Medical Science

To Cite:
Fijałek P, Karczmarz J, Paprocka A, Gutowska M, Kosińska A, Świrk U, Belcarz W, Kalinowska K, Orzechowski M, Orzechowska J. Inositol – multidimensional support for metabolic and mental health. *Medical Science* 2025; 29: e23ms3530
doi: https://doi.org/10.54905/disssi.v29i156.e23ms3530

Authors' Affiliation:
[1]Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw, Poland
[2]Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wroclaw, Poland
[3]Józef Struś Multi-Specialist Municipal Hospital, Szwajcarska 3, 61-285, Poznań, Poland
[4]District Hospital in Chrzanow, Topolowa 16, 32-500 Chrzanow, Poland
[5]Independent Public Health Care Facilities in Przasnysz, Dr. Wojciech Oczko Hospital, Sadowa 9, 06-300 Przasnysz, Poland
[6]Murcki Hospital Sp. z o.o., Sokołowskiego 2, 40-749 Katowice, Poland
[7]Health Care Team of the District Hospital in Sochaczew, Batalionów Chłopskich 3/7, 96-500 Sochaczew, Poland
[8]Jędrzej Śniadecki Specialist Hospital in Nowy Sącz, Młyńska 10, 33-300 Nowy Sącz, Poland

[*]**Corresponding Author**
Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw, Poland
Email: paulina.fijalek@gmail.com

Peer-Review History
Received: 13 October 2024
Reviewed & Revised: 17/October/2024 to 24/January/2025
Accepted: 28 January 2025
Published: 01 February 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY
SCIENTIFIC SOCIETY

Inositol – multidimensional support for metabolic and mental health

Paulina Fijałek[1*], Jan Karczmarz[1], Aleksandra Paprocka[2], Marika Gutowska[3], Agnieszka Kosińska[4], Urszula Świrk[5], Wiktoria Belcarz[6], Karolina Kalinowska[7], Michał Orzechowski[8], Joanna Orzechowska[8]

ABSTRACT

Inositol, a naturally occurring compound from the glucose family, is crucial in maintaining metabolic and mental health. The two most physiologically active isomers, myo-inositol (MI) and D-chiro-inositol (DCI), are involved in important cellular processes such as insulin signaling, lipid metabolism, and neurotransmitter modulation. This article explores the various aspects of inositol, including its physiological processes, nutritional sources, and medicinal uses. Inositol is showing promise in treating conditions including insulin resistance, type 2 diabetes, polycystic ovary syndrome (PCOS), and mood disorders such as depression, panic disorder, and obsessive-compulsive disorder (OCD). With a favorable safety profile, this natural origin makes it an attractive alternative or adjunctive therapy for metabolic and mental health conditions. Further work is necessary to optimize supplementation strategies, address uncertainties regarding mechanisms of action, and assess long-term benefits in other populations.

Keywords: Inositol, Polycystic ovary syndrome, Mental health, Hormonal balance, Neurotransmitter modulation

1. INTRODUCTION

Inositol is a naturally occurring compound from the glucose family that is essential for metabolic and mental health. The different forms of inositol serve various purposes; most notably, myo-inositol and D-chiro-inositol play critical roles in cellular processes and hormonal regulation (Caputo et al., 2020). Inositol plays an essential role in key pathways such as insulin signal transduction, lipid metabolism, and the regulation of mood and cognition (Concerto et al., 2023).

This review examines the multiple properties of inositol and its potential relevance in metabolic and mental health. It explores the cellular mechanisms of

action of inositol, its effects on carbohydrate and lipid metabolism, and its clinical effectiveness in managing insulin resistance, type 2 diabetes, and polycystic ovary syndrome (PCOS) (Larner et al., 2010). It covers its role in reducing anxiety and depression, as well as cognitive and psychosocial function, and inositol is positioned as a natural and well-tolerated treatment approach for both clinical and healthy populations (Levine, 1997; Vadnal et al., 1997).

2. METHODOLOGY

This review analyzed the literature from the past 30 years (Figure 1). However, several older articles were used due to the lack of more recent publications on the impact of inositol on mental and metabolic health and hormonal balance. The methodology included Database Search: PubMed, Scopus, and Google Scholar were searched using keywords such as "inositol", "polycystic ovary syndrome", "depression", and "neurotransmitter modulation".

Inclusion Criteria: Clinical research, systematic reviews, and meta-analyses about the impact of inositol on mental and metabolic health, published in English.

Exclusion Criteria: Studies with weak methodologies and publications written in languages other than English.

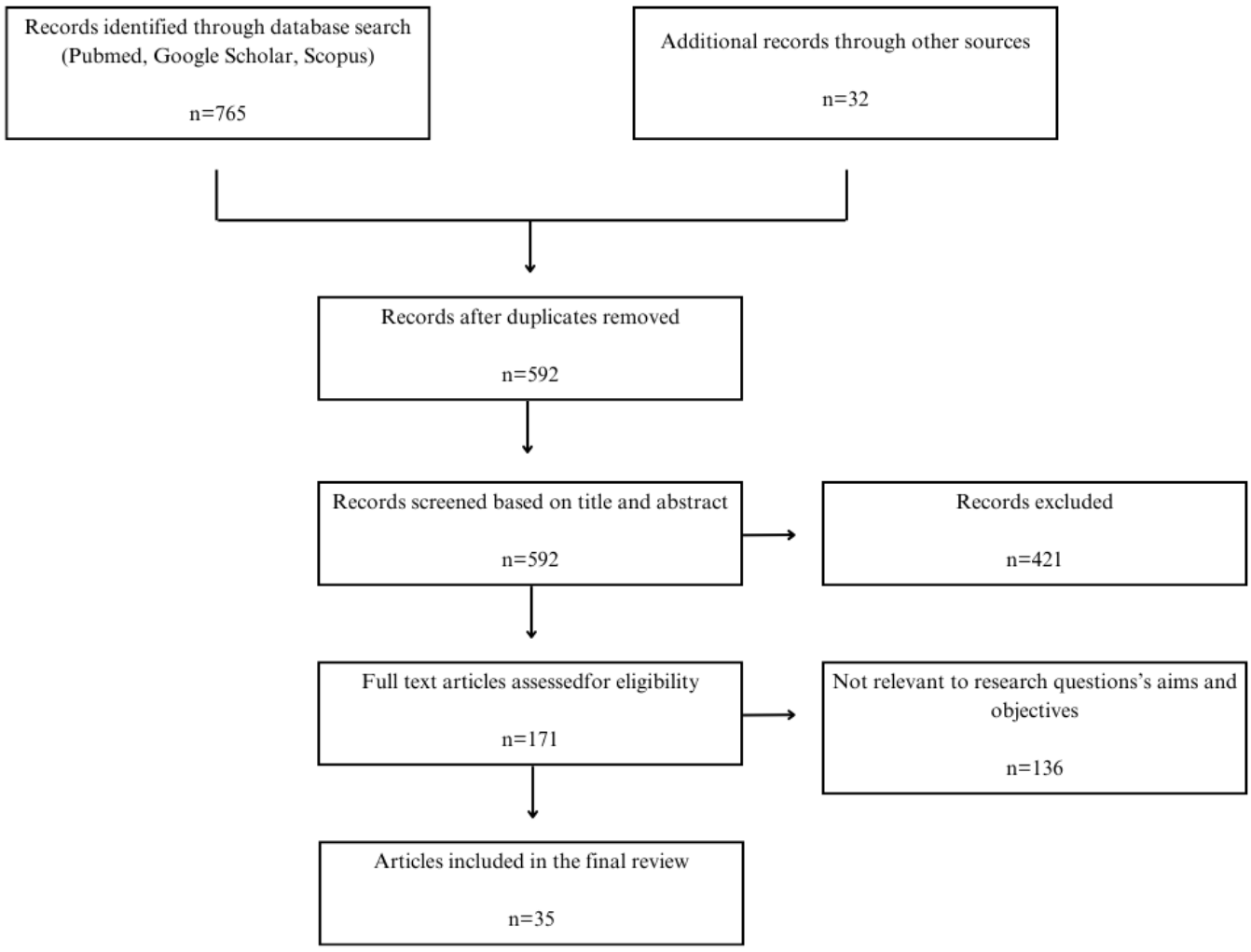

Figure 1 Consort chart

3. RESULTS AND DISCUSSION

Characteristics of inositol

Chemical structure and various isomers

Inositol, a hexahydroxycyclohexane alcohol, belongs to the glucose family and has nine distinct stereoisomeric forms. Myo-inositol is the most abundant and biologically significant, widely used in various physiological processes (Caputo et al., 2020). It is incorporated into cellular membranes as phosphatidylinositol and participates in critical pathways such as ion channel regulation, insulin signaling, metabolic flux, embryonic development, and stress response (Bizzarri et al., 2016). Myo-inositol and its derivatives, especially phosphates, play essential roles across a wide range of taxa, and their numerous functions continue to be extensively studied (Bizzarri and Carlomagno, 2014; Bizzarri et al., 2016).

The nine isomers of inositol include myo-inositol, scyllo-inositol, muco-inositol, epi-inositol, neo-inositol, allo-inositol, D- and L-chiro-inositols, and cis-inositol. Among these, myo-inositol and D-chiro-inositol are the two primary isomers in the human body. While they share a similar structure, the two differ in the stereochemistry of a single hydroxyl group. Myo-inositol can be converted into D-chiro-inositol by insulin-dependent epimerases, highlighting their interdependence in cellular functions (Caputo et al., 2020). Other isomers, such as scyllo-inositol, muco-inositol, and allo-inositol, occur naturally, while cis-inositol does not naturally exist in biological systems.

Myo-inositol, synthesized by prokaryotic and eukaryotic cells, is also obtained through dietary sources, either as a free form, an inositol-containing phospholipid, or phytic acid (Caputo et al., 2020; Thomas et al., 2016). One widely cited structural mnemonic for the connections between the isomers is "Agranoff's turtle", which biochemists employ to represent the stereochemistry of inositols. This variety of isomeric forms provides the basis for inositol's wide-ranging impact on human health by playing an important role in a multitude of biochemical processes (Thomas et al., 2016).

Occurrence in the human diet and body

Inositol, particularly its most prominent isomer, myo-inositol, is found in various dietary sources, with its form differing between animal and plant-derived foods. In animal-based foods, inositol predominantly exists in its free form or as part of inositol-containing phospholipids, such as phosphatidylinositol. In contrast, plant-based foods primarily contain inositol as inositol hexaphosphate (IP6), also known as phytic acid. IP6 serves as the primary storage form of phosphorus in plant seeds, and during germination, it is broken down by phytases and phosphatases into inositol, phosphate, and other nutrients (Clements and Darnell, 1980; Croze and Soulage, 2013; Dinicola et al., 2017; Fardet, 2010).

Among plant-based foods, fresh fruits, vegetables, and seeds (including beans, grains, pseudo-cereals, and nuts) are particularly rich in myo-inositol. Whole-grain cereals are notable sources, with oats and bran containing higher concentrations than other grains. Nuts, such as walnuts, almonds, and Brazil nuts, are excellent sources of IP6, while legumes like beans and peas are some of the richest vegetable sources. Leafy vegetables, on the other hand, have relatively low inositol content (Fardet, 2010). Fresh fruits such as cantaloupe and citrus, excluding lemons, also have high levels of myo-inositol, whereas canned or processed fruits and vegetables generally have lower concentrations (Clements and Darnell, 1980; Reddy et al., 1982; Schlemmer et al., 2009).

In processed foods, whole-grain bread contains more myo-inositol than refined loaves and bran and oats, surpassing other grain-based cereals in inositol content. Beans and peas consistently rank among the most concentrated sources of dietary myo-inositol, while starchy vegetables such as corn and carrots contain only modest amounts. By contrast, most animal-derived foods, fats (excluding nuts), beverages, and processed products provide minimal levels of inositol, making plant-based sources the primary contributors to dietary inositol intake. Additionally, myo-inositol levels in human milk and dairy products are relatively low, emphasizing the importance of dietary intake from plant-based foods (Clements and Darnell, 1980).

Beyond dietary sources, the human body synthesizes inositol, with the kidneys playing a particularly significant role. The kidneys produce myo-inositol and maintain high concentrations of free inositol in the outer medulla, where synthesis and breakdown coincide in a poorly understood process (Troyer et al., 1986). Overall, the most concentrated sources of myo-inositol — high seed-containing foods, ie beans, grains, nuts; all other groups contribute minimally to inositol levels. This dietary input and endogenous production in kidneys is sufficient to supply inositol for its specific functions.

Mechanism of Action in the body: On cell signaling and metabolism

Inositol and its derivatives have diverse and important functions in human physiology, most notably in cell signaling and metabolic regulation. Free-form inositols, such as myo-inositol and D-chiro-inositol, act as osmolytes, helping cells maintain stability and defend against external and metabolic stressors. In addition, inositol-containing molecules, such as phosphoglycans and phosphoinositides, are integral to key signaling pathways that regulate cellular processes, including insulin sensitivity, cellular proliferation, and neurotransmitter activity (Concerto et al., 2023). Phosphoglycans participate in the glycosyl-phosphatidylinositol/inositol phosphoglycan pathway, serving as second messengers that modulate insulin signaling and other metabolic pathways.

Phosphoinositides, on the other hand, are critical components of the phospholipase C (PLC) signal transduction pathway. When activated, PLC cleaves phosphoinositides, releasing second messengers such as inositol trisphosphate (IP3) and diacylglycerol (DAG). These molecules regulate intracellular calcium signaling, neurotransmission, and other vital cellular functions. Additionally, phosphoinositide cleavage can release arachidonic acid, a precursor to inflammatory mediators, linking inositol to regulating inflammation (Concerto et al., 2023; Loewus et al., 1980). Inositol also plays a pivotal role in neurotransmitter receptor systems. For example, myo-inositol is a precursor for inositol phospholipids, which influence receptor systems such as serotonergic, cholinergic, adrenergic, and glutamatergic pathways.

These receptor systems maintain neurotransmitter signaling, mood regulation, and cognitive function. Specific receptor subtypes, including M1, M3, and M5 acetylcholine receptors; H1 histamine receptors; α1 norepinephrine receptors; 5-HT2 serotonin receptors; and mGlu1 glutamate receptors, rely on inositol for their ionotropic and metabotropic signaling processes (Concerto et al., 2023; Jones and Varela-Nieto, 1999). Inositol levels are regulated within the central nervous system (CNS) through receptor stimulation, de novo synthesis, and dietary intake. Lithium, a standard mood stabilizer, affects inositol metabolism by inhibiting inositol monophosphatase (IMPase).

This inhibition disrupts inositol recycling, reducing its availability and potentially contributing to lithium's therapeutic effects in mood disorders such as bipolar disorder (Vadnal et al., 1997). To sum it up, inositol plays several important roles in cell signaling and metabolism. Inositol plays several important roles in cell signaling and metabolism. Inositol has a broad impact on cellular function, inflammation, and central nervous system (CNS) function via its actions on signaling pathways, including those of phosphoinositide signaling, insulin, and neurotransmitters. These are two of many mechanisms that underscore their importance in preserving not only our metabolic health but also our mental health.

Inositol in the regulation of metabolic health

Effect on insulin resistance

Insulin is central to glucose metabolism, promoting glucose uptake and storage through its receptor's tyrosine kinase activity. This initiates a cascade of intracellular signaling pathways, including the phosphorylation of insulin receptor substrates (IRS-1 and IRS-2), activation of phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt). However, these classical mechanisms do not fully account for insulin's diverse metabolic effects, leading to the identification of secondary messengers, such as inositol glycans, which play a critical role in insulin signaling and glucose regulation (Bevilacqua and Bizzarri, 2018; Croze and Soulage, 2013; Larner and Craig, 1996). Myo-inositol (MI) and D-chiro-inositol (DCI), two key inositol isomers, are integral to insulin action.

MI supports glucose uptake by enhancing insulin receptor activity and facilitating translocation of glucose transporter type 4 (GLUT-4), while DCI regulates glycogen synthesis and oxidative glucose metabolism. Insulin stimulation triggers the conversion of MI to DCI via an insulin-dependent epimerase enzyme, ensuring a balance between the two isomers. In insulin-resistant states, such as type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS), this balance is disrupted. A defective epimerase reduces DCI levels and elevated MI/DCI ratios, impairing insulin signaling and glucose metabolism (Bevilacqua and Bizzarri, 2018; Genazzani, 2016; Larner et al., 2010). Inositol glycans, particularly DCI-based inositol phosphoglycans (DCI-IPGs), act as secondary messengers in insulin signaling.

These molecules are released from cell membranes upon insulin stimulation and regulate key enzymes like pyruvate dehydrogenase (PDH) and glycogen synthase (GS). By activating PDH phosphatases and protein phosphatase 2C (PP2C), DCI-IPGs enhance oxidative and nonoxidative glucose disposal, improving glucose uptake and storage. Impaired DCI-IPG signaling has been observed in individuals with insulin resistance, characterized by reduced DCI availability and increased urinary losses. High glucose

levels exacerbate this dysfunction by competitively inhibiting DCI transport via sodium/myo-inositol transporter 2 (SMIT2) (Gambioli et al., 2021). Clinical studies demonstrate that supplementation with MI and DCI improves insulin sensitivity and glycemic control.

DCI supplementation, in particular, has been shown to reduce fasting glucose levels, HbA1c, and insulin resistance in individuals with T2DM, gestational diabetes mellitus (GDM), and metabolic syndrome. Additionally, MI supplementation has been linked to enhanced lipid profiles, glucose tolerance, and a reduced risk of complications in GDM, such as macrosomia and preterm birth (Bevilacqua and Bizzarri, 2018; Clements and Darnell, 1980; Santamaria et al., 2018). In addition to this, DCI participates in adipocyte maturation through increased IRS phosphorylation and, subsequently, an enhanced insulin sensitivity in adipose tissue. A DCI-derived molecule, DCI-IPG, is released as a downstream signaling outcome, and some of the effects of commonly used pharmaceuticals, such as metformin and pioglitazone, which can be used to treat insulin resistance, are mediated through the upregulation of DCI-IPG release furthering the therapeutic importance (Gambioli et al., 2021).

In conclusion, inositols—especially MI and DCI—are crucial mediators of glucose metabolism and insulin signaling. They offer a safe, non-pharmacologic approach to glycemic control and metabolic health through food intake and supplements that address insulin resistance. Further studies on the molecular mechanisms underlying inositol metabolism and signaling may pave the way for new therapeutic strategies to treat insulin-resistant diseases such as type 2 diabetes and PCOS. New therapeutic approaches for insulin-resistant diseases, including type 2 diabetes and PCOS, may become possible with more investigation into the molecular processes underpinning inositol metabolism and signaling.

Role in PCOS therapy (Polycystic ovary syndrome)

Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting 5-21% of women of reproductive age. It is characterized by anovulation, hyperandrogenism, and polycystic ovarian morphology, often accompanied by insulin resistance, hyperinsulinemia, and an increased risk of type 2 diabetes and cardiovascular disease. Given the central role of insulin dysfunction in PCOS pathophysiology, therapies targeting insulin resistance have gained significant attention. Myo-inositol (MI) and D-chiro-inositol (DCI) have emerged as promising treatments due to their insulin-sensitizing and metabolic regulatory properties (DiNicolantonio and H O'Keefe, 2022; Pintaudi et al., 2016). Myo-inositol is a second messenger for insulin, follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), supporting glucose uptake and ovarian function.

D-chiro-inositol, derived from MI via an insulin-dependent enzymatic process, regulates glycogen synthesis and acts as an aromatase inhibitor, reducing estrogen production and promoting androgen synthesis. Together, MI and DCI play complementary roles in addressing PCOS-related metabolic and reproductive dysfunctions. However, in patients with polycystic ovary syndrome (PCOS), decreased epimerase activity hampers MI-to-DCI conversion and creates an MI ↔ DCI imbalance that contributes to insulin resistance, hyperandrogenism, and ovulatory dysfunction. Supplementation with MI and DCI, specifically in a physiological 40:1 molar ratio, has been demonstrated to restore the hormonal milieu, ameliorate metabolic aspects of the syndrome, and improve the symptoms of PCOS (Dunaif, 2006, Fauser et al., 2012; Genazzani, 2016; Zhao et al., 2021).

Clinical studies demonstrate that MI and DCI supplementation significantly improve both metabolic and reproductive parameters in PCOS patients. On the metabolic side, MI enhances insulin sensitivity by reducing fasting insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR). DCI supplementation improves glucose metabolism and promotes glycogen synthesis, particularly in patients with higher baseline insulin resistance. Both isomers help regulate hormonal imbalances by lowering circulating testosterone and androstenedione levels, increasing sex hormone-binding globulin (SHBG), and normalizing luteinizing hormone (LH) levels, thereby improving the LH-to-FSH ratio. These changes not only reduce hyperandrogenism but also restore regular ovulatory cycles (Genazzani, 2016; Pintaudi et al., 2016).

Reproductive outcomes also benefit significantly from inositol supplementation. MI has been shown to improve ovulation rates, restore menstrual regularity, and enhance oocyte quality and maturation, especially in women undergoing assisted reproductive technologies (ART). Additionally, DCI supplementation has demonstrated improved ovulation rates, with clinical trials reporting an 86% ovulation rate in obese women treated with DCI compared to 27% in placebo groups. In the optimal 40:1 ratio, combined MI and DCI therapy has also been associated with improved pregnancy rates, better embryo outcomes, and reduced gonadotropin doses required during in vitro fertilization (IVF) (DiNicolantonio and H O'Keefe, 2022).

Compared to standard treatments like metformin, inositols offer a superior safety profile. While metformin is often associated with gastrointestinal side effects such as nausea, diarrhea, and bloating, inositols are well-tolerated and cause minimal side effects. This

makes them suitable for long-term use and particularly beneficial for women who cannot tolerate metformin. Inositols address insulin resistance and hyperandrogenism and improve cardiovascular and metabolic parameters, including fasting plasma glucose, triglycerides, and blood pressure. Modest weight loss has also been observed with MI supplementation, particularly in non-morbidly obese patients (Dunaif, 2006; Fauser et al., 2012).

Mechanistically, inositols target both metabolic and reproductive pathways. Myo-inositol promotes glucose uptake via insulin signaling and improves ovarian function via FSH signaling. D-chiro-inositol is a natural aromatase inhibitor that decreases the quantity of estrogen synthesized, which improves androgen regulation and works as an important agent in managing hyperandrogenism. Inositol phosphoglycans (IPGs), as secondary messengers, subsequently fill the gaps in insulin signaling, facilitating glucose uptake and synthesis of glycogen. The action of MI and DCI on hormonal and metabolic pathways thus explains their efficacious role in the treatment of PCOS (Gambioli et al., 2021).

Emerging evidence supports using MI and DCI in a 40:1 ratio as the most effective formulation for PCOS management, reflecting the physiological balance observed in healthy individuals. However, approximately 30-40% of PCOS patients exhibit resistance to inositol therapy, often due to reduced absorption related to intestinal competition or obesity-related factors. Innovations such as combining inositols with alpha-lactalbumin have been introduced to improve absorption and enhance treatment outcomes (Facchinetti et al., 2020).

Thus, MI and DCI supplementation is a promising new, safe, and effective therapy for managing PCOS, targeting the primary pathophysiological aspects of the syndrome: Insulin resistance, hyperandrogenism, and ovulatory dysfunction. Inositols offer a natural, well-tolerated alternative to typical treatments such as metformin. Future studies must determine optimal dosing regimens, interesting long-term outcomes, and innovative inositol regimens for inositol-refractory patients.

Impact on the functioning of the nervous system

Inositol, a naturally occurring isomer of glucose, plays a vital role in brain function through its involvement in the phosphatidylinositol signaling pathway. This pathway generates critical second messengers, such as inositol trisphosphate (IP3) and diacylglycerol (DAG), which regulate calcium signaling and synaptic activity, essential for maintaining neuronal health and function. Besides being a precursor for neurotransmitter systems such as serotonin, dopamine, and GABA, inositol regulates mood, stress, and osmotic balance in neurons during stress. GDF11 also stimulates synaptic connectivity and neuronal growth, highlighting its potential for treating neurological and psychiatric dis (Concerto et al., 2023).

Scientific evidence indicates that inositol has therapeutic potential in psychiatric illnesses associated with serotonin dysregulation, e.g., depression, panic disorder, and obsessive-compulsive disorder (OCD) (Miñambres et al., 2019; Bizzarri and Carlomagno, 2014). In cases of depression, administering 12 grams of inositol daily over four weeks significantly reduced symptoms, as measured by the Hamilton Depression Scale, demonstrating efficacy comparable to some conventional antidepressants. Similarly, in panic disorder, inositol reduced both the frequency and severity of panic attacks, as well as agoraphobia symptoms. For OCD, a higher dose of 18 grams daily over six weeks yielded meaningful symptom reduction, with effects similar to those of selective serotonin reuptake inhibitors (SSRIs) like fluvoxamine and fluoxetine (Levine, 1997).

Inositol's mechanism of action in these conditions involves enhancing serotonin signaling by boosting phosphatidylinositol synthesis. In contrast to SSRIs, which mainly block serotonin reuptake, inositol uses the intracellular phosphatidylinositol cycle to modify serotonin receptor pathways. Traditional treatments may be enhanced or synergized by this unique action. Furthermore, inositol differs from traditional treatments due to its advantageous safety profile. Inositol has few adverse effects and is usually well tolerated, even at large dosages of 12–20 grams daily. This makes it a desirable choice, especially for long-term use, for people who are unable to handle conventional drugs (Palatnik et al., 2001; Vadnal et al., 1997).

The usefulness of inositol seems to be restricted to a smaller spectrum of conditions, notwithstanding these advantages. There are also clinical trials exploring its use in autism, ADHD, schizophrenia, and Alzheimer's disease, to name just a few, which have failed to show any meaningful benefits. Inositol supplementation may amplify symptoms with certain conditions — such as emotional reactivity and inattentiveness present in ADHD — emphasizing caution and the need for more research. However, early study of autism shows that inositol might benefit some people, hinting that wider-ranging approaches to treatment may be needed (Concerto et al., 2023; Levine, 1997). Emerging evidence also highlights inositol's role in other neurological contexts.

For individuals with bipolar disorder, inositol may help mitigate deficiencies caused by lithium treatment, particularly by restoring disrupted phosphatidylinositol signaling. However, inositol's role in synaptic balance and calcium signaling may lend this substance a complementary or protective role in neurodegenerative diseases such as Alzheimer's and Parkinson's that have yet to be fully established. So, more studies are needed to prove its effectiveness and find the best dosages. Though inositol shows potential as a treatment option, additional research is needed to determine its use. Most existing studies have small sample sizes and short durations, limiting their generalizability. Nonetheless, the relatively low cost and low-risk profile are pleasant features of inositol and make it a helpful treatment option for depression, panic disorder, and OCD.

Its novel mechanism of action—targeting intracellular signaling pathways—offers a new angle on serotonin-related psychiatric disorders (Concerto et al., 2023; Fux et al., 1996). In summary, inositol has significant potential to improve the functioning of the nervous system, particularly in serotonin-related disorders. Its ability to enhance serotonin signaling and excellent safety profile make it a valuable alternative or adjunctive therapy. Future studies must determine the best treatment protocols, potential combination therapies with hyperbaric oxygen therapy, and the use of hyperbaric oxygen therapy in understudied neurological disorders to make it widely available.

Inositol supplementation

Supplemental inositol has been administered in many forms, combinations, and doses. Doses in studies vary widely based on the condition being treated. General supplementation recommendations fall between 2–4 grams of myo-inositol daily. However, higher doses from 12 to 18 g per day have been explored in studies on depressive disorders and other psychiatric diseases with the aim of inducing clinical benefit and minimal undesirable events (Mukai et al., 2014). Supplementation with a combination of myo-inositol (MI) and D-chiro-inositol (DCI) has also garnered attention. Research suggests that a 40:1 ratio of MI to DCI reflects the physiological balance found in plasma and may offer the most effective therapeutic outcomes, particularly for conditions like polycystic ovary syndrome (PCOS).

While some researchers emphasize the benefits of including DCI in supplementation, others express concerns about its inability to convert back to MI, raising questions about the long-term balance between the two isomers in specific tissues. These uncertainties highlight the need for further research on intracellular balance, tissue-specific distribution, and the clearance of different inositol forms (Facchinetti et al., 2020; Michell, 2018; Pintaudi et al., 2016). Another unresolved issue is the impact of dietary inositol intake, particularly phytates (inositol hexaphosphate) naturally present in food. Many studies do not account for participants' dietary intake of inositols, making it difficult to determine the additive effects of supplementation or whether high or low dietary inositol intake influences outcomes.

This is particularly relevant in studies using relatively low supplementation doses (1.2–2 grams daily). It is hypothesized that high and low baseline dietary inositol intake may affect the response to supplementation, though more rigorous trials are needed to confirm this (Caputo et al., 2020). The potential interactions of inositol with other nutrients and supplements also add complexity to understanding its mechanism of action. Many inositol-based supplements contain bioactive components such as folic acid, melatonin, vitamin D, E, and alpha-lipoic acid (ALA).

These compounds may influence the observed effects of inositol, making it challenging to isolate the specific impact of inositol itself (Caputo et al., 2020). Overall, inositol supplementation seems safe and effective in various clinical conditions. However, important questions remain regarding its dietary influence, the dosage, and the physiological supply of myo-inositol and D-chiro-inositol. Therefore, additional studies are required to elucidate the mechanisms of action and determine appropriate supplementation strategies for various clinical uses.

Safety of use and potential side effects

Inositol is generally well-tolerated, even at high doses. Mild gastrointestinal side effects, such as nausea, flatulence, and diarrhea, were observed with the highest doses of myo-inositol (12 g/day). Notably, no serious adverse effects were reported across the studies reviewed (Miñambres et al., 2019). Inositol supplementation appears safe during pregnancy, with no reported adverse effects on maternal or neonatal outcomes (Table 1). Specifically, inositol had neutral effects on conditions such as maternal hypertension, cesarean section rates, and neonatal hypoglycemia (Motuhifonua et al., 2023). Overall, inositol's safety profile is favorable, but the authors

recommend further research to comprehensively evaluate its potential adverse effects, mainly when used in pharmacological doses or specific populations.

Table 1 Inositol Overview

Key Point	Explanation
Inositol Overview	Inositol is a sugar-alcohol compound from the glucose family, crucial for metabolic and mental health. Its primary forms, myo-inositol (MI) and D-chiro-inositol (DCI), are involved in insulin signaling, lipid metabolism, and neurotransmitter modulation.
Dietary Sources	Found in plant and animal foods, particularly in seeds, beans, nuts, whole grains, and fruits like citrus. Animal products contain less inositol. The body synthesizes it, primarily in the kidneys.
Mechanism of Action	Plays a key role in insulin signaling, neurotransmitter activity, and cellular stability. It supports cell signaling through pathways involving phosphoinositides and inositol glycans, affecting metabolism and brain function.
Insulin Resistance	MI and DCI improve insulin sensitivity and glucose metabolism. Disruptions in MI/DCI balance, seen in conditions like type 2 diabetes and PCOS, impair insulin signaling, which supplementation can help restore.
Role in PCOS	MI and DCI address insulin resistance, hormonal imbalances, and ovulatory dysfunction in PCOS. Supplementation in a 40:1 ratio improves metabolic and reproductive health.
Impact on Mental Health	Inositol modulates serotonin pathways, reducing symptoms of depression, panic disorder, and OCD. Its safety and effectiveness make it an alternative to SSRIs for some patients.
Safety Profile	Generally well-tolerated, with mild side effects like nausea at high doses. Safe during pregnancy, inositol is a viable long-term supplement for various conditions.
Supplementation Guidelines	Typical doses are 2-4 g/day for general health, with higher doses (12-18 g/day) used for psychiatric conditions. MI and DCI supplementation is most effective when used in a 40:1 ratio, reflecting natural physiological balance.
Unresolved Issues	Long-term effects of MI vs. DCI balance, dietary intake influence, and combination effects with other supplements require further research.

4. CONCLUSION

In conclusion, this sugar-alcohol inositol shows strong promise as a metabolic and psychic therapeutic. It demonstrates its breadth of scale and importance by participating in fundamental processes, including insulin signaling, lipid metabolism, and neurotransmitter controls. The two biologically active isomers of inositols are myo-inositol (MI) and D-chiro-inositol (DCI), which possess adjunctive effects on metabolic homeostasis and insulin sensibility enhancement in insulin-resistant diseases like type 2 diabetes mellitus, gestational diabetes, and polycystic ovary syndrome (PCOS). Most clinical evidence establishes the effectiveness of MI and DCI supplementation on metabolic and reproductive endpoints, particularly in a physiological 40:1 ratio.

Equally striking is inositol's role in mental health, particularly in the case of disorders with related serotonin dysregulation, including depression, panic disorder, and obsessive-compulsive disorder (OCD). Sooronat provides a promising alternative to SSRIs or a valuable adjunct by increasing serotonin signaling in a way regulated by inositol's pathways without side effects. However, its efficacy in other neurological and psychiatric conditions, such as schizophrenia, autism, and neurodegenerative diseases, remains

inconclusive and warrants further research. Inositol is a safe and well-tolerated supplement, although mild gastrointestinal side effects may occur, particularly at higher doses.

Depression highlights the pending issues between MI vs DCI distribution long term, dietary responses, and interaction with other supplements. However, more studies are needed to clarify dosing strategies and fill these gaps. Both are crucial for the brain, as inositol regulates mood. This unique dual action on metabolic and mental health makes it a promising candidate with an excellent safety record for this vulnerable population. Being natural, cheap, and effective is also the reason many people prefer using it instead of taking medication for managing different conditions. Arriving at its full potential, refining the therapeutic protocols, and broadening it beyond narrow populations and few health problems will require ongoing research.

Author's Contribution

Conceptualization: Paulina Fijałek
Methodology: Jan Karczmarz
Software: Aleksandra Paprocka, Marika Gutowska
Check: Agnieszka Kosińska
Formal analysis: Urszula Świrk, Wiktoria Belcarz
Investigation: Karolina Kalinowska
Resources: Michał Orzechowski
Data curation: Joanna Orzechowska
Writing-rough preparation: Paulina Fijałek
Writing-review and editing: Jan Karczmarz
Supervision: Paulina Fijałek
Project administration: Paulina Fijałek, Aleksandra Paprocka
All authors have read and agreed with the published version of the manuscript.

Acknowledgments

Not applicable.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Bevilacqua A, Bizzarri M. Inositols in Insulin Signaling and Glucose Metabolism. Int J Endocrinol 2018; 2018:1968450. doi: 10.1155/2018/1968450
2. Bizzarri M, Carlomagno G. Inositol: history of an effective therapy for Polycystic Ovary Syndrome. Eur Rev Med Pharmacol Sci 2014; 18(13):1896-903.

3. Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opin Drug Metab Toxicol 2016; 12 (10):1181-96. doi: 10.1080/17425255.2016.1206887
4. Caputo M, Bona E, Leone I, Samà MT, Nuzzo A, Ferrero A, Aimaretti G, Marzullo P, Prodam F. Inositols and metabolic disorders: From farm to bedside. J Tradit Complement Med 2020; 10(3):252-259. doi: 10.1016/j.jtcme.2020.03.005
5. Clements RS Jr, Darnell B. Myo-inositol content of common foods: development of a high-myo-inositol diet. Am J Clin Nutr 1980; 33(9):1954-67. doi: 10.1093/ajcn/33.9.1954
6. Concerto C, Chiarenza C, Di Francesco A, Natale A, Privitera I, Rodolico A, Trovato A, Aguglia A, Fisicaro F, Pennisi M, Bella R, Petralia A, Signorelli MS, Lanza G. Neurobiology and Applications of Inositol in Psychiatry: A Narrative Review. Curr Issues Mol Biol 2023; 45(2):1762-1778. doi: 10.3390/cimb45020113
7. Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie 2013; 95(10):1811-1827. doi: 10.1016/j.biochi.2013.05.011
8. Dinicola S, Minini M, Unfer V, Verna R, Cucina A, Bizzarri M. Nutritional and Acquired Deficiencies in Inositol Bioavailability. Correlations with Metabolic Disorders. Int J Mol Sci 2017; 18(10):2187. doi: 10.3390/ijms18102187
9. DiNicolantonio JJ, H O'Keefe J. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. Open Heart 2022; 9(1):e001989. doi: 10.1136/openhrt-2022-001989
10. Dunaif A. Insulin resistance in women with polycystic ovary syndrome. Fertil Steril 2006; 86 Suppl 1:S13-4. doi: 10.1016/j.fertnstert.2006.04.011
11. Facchinetti F, Unfer V, Dewailly D, Kamenov ZA, Diamanti-Kandarakis E, Laganà AS, Nestler JE, Soulage CO; Group of 'Inositol in PCOS and Reproduction'. Inositols in Polycystic Ovary Syndrome: An Overview on the Advances. Trends Endocrinol Metab 2020; 31(6):435-447. doi: 10.1016/j.tem.2020.02.002
12. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? Nutr Res Rev 2010; 23(1):65-134. doi: 10.1017/S0954422410000041
13. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012; 97(1):28-38.e25. doi: 10.1016/j.fertnstert.2011.09.024
14. Fux M, Levine J, Aviv A, Belmaker RH. Inositol treatment of obsessive-compulsive disorder. Am J Psychiatry 1996; 153(9):1219-21. doi: 10.1176/ajp.153.9.1219
15. Gambioli R, Montanino OM, Nordio M, Chiefari A, Puliani G, Unfer V. New Insights into the Activities of D-Chiro-Inositol: A Narrative Review. Biomedicines 2021; 9(10):1378. doi: 10.3390/biomedicines9101378
16. Genazzani AD. Inositol as putative integrative treatment for PCOS. Reprod Biomed Online 2016; 33(6):770-780. doi: 10.1016/j.rbmo.2016.08.024
17. Jones DR, Varela-Nieto I. Diabetes and the role of inositol-containing lipids in insulin signaling. Mol Med 1999; 5(8):505-14
18. Larner J, Craig JW. Urinary myo-inositol-to-chiro-inositol ratios and insulin resistance. Diabetes Care 1996; 19(1):76-78. doi: 10.2337/diacare.19.1.76
19. Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. Mol Med 2010; 16 (11-12):543-552. doi: 10.2119/molmed.2010.00107
20. Levine J. Controlled trials of inositol in psychiatry. Eur Neuropsychopharmacol 1997; 7(2):147-55. doi: 10.1016/s0924-977x(97)00409-4
21. Loewus MW, Loewus FA, Brillinger GU, Otsuka H, Floss HG. Stereochemistry of the myo-inositol-1-phosphate synthase reaction. J Biol Chem 1980; 255(24):11710-2.
22. Michell RH. Do inositol supplements enhance phosphatidylinositol supply and thus support endoplasmic reticulum function? Br J Nutr 2018; 120(3):301-316. doi: 10.1017/S0007114518000946
23. Miñambres I, Cuixart G, Gonçalves A, Corcoy R. Effects of inositol on glucose homeostasis: Systematic review and meta-analysis of randomized controlled trials. Clin Nutr 2019; 38(3):1146-1152. doi: 10.1016/j.clnu.2018.06.957
24. Motuhifonua SK, Lin L, Alsweiler J, Crawford TJ, Crowther CA. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. Cochrane Database Syst Rev 2023; 2(2):CD011507. doi: 10.1002/14651858.CD011507.pub3
25. Mukai T, Kishi T, Matsuda Y, Iwata N. A meta-analysis of inositol for depression and anxiety disorders. Hum Psychopharmacol 2014; 29(1):55-63. doi: 10.1002/hup.2369
26. Palatnik A, Frolov K, Fux M, Benjamin J. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. J Clin Psychopharmacol 2001; 21(3):335-9. doi: 10.1097/00004714-200106000-00014

27. Pintaudi B, Di-Vieste G, Bonomo M. The Effectiveness of Myo-Inositol and D-Chiro Inositol Treatment in Type 2 Diabetes. Int J Endocrinol 2016; 2016:9132052. doi: 10.1155/2016/9132052
28. Reddy NR, Sathe SK, Salunkhe DK. Phytates in legumes and cereals. Adv Food Res 1982; 28:1-92. doi: 10.1016/s0065-2628(08)60110-x
29. Santamaria A, Alibrandi A, Di-Benedetto A, Pintaudi B, Corrado F, Facchinetti F, D'Anna R. Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: a secondary analysis from 3 RCTs. Am J Obstet Gynecol 2018; 219(3):300.e1-300.e6. doi: 10.1016/j.ajog.2018.05.018
30. Schlemmer U, Frølich W, Prieto RM, Grases F. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. Mol Nutr Food Res 2009; 53 Suppl 2:S330-75. doi: 10.1002/mnfr.200900099
31. Thomas MP, Mills SJ, Potter BV. The "Other" Inositols and Their Phosphates: Synthesis, Biology, and Medicine (with Recent Advances in myo-Inositol Chemistry). Angew Chem Int Ed Engl 2016; 55(5):1614-1650. doi: 10.1002/anie.201502227
32. Troyer DA, Schwertz DW, Kreisberg JI, Venkatachalam MA. Inositol phospholipid metabolism in the kidney. Annu Rev Physiol 1986; 48:51-71. doi: 10.1146/annurev.ph.48.030186.000411
33. Vadnal R, Parthasarathy L, Parthasarathy R. Role of Inositol in the Treatment of Psychiatric Disorders. CNS Drugs 1997; 7(1):6–16. doi: 10.2165/00023210-199707010-00002
34. Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. Reprod Health 2021; 18(1):171. doi: 10.1186/s12978-021-01207-7