 (diphosphoinositol tetrakisphosphate), [PP]2-InsP3 (bis-diphosphoinositol tetrakisphosphate), and [PP]2-InsP4 (bis-diphosphoinositol pentakisphosphate). Human cells did

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not contain kinases, but monophosphorylated, diphosphorylated, and triphosphorylated forms could still be produced by dephosphorylating other phosphorylated forms using certain hydrolysis and phosphatase enzymes.

Natural inositol isomers included myo-inositol, chiro-inositol, muco-inositol, scyllo-inositol, and neo-inositol. Myo-inositol could be transformed in vivo to DCI in tissues that expressed the specific epimerase. Radiolabelled [3H]-MI was shown to convert to [3H]-D-chiro-inositol at a rate of 7.6 percent in the rat bloodstream and 8.8 percent in rat liver and muscle, according to Pak et al. (1992). An epimerase inside the bovine brain interconverted myo-inositol, scyllo-inositol, and also generated neo-inositol [17]. Scyllo-inositol, neo-inositol, and muco-inositol were the least often radiolabelled inositol isomers in the studies, accounting for just 0.06% of the radiolabelled myo-inositol isomer [18].

Finally, myo-inositol was predominantly present in its free form and potentially covalently bound to phospholipids, forming the structural foundation for certain secondary signalling molecules. These included IP3, phosphatidylinositol, and polyphosphoinositides. In mammalian cells, a small portion of myo-inositol underwent conversion to methylated derivatives. Phosphatidylinositols were produced from cytidine diphosphate-diacylglycerol (CDP-DAG) and phosphatidylinositol. Phosphatidylinositol synthase catalysed this synthesis, exhibiting a relatively high Km for myo-inositol within the range of 1.5 to 2.5 mM, making intracellular myo-inositol homeostasis highly important for a number of different cell activities [19,20]. Phosphatidylinositol 3-kinases functioned on phosphatidylinositol to create phosphoinositide phosphate lipids. Phospholipase C plays a pivotal role in the hydrolysis of phosphatidylinositol phosphates, yielding a diverse array of inositol phosphates. Crucial for cellular signalling, these compounds can be synthesized or regenerated through the control of their phosphorylation state. This regulatory mechanism ensures their availability for various signalling processes within the cell.

Both myo- and D-chiroinositol (DCI) could be linked to glycosyl-phosphatidylinositol anchor points and inositol phosphoglycans. These components served as second messengers in the GPI/IPG pathway, contributing to insulin action.

Myo-inositol catabolism

The kidney stood out as the primary organ of interest in myo-inositol metabolism, as evidenced by the reduction of [2-14C]-inositol to 14-carbon dioxide observed in rats with placebo surgery but not in nephrectomised rats [11,20]. In the kidneys, myo-inositol underwent catabolism primarily through the action of the enzyme myo-inositol oxygenase (MIOX). MIOX catalysed the conversion of myo-inositol to D-glucuronic acid. The D-glucuronic acid produced from myo-inositol catabolism underwent further metabolic transformations. It could be converted into D-xylulose-5-phosphate, a compound that participates in the pentose phosphate pathway. A small amount of myo-inositol was excreted through urine. Consequently, in humans, the kidney appeared to be significant in regulating plasma inositol levels by both catabolizing and excreting myo-inositol.

5. Tolerance

Myo-inositol, when administered orally, had an oral LD50 in mice of 10 g/kg body weight. Supplementation was highly tolerated and generally considered safe. Individuals could safely and effectively consume daily doses of up to 18 g orally for a period of three months or 2 g daily for one year. When side effects did occur, they were often mild and related to digestion (nausea, flatulence, and diarrhoea) [4].

Linking inositol metabolism abnormalities with insulin resistance

Myo-inositol and DCI played essential and diverse roles in various cellular processes, and metabolic abnormality have been directly associated with the onset of insulin resistance and complications associated with diabetes. These diseases included depression, bipolar disorder, panic disorder, Alzheimer's disease, and complications associated with diabetic neuropathy. In major sites for the emergence of diabetes microvascular issues in diabetic animal models and humans, a contemporaneous reduction of intracellular sorbitol and myo-inositol was generally documented in the retina, lens, sciatic nerve, and kidney [21]. In addition, people with type 2 diabetes and laboratory animals (rhesus monkeys and Goto-Kakizaki (GK) rats) exhibited increased excretion of myo-inositol and inadequate levels of DCI in urine, a

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condition known as inosituria [22,23]. The observed excretion pattern resulted in a decline in the myo-inositol to DCI urine ratio. A similar aberrant inositol pattern was noted in the liver, cardiac muscle, fat-accumulated tissue, and renal tissues of both individuals and animals with diabetes [23,24].

6. Depletion of intracellular myo-inositol: Potential mechanisms

The intracellular concentration of myo-inositol was affected by the absorption of extracellular myo-inositol, de novo production, activation of the phosphoinositide cycle, outflow, and metabolism. Inositol intracellular anomalies could be caused by changes in one or more of these pathways. Potential reasons for the reduction of intracellular myo-inositol levels in diabetes mellitus may have involved the reduction in the uptake of myo-inositol, alterations in myo-inositol synthesis, increased myo-inositol efflux due to intracellular sorbitol accumulation, and increased myo-inositol metabolism [25]. Similarly, the absorption of myo-inositol was reduced in aortas and nerve cells cultured with glucose [26–28].

The structural similarities between the myo-inositol and glucose moieties led to competition for myo-inositol (H-Myo-inositol transporter and SMIT) transporters, resulting in the suppression of myo-inositol [29]. As a result, in hyperglycaemic settings, a high glucose environment in diabetes could inhibit extracellular myo-inositol absorption, contributing to intratissular depletion of myo-inositol.

However, A significant aspect of comprehending diabetic complications, especially in the context of hyperglycaemia, involves the consideration of aldose reductase inhibitors. These inhibitors play a crucial role in modulating intracellular sorbitol levels and their consequent impact on myo-inositol levels. In hyperglycaemic conditions, the enzyme aldose reductase became more active and catalysed the production of sorbitol from glucose, a sugar alcohol. The increased activity of the aldose reductase pathway led to the accumulation of sorbitol within cells and the resulting reduction in intracellular inositol. However, hyperglycaemia alone was inadequate to describe this intratissular myo-inositol depletion.

Rapid accumulation of intracellular sorbitol could induce osmotic stress in brain tissues equipped with osmolyte efflux systems. Osmotic stress could induce a net outflow of osmolytes through osmolyte anion channels, resulting in a decrease in intracellular myo-inositol levels [25]. While the osmotic stress induced by sorbitol in diabetic lenses was significant, in other tissues, this might not have been the primary cause of myo-inositol depletion [30,31].

It was discovered that the gametes of diabetic mice had drastically decreased (by 50%) MIPS activity, the enzyme that controls the crucial initial stage of myo-inositol production [31]. Despite the naturally higher rate of myo-inositol generation in the testes, there were no alterations in MIPS activity observed in organs like nerves, kidneys, and the brain. It remained unclear how this reduction in MIPS activity contributed to the intracellular depletion of myo-inositol [25].

Last but not least, STZ-diabetic rats and db/db mice, diabetic animal models, revealed an increase in MIOX in the kidneys [32]. Insulin-resistant (C57BL6 mice, high-fat diet-induced diabetes) and hypertensive (SHR rats) animals have exhibited dysregulation of an enzyme involved in myo-inositol breakdown. In hyperglycaemic STZ-rat models, normoglycemic hypertensive rat models, and insulin-resistant mice models, MIOX overexpression was connected to an intra-renal myo-inositol insufficiency [25]. Based on these findings, the decrease in myo-inositol levels in the kidney was not associated with elevated glucose levels. Instead, it was, in part, linked to the increased activity of MIOX, which stimulates the glucuronate-xylulose pathway. After myo-inositol was converted to D-glucuronic acid, it could further metabolize into xylulose and enter the pentose phosphate pathway. In diabetic conditions, there was an upregulation of MIOX activity in the kidney. This upregulation led to increased conversion of myo-inositol to D-glucuronic acid, contributing to the upregulation of the xylulose and glucuronate cascade, as evidenced by increased activity of the MIOX enzyme.

The development of diabetic nephropathy was also connected to the stimulation of fibronectin, a high-molecular-weight glycoprotein. Fibronectin plays a role in various cellular processes. The activation of fibronectin and MIOX led to increased metabolism of

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myo-inositol and contributed to the pathogenesis of diabetic nephropathy [33].

7. Depletion of Myo-inositol: Possible Link to Microvascular Complications in Diabetes

Inositol played a crucial role in various cellular activities and acted as a precursor to phosphoinositides and phosphatidylinositol. The production and availability of phosphatidylinositol and phosphatidylinositol phosphates in cells might have been negatively impacted when intracellular myo-inositol was depleted, given the relatively high Km for the formation of phosphatidylinositol from myo-inositol. In the Streptozotocin diabetic rat model, abnormal phosphatidylinositol metabolism linked with myo-inositol deficit was reported in the sciatic nerve [9]. Intracellular myo-inositol insufficiency might have led to abnormal sodium–potassium pump activity, potentially providing a pathway for the development of diabetic microvascular complications. Deficient sodium–potassium pump activity was linked to altered phosphatidylinositol turnover. Indeed, the presence of sodium (Na) and potassium (K) ions was crucial for maintaining the membrane potential in neuronal cells, particularly during the process of neurotransmitter-induced excitation. Changes in sodium–potassium pump activity were linked to impaired nerve conductivity, as reported by Sima et al. (1997). Additionally, the alterations in ion channel function and the subsequent changes in neuronal membrane potential were closely linked to the pathological condition seen in conditions like axonal demyelination and degeneration, particularly in the context of diabetic neuropathy [34,35].

The onset of glomerulosclerosis and proteinuria, as well as hemodynamic anomalies in the diabetic kidney, were both associated with hyperglycaemia-induced myo-inositol depletion [20]. On the other hand, myo-inositol depletion might have impaired the renal tubular epithelial cells' typical physiological activity, increasing the accumulation of extracellular matrix, potentially leading to renal tubule interstitial fibrosis. Because of this, myo-inositol depletion was crucial in the development of diabetic nephropathy [32,36].

Due to the absence of clearly delineated common etiological mechanisms, the decrease in myo-inositol levels in insulin-insensitive tissues amidst hyperglycaemia is considered significant to contribute to the onset and progression of diabetic microvascular complications. This decreases, along with the four principal pathways known for their involvement, enhanced formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), disruption of the sorbitol pathway, and elevation of hexosamine levels [20].

8. Possible Mechanisms of Inosituria

Urinary excretion of DCI (D-chiro-inositol) was reduced, while myo-inositol levels were elevated in individuals with Type 2 Diabetes, both in humans and rhesus monkeys. These levels were approximately ten times higher than those observed in healthy individuals [21]. Similar urine excretion profiles were found in research using the Goto-Kakizaki rat [37]. Despite the fact that this phenomenon had been known since 1859, a thorough examination of the mechanism causing this aberration was not possible at the time, due to the complexity of inositol analytic procedures [38]. Contrary to polyuria, the rise in inositol clearance observed in diabetes mellitus has been associated with glycosuria. This suggests a potential connection between altered inositol metabolism and the presence of elevated glucose levels in the urine, highlighting a unique aspect of diabetic pathophysiology [39]. Research involving both humans and monkeys, as conducted, demonstrated a correlation between decreased levels of urinary D-chiro-inositol (DCI) and the severity of insulin resistance. This correlation was established using five distinct parameters to measure insulin resistance. These findings suggested that the altered urinary inositol profile, particularly characterized by reduced DCI, was closely linked to insulin resistance [40]. The detection of elevated myo-inositol levels coupled with reduced chiro-inositol in urine has been suggested as a potential biomarker for insulin resistance among human patients. This ratio could therefore serve as a useful diagnostic tool in identifying and managing insulin resistance-related conditions [41].

A unique ratio of DCI to myo-inositol was identified in the muscles of patients with type 2 diabetes following autopsy and muscle biopsy. Chiro-inositol levels in postmortem muscle, urine, and hemodialysate samples were approximately 50% lower than those of control persons [23]. DCI was not detected in the muscle biopsy samples from individuals with type 2 diabetes, either

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before or after receiving insulin treatment. Myo-inositol was more abundant in samples from individuals with type 2 diabetes compared to controls, and its levels increased further after insulin treatment [21]. The deficiency in myo-inositol to DCI epimerization activity was identified as the underlying cause of the inositol imbalance linked to insulin resistance. This hypothesis was validated through both in vitro and in vivo experiments demonstrating the conversion of myo-inositol to DCI under insulin-driven conditions [18,42]. The epimerase activity was subsequently shown to be time, pH, tissue, and co-factor dependent, with maximum activity achieved only in the presence of NADH and NADPH in the liver and kidney, respectively. When comparing type 2 diabetic rats (Goto-Kakizaki) to control rats (Wistar), a notable reduction in the conversion of radioactive isotope myo-inositol to radioactive isotope D-chiro-inositol was observed in the liver, muscle, and fat tissues at the cytosolic level. The conversions, which ranged from 20 to 25 percent in controls, were reduced to baseline values of 5 to 10 percent in Goto-Kakizaki rats [25]. The DCI to myo-inositol ratio recorded in some tissues and observed in the human autopsy of type 2 diabetics were both consistent with a 2- to 3-fold reduction in epimerase activity in Goto-Kakizaki rats [23].

The observed reduction in the levels of DCI in both urine and various tissues, along with a corresponding decrease in the ratios of DCI to myo-inositol, could be further explained by a notable decrease in the activity of the myo-inositol to DCI epimerase enzyme. This enzymatic activity reduction was particularly evident in the insulin-sensitive tissues of the Goto-Kakizaki rat, a well-established animal model used to study the mechanisms and characteristics of insulin resistance.

Inosituria and Altered DCI/Myo-Inositol Ratios in Diabetic Tissues

In tissues that predominantly depended on the import of extracellular myo-inositol, an increased excretion of myo-inositol in the urine led to a decrease in its plasma concentrations, thereby exacerbating the depletion of myo-inositol within cells. Consequently, the decreased conversion of myo-inositol to DCI resulted in lower intracellular availability of DCI for integration into inositolphosphoglycans (IPGs), which are believed to function as secondary messengers in the insulin signalling pathway. Notably, individuals suffering from type 2 diabetes mellitus were observed to have lower levels of IPGs in their muscular tissues [21]. Reduced insulin signal transduction utilizing IPGs might have occurred from the reduction of DCI concentration in the tissues, which could worsen or contribute to insulin resistance within these cells. The relationship between decreased plasma DCI and insulin resistance was highlighted by the fact that patients with PCOS (a condition characterized by insulin resistance and hyperinsulinemia) had decreased plasma DCI levels.

In conclusion, three factors were linked to diabetes and insulin resistance: 1) abnormally low DCI levels in urine, liver, muscle, fat, and plasma; 2) elevated myo-inositol urinary excretion; and 3) a deficiency of intracellular myo-inositol in the kidney, sciatic nerve, lens, and retina.

The depletion of myo-inositol in specific tissues might have contributed to the onset or worsening of diabetic microvascular complications, while a deficiency in DCI may have exacerbated insulin resistance, leading to neuropathy, nephropathy, and retinopathy. Therefore, it was logical to hypothesize that supplementation with myo-inositol and/or DCI could reduce the risk of diabetes by replenishing intra-tissue levels of myo-inositol and/or DCI.

9. Significance of myo-inositol supplementation in diabetes.

Evidence from preclinical studies

Numerous research studies focusing on diabetes mellitus utilized various models, including STZ-induced diabetic rats, rhesus monkeys, ob/ob mice, and human subjects, to investigate the effectiveness of certain inositol isomers and derivatives, especially DCI (D-chiro-inositol) and D-pinitol. These studies aimed to assess the impact of these compounds on lowering blood glucose levels after meals, providing valuable insights into potential treatments for managing diabetes [40,43,44]. Studies found a connection between this effect and DCI's ability to increase insulin sensitivity. The 5-O-methyl form of myo-inositol (Sequoyitol), found in several herbal ingredients, was shown in rats to have anti-diabetic effects. In fact, over the course of 8–10 weeks, sequoyitol, administered subcutaneously and orally to ob/ob insulin-resistant mice, decreased hyperglycaemia,

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improved insulin signalling in the liver, and reduced glucose intolerance [45].

Initially demonstrated in one of the insulin-resistant animal models (Rhesus monkey), the effect of administering large doses of myo-inositol on glycemia in the postprandial state led to a patent in 1998 for the management of hyperglycaemia in diabetes [46–48]. However, a previous study on Streptozotocin-induced diabetic rats had not been able to verify that dietary myo-inositol reduced hyperglycaemia [49,50]. This observation could be attributed to the fact that an increase in insulin sensitivity mediates the hypoglycaemic action of myo-inositol, which is why it cannot counteract hyperglycaemia in type 1 diabetic animal models when insulin is missing [4].

Furthermore, under hyperglycaemic conditions, the impact of myo-inositol was likely diminished because glucose limits cellular absorption of myo-inositol. The studies conducted by Croze et al. (2013) and Dang et al. (2010) on healthy animals provided compelling evidence regarding the impact of myo-inositol on blood glucose levels and insulin sensitivity. These studies demonstrated that administering large doses of myo-inositol, either suddenly or continuously, effectively reduced blood glucose levels following a glucose load.

These investigations revealed a significant result: an improved translocation of the GLUT-4 glucose transporter to the plasma membrane in skeletal muscles during high blood sugar conditions. This cellular process was linked to a rise in peripheral insulin sensitivity. To assess insulin sensitivity, the studies conducted in vivo insulin tolerance tests, providing a direct measure of the body's response to insulin under these conditions.

The correlation between myo-inositol administration, enhanced GLUT-4 translocation, and improved peripheral insulin sensitivity suggested a potential therapeutic avenue for managing hyperglycaemia and enhancing overall insulin responsiveness. These findings contributed valuable insights to our understanding of the intricate mechanisms involved in glucose metabolism and insulin action, opening avenues for further research and potential applications in the field of metabolic disorders [51].

Clinical Evidence

The effectiveness of inositol, whether it be DCI or myo-inositol, was established in enhancing insulin sensitivity and optimizing ovulatory cycle function, especially among adolescent women diagnosed with polycystic ovary syndrome (PCOS). This promising outcome prompted an investigation into the potential of myo-inositol supplementation to address insulin resistance in diverse populations, encompassing postmenopausal women diagnosed with metabolic syndrome and pregnant women facing the risk of, or already diagnosed with, gestational diabetes.

In postmenopausal women exhibiting metabolic syndrome [52,53] and women diagnosed with gestational diabetes [54], administering a daily dose of 2 grams of myo-inositol, along with adherence to a regulated diet for a duration of eight weeks, led to a significant rise in both fasting blood glucose and serum insulin levels. This outcome highlighted the impact of myo-inositol supplementation on key metabolic parameters in the study. This effect was conspicuous when compared to diet treatment alone, showcasing a reduction of 50 percent in women with gestational diabetes at 8 weeks compared to a 29 percent decrease in the placebo group with diet alone. Furthermore, in postmenopausal women, long-term effects were noted when using myo-inositol. Over periods of 6 and 12 months, these women experienced a significant 75% decrease in their HOMA-IR index, a measure of insulin resistance, compared to a 42% reduction observed in the control group who were on a diet-only regimen. Additionally, pregnant women with a genetic risk for Type 2 Diabetes also saw notable benefits from taking a daily supplement of 4 grams of myo-inositol. This regimen resulted in a 40% lower risk of developing gestational diabetes, with reported cases dropping to 6.3% in the myo-inositol group versus 15.3% in the group receiving a placebo. The calculated odds ratios of 0.35 further underscored a substantial 65% reduction in the probability of gestational diabetes among those supplemented with myo-inositol.

Beyond glycaemic control, myo-inositol supplementation exhibited favourable outcomes in pregnancy-related complications associated with hyperglycaemia, including a notable reduction in foetal macrosomia and mean foetal weight. Additionally, postmenopausal women experienced improvements in

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cardiovascular risk markers, with reductions in blood pressure, triglycerides (34% decrease), and cholesterol, along with a noteworthy increase in HDL cholesterol (21% elevation).

Extended supplementation over six months to a year demonstrated comprehensive enhancements in metabolic parameters, leading to the effective management of metabolic syndrome in 20 percent of postmenopausal women, whereas only 2.5 percent in the placebo group achieved similar outcomes.

Specifically, the reduction in triglycerides was most pronounced with pioglitazone (50% reduction), followed by myo-inositol (34% reduction), and then rosiglitazone (20% reduction). This comparison highlighted the varying degrees of efficacy among these treatments in managing lipid profiles, particularly in the context of insulin resistance and related metabolic conditions. Noteworthy findings indicated a 21 percent enhancement in HDL cholesterol levels following myo-inositol dietary supplementation for one-year, surpassing results observed with pioglitazone and rosiglitazone. In contrast, a 12-month study involving metformin demonstrated a modest increase in HDL cholesterol (2.4%), with no significant change in triglyceride levels [53].

To sum up, data from four randomized controlled trials reinforced the safety and effectiveness of supplementing diets with myo-inositol (ranging from 2 to 4 g/day). This supplementation was shown to alleviate insulin resistance and related cardiovascular health issues in women suffering from conditions such as gestational diabetes, postmenopausal metabolic syndrome, and polycystic ovary syndrome (PCOS) [4]. However, the precise mechanistic insights into myo-inositol supplementation remain elusive, warranting further research on larger and more diverse populations, encompassing different demographics, genders, and employing double-blind methodologies. These endeavours will be pivotal in establishing myo-inositol supplementation as a validated and effective insulin-sensitizing intervention beyond the scope of hormonal conditions explored thus far.

10. Conclusion

In conclusion, myo-inositol, an intrinsic polyol present in cells and a key component of essential biological molecules such as IPGs, IP3, and PIP2-PIP3, was crucial in a range of biological functions. Its involvement in pathological states underscored its importance, especially in relation to diabetes-induced complications in various tissues. These tissues included the kidney, sciatic nerve, lens, and retina, where myo-inositol's role was particularly critical in the context of diabetes management and the prevention of related complications. This highlighted the broader significance of myo-inositol in both cellular processes and disease pathology. Although it was unsuccessful in addressing diabetic nephropathy in animal models, dietary supplementation of myo-inositol showed promise in mitigating or delaying the onset of several microvascular complications in motor neurons and the lens.

In the context of insulin resistance, altered levels of myo-inositol and DCI in urinary excretion were observed, with lower urinary DCI levels correlating with increased insulin resistance. Tissues exhibiting insulin resistance, such as skeletal muscles, displayed changes in DCI to myo-inositol ratios, along with diminished IPG concentration, action, and responsiveness of these compounds to insulin. Given that IPGs are key facilitators in the mechanism of insulin action, a decrease in their levels or effectiveness in insulin-sensitive tissues could impede insulin's normal functioning.

Dietary supplementation of diets with isomers of inositol, such as myo-inositol, D-pinitol, and DCI, proved effective in mitigating post-prandial hyperglycaemia across various models exhibiting diabetes or insulin resistance. These beneficial effects were thought to stem from the insulin-like properties of inositol, potentially linked to its role in generating inositol glycan second messengers, involving forms like myo-inositol or DCI. This suggested a significant potential for inositol isomers in

managing blood glucose levels. However, to fully understand the scope and mechanisms of myo-inositol's impact, more extensive research was necessary. Such studies were crucial for a deeper understanding of how myo-inositol functions at the molecular level and for providing clarity on the actual role and efficacy of inositolphosphoglycans (IPGs) in these metabolic processes.

Promising results from randomized controlled studies involving myo-inositol dietary supplements in specific populations, such as postmenopausal women with

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metabolic syndrome or gestational diabetes, demonstrated its potential in reducing impaired insulin sensitivity and cardiovascular risk. To validate the previous observations with gestational diabetes (GDM), metabolic disorders in menopause, and polycystic ovary syndrome (PCOS), and to explore potential applications for a wider population already exhibiting impaired insulin sensitivity or at risk due to genetic predisposition, extensive double-blind trials involving diverse populations beyond Caucasians and males were imperative.

In conclusion, myo-inositol supplementation demonstrated promising effects in improving insulin sensitivity, reducing cardiovascular risk, and mitigating gestational diabetes risk in various populations of women. The significant reduction in insulin resistance, coupled with favourable metabolic outcomes, suggested its potential as a valuable intervention. However, the precise mechanism of action and generalizability to broader populations remained unclear. Further extensive and diverse research, including larger double-blind trials involving various ethnicities and genders, was essential to establish myo-inositol's safety and efficacy as an insulin-sensitizing drug across different contexts.

Credit authorship contribution statement

Kamalesh DR: Review, Formal analysis, Writing – original draft.

Dr. Geetha K.M: Conceptualization, Visualization, Data curation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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