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Metformin and Myo-Inositol: A Comparative Analysis

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Abstract
Background: In the field of polycystic ovary syndrome (PCOS), metformin and myo-inositol are frequently employed to treat the endocrine-metabolic aspects of the condition. Accordingly, myo-inositol is sometimes considered as a nutraceutical alternative for metformin. Both compounds have undergone repurposing efforts to identify new applications; however, the mechanisms of both these compounds differ considerably, as does their potential in conditions outside of PCOS. ***Objectives:*** This paper discusses contrasts both molecules in terms of mechanism, possible adverse effects, and novel indications, with an aim of detangling the unique properties of each molecule. ***Methods:*** A narrative review was conducted independently by the authors using the search platforms PubMed, Google Scholar, and Web of Science between August and November 2024. ***Conclusions and Outlook:*** Myo-inositol has a more acceptable safety profile than metformin, which is known to be associated with gastrointestinal adverse effects and, in rare cases, lactic acidosis. Myo-inositol is a naturally present molecule in physiological conditions, which underlines its importance in a variety of biological functions, as opposed to the strict pharmacological action of metformin. Both myo-inositol and metformin have been investigated in several pathological fields, particularly in gynecology where they may improve pregnancy outcomes and fertility care. The safety profile of these molecules seems quite different since data, even if incomplete, sustain high tolerance of myo-inositol, while the safety of metformin use during pregnancy is still controversial. However, further study is required to fully understand the potential of each of these molecules, specifically within the fields of mental health and oncology.

Introduction

Obesity has become an increasingly significant global health concern, with an estimated 39–49% of the world's population being overweight or obese [1]. A common comorbidity of obesity is insulin resistance; therefore, there exists an increasing need to monitor and ensure correct insulin function. Impaired insulin function can lead to the developing of conditions including type 2

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Table 1. Summary of the key mechanisms and clinical advantages of metformin and myo-inositol

Patients/condition	Metformin advantages	Myo-inositol advantages
Elevated HOMA-IR and severe insulin resistance	Greater glycemic control, greater IR control	Reduced side effects and comparable efficacy
BMI >25–26 kg/m^2	Greater metabolic improvements and pregnancy rates	Reduced gastrointestinal adverse events
IVF/ICSI cycles with elevated OHSS risk	Reduction of OHSS incidence	Documented overlapping benefits and reduction of rFSH doses
Hyperandrogenic phenotypes/ diabetes predisposition	Efficacy in the systemic activity affecting androgens and metabolism	Lower systemic impact but greater tolerability

diabetes (T2DM), polycystic ovary syndrome (PCOS), and gestational diabetes mellitus (GDM). As these syndromes increase so does the reliance on pharmaceutical and alternative approaches to manage insulin sensitivity. Initially utilized for the treatment of T2DM, the biguanide metformin represents the current gold standard pharmaceutical insulin sensitizer and is regularly used in the treatment of T2DM. Besides diabetes, metformin has found off-label applications, most notably in PCOS and weight management, but also in other areas as cardiovascular diseases, oncology, and neurological disorders [2].

Despite being generally well tolerated, metformin can cause gastrointestinal discomfort, which may limit its use for certain patients [3]. As insulin resistance is frequently retrieved in women with PCOS, metformin is useful to treat these patients. In women with PCOS, where insulin resistance and hormonal imbalances often coexist, metformin represents a valuable therapeutic option. However, in cases where tolerance or response is suboptimal, nutraceutical alternatives such as inositols – particularly the stereoisomer myo-inositol – have gained attention. Myo-inositol has demonstrated insulin-sensitizing properties and, according to several meta-analyses, exhibits comparable metabolic and hormonal benefits to metformin in PCOS, with generally better tolerability. This article explores the mechanisms of action of both metformin and myo-inositol, compares their potential applications beyond PCOS, and reviews their known side effects. A summary of the evidence discussed is presented in Table 1.

Methodology

A narrative review of the available literature was conducted. The authors performed an independent literature search, with search terms including metformin, myo-inositol, inositol, adverse effects, pregnancy, thyroid health, hypothyroidism, fertility care, assisted reproductive techniques, mood disorders, anxiety disorders, psychological disorders, mental health, and cancer. The literature search was conducted using the following databases: PubMed, Web of Science, and Google Scholar and conducted between August and November 2024. We performed a targeted literature search focusing on studies involving myo-inositol and metformin within the clinical areas discussed in the manuscript. Priority was given to randomized control trials (RCTs), particularly those with large sample sizes, robust statistical methodology, placebo controls, and conclusions well supported by both results and existing literature. We included peer-reviewed human studies and excluded preclinical-only reports, conference abstracts, and studies lacking methodological transparency. Where high-quality RCTs were unavailable or insufficient, we integrated clinical studies of other designs to help address data gaps. In some instances, we included studies assessing co-treatment regimens involving either metformin or myo-inositol, especially when monotherapy data were limited but clinically relevant. In addition, we searched for follow-up studies to explore long-term outcomes particularly regarding the effects of treatments on offspring. To provide a more detailed understanding of mechanisms of action, we also incorporated relevant in vivo and in vitro studies that offered molecular-level insights.

Underlying Mechanism of Metformin

The complex molecular mechanism of metformin is still not well understood, while the potential applications of metformin are constantly increasing. Metformin has a limited oral bioavailability and is typically absorbed in

the upper small intestine [4]. Upon absorption, metformin has a relatively short half-life in plasma (2–6 h) [5]; however, it is known to accumulate in certain tissues, such as liver and kidneys [6]. Primarily acting within the liver, metformin influences hepatic glucose production via AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms within liver mitochondria [7]. AMPK-dependent metformin action occurs through activation of the liver kinase B1 (LKB1)-AMPK signaling pathway; however, a quantitative proteomic approach in LKB1-AMPK-knockout mice treated with metformin revealed that approximately 50% of the phosphorylation events were independent of the LKB1-AMPK signaling pathway [8], suggesting other key players in metformin function.

In addition to hepatic function, metformin possess microbiota mediating properties [9], as it can favor the enrichment of two operational taxonomic units from *Bacteroides* and reduce abundance of one operational taxonomic unit from Fecalibacterium [10]. These changes may vary with ethnicity and metformin dose; however, similar effects have been observed in both patients with T2DM and healthy people receiving metformin treatment [11]. These data suggest that this change in microbiota is independent of impaired insulin function. Similar microbial changes are observed in rodent models that were fed a regular or a high-fat diet (HFD) following metformin treatment [12, 13]. In addition, following fecal microbiota transplants from metformin treated rats, HFD-fed rats demonstrated an increase across various metabolic markers, suggesting a net positive effect on microbiota following metformin treatment [14]. Moreover, the use of antibodies to deplete gut microbiota has been observed to reduce metformin activity [15]; however, this is up for debate as other studies have demonstrated metformin can reduce glucose function in HFD-fed rats undergoing antibiotic treatments [16]. Metformin appears to have a synergistic relationship with a healthy gut microbiota environment, as coadministration of metformin with probiotics improved metabolic function in patients with T2DM [17]. It should be noted that gut microbiota may play a role in metformin-related gastrointestinal adverse effects. The gut microbiota profile of metformin receptive patients appears to differ significantly to metformin resistant patients and may provide an explanation for the lack of tolerability in some patients [18], further supporting the coadministration of metformin with pro- and prebiotic supplementation.

Obesity, T2DM, and other cardiometabolic diseases are known to be associated with inflammation [19]. A crucial factor behind the repurposing of metformin across a multitude of disease areas is its reported anti-inflammatory properties. In detail, metformin inhibits mitochondrial respiratory chain complex one, leading to the inhibition of multiple cell-specific inflammatory processes via both AMPK-dependent and AMPK-independent mechanisms [20]. In turn, these anti-inflammatory properties may lead to potential therapeutic effects such as increased cancer cell death and insulin sensitivity in addition to reduced pulmonary inflammation and tumorigenesis [21].

Underlying Mechanism of Myo-Inositol

Myo-inositol is an endogenous mediator that plays an important role in numerous biological processes including insulin signaling in addition to acting as a second messenger for follicle-stimulating hormone (FSH), thus modulating steroidogenesis [22]. Myo-inositol is transported into the cell via sodium myo-inositol coupled transporters (SMIT1 and SMIT2) and, upon entering, facilitates glucose uptake via promoting glucose transporter type 4 translocation to the plasma membrane [23]. Under insulin stimulation, myo-inositol is unidirectionally converted to its stereoisomer D-chiro-inositol via tissue-specific epimerase [24]. D-chiro-inositol also functions as an insulin sensitizer, promoting glycogen storage, and the combined action of these molecules gives rationale to their use in hyperandrogenic-insulin-dependent PCOS [25].

Aside from insulin signaling, myo-inositol is also incorporated in the cell membranes of eukaryotes and serves as a precursor to inositol triphosphate 3, a second messenger for FSH and thyroid-stimulating hormone (TSH) [22]. Myo-inositol supplementation increases FSH activity, which in turn increased protein kinase A activity, stimulating aromatase production. Aromatase is a vital enzyme that facilitates the conversion of androgens to estrogens, causing a reduction in localized and systemic androgen levels [26]. The combination of this antiandrogenic and anti-insulinemic effect has given rise to the use of myo-inositol for the treatment of PCOS.

Metformin and Myo-Inositol Applications outside of Metabolic Diseases

Myo-inositol, in contrast to metformin, reports to be much better tolerated, displaying an excellent safety profile. For this reason, the medical community has

considered investigating the use of inositol as a "safer" and "natural" alternative to metformin in PCOS treatment, given that both treatments address the insulin resistance. As previously stated, this similarity has been the subject of numerous meta-analyses, which have demonstrated no difference in addressing the metabolic aspects of the condition [27]; however, this oversimplification underplays the unique molecules. As such, the following section reports the available evidence that address the non-PCOS potential for both treatments.

Metformin and Myo-Inositol in Hypothyroidism

Both myo-inositol and metformin have been investigated as potential treatments for subclinical hypothyroidism (SCH), as each treatment can reduce TSH levels. An initial meta-analysis of 7 studies conducted by Lupoli et al. [28] demonstrated that metformin reduced TSH levels in patients with hypothyroidism and SCH, while euthyroid patients were unaffected. Furthermore, in a subsequent meta-analysis of 11 studies including 1,147 patients, TSH levels decreased significantly following treatment with metformin ($p < 0.001$) [29]. In addition, free thyroxine (FT4) levels increased slightly ($p = 0.34$), and like the prior meta-analysis, no effect was observed on euthyroid patients for either TSH or FT4 levels. It is notable that these studies were performed in patients with T2DM, and while hypothyroidism is common in T2DM patients, these results may not be generalizable. The exact mechanism by which metformin reduces TSH levels in SCH patients is unclear and is likely multifactorial. Leading theories include that metformin may alter the number of thyroid hormone receptors, increase central dopaminergic tone, and mediate TSH regulation in the pituitary gland [30–32]. It is apparent that further studies are required to fully understand the function of metformin in SCH.

Myo-inositol has also been investigated as a potential treatment for SCH, due to its role as a second messenger of TSH, and to mediate hydrogen peroxide production, which is required for the biosynthesis of thyroid hormones. As such, it has been theorized that impairment of inositol-dependent signaling may result in a predisposition to hypothyroidism [33]. The impact of combined myo-inositol (600 mg) and selenium supplementation (83 μg) vs. selenium supplementation alone was evaluated by Nordio et al. [34], who observed a 31% decrease in TSH levels after 6 months of combined treatment. Furthermore, a reduction of the antibody biomarkers thyroid peroxidase antibodies (44%) and thyroglobulin antibody (48%) was observed with myo-inositol, while the selenium group only demonstrated a minor reduction in antibody levels [34]. A larger study in patients with Hashimoto's thyroiditis evaluated the same combination of myo-inositol and selenium also observed significant reductions in TSH, thyroid peroxidase antibodies, thyroglobulin antibody, in addition to a significant increase in FT4 levels, while no change was observed in the selenium group [35]. The efficacy of a combined treatment with myo-inositol and selenium has also been observed in pregnant women, whereby TSH, free tri-iodothyronine, and FT4 levels were within healthy ranges in 94.1% of the treatment group compared to 68.7% in the untreated control [36]. As long-term complications of metformin use during pregnancy are not well established, myo-inositol may be considered as viable solution for pregnant patients with SCH.

To the best of our knowledge, no direct comparison exists between the efficacy of myo-inositol and metformin in patients with thyroid disorders; however, the combination of the molecules may have merit. Morgante et al. [37] measured TSH levels in insulin-resistant PCOS patients treated with either metformin or a combination of metformin and myo-inositol and observed a significant reduction in TSH levels ($p < 0.05$) in the combination group vs. metformin alone.

Metformin and Myo-Inositol in Fertility Care

Insulin plays an important role in ovarian steroidogenesis and, because of this, insulin sensitizers have been investigated to improve infertility outcomes, including lowering the risk of ovarian hyperstimulation syndrome (OHSS) [38]. This is particularly true in PCOS patients where insulin resistance can play a role in the underlying fertility issues including menstrual cycle disruption [39]. Metformin may be used to induce ovulation in insulin-resistant women seeking pregnancy; however, it is inferior to the use of gold standard ovulation induction agents such as clomiphene citrate [40].

To evaluate the potential for metformin in IVF and intracytoplasmic sperm injection (ICSI) procedures, Tso et al. [41] conducted a Cochrane intervention review of 13 RCTs involving a total of 1,132 women with PCOS who were treated with metformin prior to and/or during fertility procedures. In total, this study found no evidence that metformin improved life birth rates in women with PCOS versus the placebo group. In combination with long stimulation programs with gonadotropins, metformin may improve clinical pregnancy rate; however, the effect on live birth rate is unclear in these studies. In contrast, in short stimulation programs, metformin may increase live birth rates but not clinical pregnancy rates. Finally, metformin appeared to reduce

the chance of OHSS; however, its effect on miscarriage rate was unknown. Throughout this study, the authors cited the lack of high-quality data, suggesting further study is required to evaluate the effect of metformin in ART procedures. Uncertainty remains regarding metformin and its use in pregnancy regarding the long-term consequences on the infant. Of note, it is also important to highlight that there are heterogeneity and methodological limitations, including variability in study designs, populations, and treatment protocols which may weaken the overall strength of the conclusions. Indeed, the lack of statistical superiority alone is insufficient to establish clinical effectiveness. Metformin may offer clinical benefits in specific populations, such as women with severe insulin resistance, overweight, or insulin-resistant PCOS phenotypes. However, these findings are not generalizable to all patients with PCOS-related infertility. Eventually, current international clinical guidelines recommend the use of metformin only in cases of impaired glucose tolerance or when first-line treatments have failed, and not as a standard therapy for infertility management in PCOS.

Myo-inositol, which benefits from an insulin-sensitizing effect in addition to functioning as an FSH second messenger, has also been investigated within IVF/ICSI programs. In a study by Kamenov et al. [42], myo-inositol was able to induce ovulation in 29/50 anovulatory women with PCOS and insulin resistance. In inositol-resistant women, further 13/18 ovulated following combined myo-inositol and clomiphene citrate treatment, showing the potential of myo-inositol as an ovulation inducer alone and in combination with gold standard treatment. In addition, in 2017, a meta-analysis evaluated the effect of combined myo-inositol and folic acid supplementation prior to and during IVF/ICSI programs across 7 studies which incorporated 935 women [43]. In comparison to control groups which were given folic acid alone, myo-inositol was associated with a significantly improved pregnancy ($p = 0.03$) and abortion rate ($p = 0.0006$). Furthermore, the number of grade 1 embryos was significantly improved ($p = 0.02$); however, the total number of oocytes was not affected. Lastly, this meta-analysis demonstrated that myo-inositol use reduced the required number of gonadotropins required for ovarian stimulation ($p = 0.001$), thus reducing the chance of OHSS in patients undergoing ART protocols, therefore protecting the health of the mother.

The effectiveness of myo-inositol supplementation during IVF procedures stems from the molecule's role in normal ovarian function. The natural role of myo-inositol as FSH second messenger within the ovary promotes the proliferation and maturation of granulosa cells. Furthermore, inositol supplementation reduces anti-Müllerian hormone levels, the combination of these effects plays an important role in oocyte maturation, transport within the oviduct, and embryo quality [22]. In obese women, the combination of myo-inositol and D-chiro-inositol in a 40:1 ratio may have potential at improving metabolic and pregnancy outcomes. This isomeric ratio, which is reflective of physiological serum levels, improved maternal outcomes in mice models in addition to improving offspring weight and the offspring glucose test score [44, 45].

Another cause of fertility issues for couples is male fertility, as one in 20 men experience fertility problems at some point in their lives [46]. The use of myo-inositol may offer assistance to these men as it has been demonstrated to increase sperm concentration, count, and progressive motility in addition to encouraging a normal morphology [47–49]. Furthermore, myo-inositol supplementation is able to restore hormonal parameters such as LH, FSH, and inhibin B to normal levels [50]. Lastly, in vitro supplementation of human sperm during cryofreezing protocols led to a 10% increase in cryopreservation, a process which typically reduces the fertility of sperm when compared to fresh samples [51].

On the other hand, evidence regarding the effects of metformin in male fertility is scarce to date and characterized by contrasting results. Particularly, the advantages observed in several studies on male fertility markers are mainly derived from improvement in metabolic pattern [52]. Indeed, also in vitro and preclinical studies lack precise indication of the molecular mechanism which may allow a beneficial effect of metformin in sperm functionality [53, 54]. A possible antioxidant activity may favor sperm motility and exert an epigenetic benefit on the chromatin conformation. In sperm samples from T2DM patients cultured with increasing dose of metformin, it enhances sperm function by activating AMPK, which increases tyrosine phosphorylation, thereby promoting sperm capacitation, acrosome reaction, hyperactivation, and fertilization potential [55]. However, further studies are necessary to better address the possible role of metformin in male fertility. A comparison of the possible applications of metformin and myo-inositol in fertility care is summarized in Table 2.

Metformin and Myo-Inositol in Psychological Disorders

Metabolic conditions like diabetes and obesity are increasingly associated with psychological disorders, with depression rates of 12% being observed in type 1 diabetes patients, while in T2DM, depression prevalence

Table 2. A comparison of the possible applications of metformin and myo-inositol in fertility care

Effect on	Metformin	Myo-inositol	Level of evidence
Ovulation induction	Induces ovulation in clomiphene resistant patients	Induces ovulation in insulin-resistant PCOS patients alone and in combination with clomiphene citrate therapy	Met: meta-analysis Myo: prospective clinical study
Gonadotropin stimulation	May reduce the probability of OHSS	Reduces required gonadotropin usage for ovarian stimulation prior to in vitro fertilization programs	Met: in vivo study Myo: meta-analysis
Pregnancy outcomes during in vitro fertilization	May increase clinical pregnancy rate with long stimulation gonadotropins protocols May increase live birth rate with short stimulation gonadotropins protocols	Improves pregnancy and abortion rates	Met: systematic review and meta-analysis Myo: meta-analysis
Embryo quality during in vitro fertilization	No conclusive evidence	Improves embryo quality	Myo: meta-analysis
Sperm quality during ICSI protocols	No conclusive evidence	Increases sperm concentration, count, progressive motility and normal morphology Increases cryopreservation of human sperm	Myo: RCT, prospective longitudinal study, in vitro study

is thought to be between 17.8% and 39% [56]. Accordingly, metformin may have application in the field of psychological disorders, with neuro-immunological, neuroplastic, neuro-oxidative, and neuro-nitrosative potential [57]. The association between the use of metformin and depression incidence was investigated in a Danish population study of patients with diabetes undergoing treatment. In this study, metformin use alone or in combination with other drugs resulted in a significant decrease in depression risk versus controls [58]. Moreover, a case-controlled study demonstrated metformin may have a protective effect against the development of new psychiatric disorders, reducing de novo mood disorders by 31% in comparison to participants without metformin therapy [59]. Metformin has also shown potential in neurodegenerative disorders including dementia. In a 6-year prospective study of participants aged 70–90 without dementia, dementia onset was significantly decreased in diabetic participants undergoing metformin treatment versus those not taking treatment ($p = 0.05$) [60].

Due to these positive effects in diabetic patients, drug repurposing programs have investigated the use of metformin in psychological disorders. In a randomized 16-week phase IV clinical trial of overweight depressed patients, metformin combined with sertraline significantly reduced the Beck Depression Inventory-II score (BDI) versus sertraline alone (ΔBDI 18.82 ± 8.78 vs. 17.50 ± 7.94, $p < 0.05$) (NCT00834652). In addition, insulin-resistant bipolar patients undergoing metformin treatment demonstrated an improvement in depression symptoms when regular insulin function was restored [61].

Despite these promising results, preclinical animal studies have demonstrated the potential for metformin to encourage anorexia like symptoms. In detail, a study on rats observed that metformin may activate the brain regions involved in appetite regulation, activating neuropeptide Y/agouti-related protein (NPY/AGRP) signaling in the hypothalamus [62]. Also, in a study on metformin-induced anorexia in mice, authors observed upregulation in the brain activity involved in hunger sating, including paraventricular nuclear, area postrema, and central amygdala. As with all weight loss medications, attention should be given to the potential of metformin abuse even if to the best of our knowledge, incidences of metformin abuse are rare.

Much like metformin, myo-inositol has also been investigated in psychological disease. Interest was sparked in 1978 when Barkai et al. [63] observed reduced myo-inositol concentration in the cerebrospinal fluid of patients with psychological disorders. In later years, reduced myo-inositol was observed in the brains of patients with major depressive disorder and bipolar

disease [64, 65]. Interestingly, in patients who undergo maniac episodes, higher concentrations of myo-inositol have been found in the cingulate cortex and the frontal lobe [66, 67]. Moreover, inositol derivatives, notably inositol phosphate-phosphoinositide, are known to play a role in several neural signaling processes, including noradrenergic, serotonergic, and dopaminergic pathways [68]. Despite the seemingly important role of myo-inositol on brain chemistry, no study to date has demonstrated positive efficacy of myo-inositol in mood disorders. Instead, applications of inositol primarily concern the side effects of current mood stabilizers such as lithium and sodium valproate. These compounds, which represent gold standard treatments of bipolar disorder, are thought to reduce the concentration of myo-inositol in the central nervous system [69]. It has been theorized that lithium salts and sodium valproate may in fact function via reducing inositol concentration within the brain; however, this inositol depletion hypothesis remains controversial. Regardless of inositol's role, the inositol-reducing effect of lithium and valproate is systemic and may lead to kidney issues, hypothyroidism, and weight gain, all of which are common side effects of gold standard bipolar therapeutics, thus supporting supplementation of inositol in these patients [70]. A concern for any modification of gold standard care is loss of efficacy; however, in a 2022 pilot study, myo-inositol:D-chiro-inositol (80:1) supplementation had no effect on the pharmacological treatment [71].

Myo-inositol has also been investigated for the treatment for anxiety disorders, demonstrating superiority over placebo in reducing panic attacks over a 4-week RCT [72]. While the effect of inositol on the other symptoms of anxiety (avoidance and intrusion) is negligible, the effect on reducing panic attacks was affirmed in a RCT, which observed a similar effect with inositol to fluvoxamine [73]. To the best of our knowledge, these RCTs have not been expanded upon and thus require further study.

Metformin and Myo-Inositol in Cancer

Another potential avenue for metformin repurposing has been the field of oncology. The potential anticancer applications of metformin were discovered serendipitously as the metabolic properties of metformin partially derive from the inhibition of complex 1 of the mitochondrial respiratory transport chain. This leads to activation of AMPK, a known suppressor of anabolic cell proliferation, which in turn is a key driver for tumoural growth [74]. Consequently, a case-controlled trial demonstrated that diabetic patients taking metformin were less likely to develop cancer when compared to patients taking other diabetes medications [75]. It has, however, not been confirmed this cellular mechanism. In detail, metformin has also been demonstrated to inhibit MTOR/AKT signaling and PI3K/AKT/MTOR, which are key oncogenic pathways for cancer growth and survival [76, 77]. It is thought that this insulin-dependent mechanism would be more relevant to patients with impaired insulin function such as diabetic cancer patients. Accordingly, metformin has been studied in combination with gold standard chemotherapeutics in a series of RCTs in breast, prostate, ovarian, endometrial, and non-small cell lung cancer; however, no study to date has demonstrated improvement over chemotherapy alone [78].

Myo-inositol and its derivative inositol hexaphosphate have been reported to engage in various anticancer mechanisms, inhibiting cell survival and proliferation via modulation of the P13K/AKT pathway [79]. Furthermore, inositol derivatives may downregulate the MAPK/ERK cascade and NF-kB, resulting in inhibition of cancer growth and anti-inflammatory properties [80]. Lastly, inositols may interfere with the Wnt signaling pathway potentially resulting in reduced cancer metastasis [81]. Despite these interesting preclinical findings, no RCTs have been performed regarding the use of myo-inositol in the field of oncology and further investigation is warranted, especially in comparison with metformin.

Adverse Effects

Metformin and myo-inositol, despite their large history of use, are not devoid of some side effects, which must be considered when tailoring the therapy to specific types of patients. The available evidence reported in the literature for both compounds is outlined below.

Metformin

Lactic Acidosis

The most severe, but also rare, adverse effect of metformin is the development of lactic acidosis. The severity of metformin-associated lactic acidosis (MALA) is such that the FDA has included a black box warning label on the pharmaceutical. MALA, while rare, has a 30–50%-associated mortality rate, with renal dialysis to remove systemic metformin representing the only therapeutic option [82]. This condition manifests from the accumulation of lactate within the body, leading to nausea, vomiting, fatigue, muscle cramps,

and eventually ataxia, altered mental state or coma. To evaluate the frequency and relative risk of adverse effects related to metformin use, Du et al. [83] published a pharmacovigilance study based upon the FDA Adverse Reports System between 2004 and 2022. In total, over 10 million case reports were retrieved from the FDA Adverse Reports System database, with lactic acidosis (51.65%), metabolic acidosis (14.48%), and hypoglycemia (14.13%) representing the three most reported adverse effects. The probability of developing MALA is increased in cases of sepsis, dehydration, excess alcohol intake, hepatic and renal impairment, acute congestive heart failure; however, acute high-dose metformin use in the absence of said risk factors can lead to the development of MALA. Due to these risks, metformin is contraindicated for patients with severe renal impairment [84].

Gastrointestinal Effects

The gastrointestinal side effects of metformin are the most well-known and discussed within literature. To fully evaluate the extent of these adverse effects, Nabradalik et al. [85] published a meta-analysis of 71 RCTs. In this study, it was observed that the overall risk of abdominal pain was increased by 50% in patients taking metformin vs. the control; however, this was not influenced by metformin dose, trial length, type of metformin used, existence of metformin pretreatment, or ethnicity. In addition, the overall diarrhea risk was significantly increased compared to the controls (RR = 2.445, 95% CI [1.656, 3.609], p = 0.0001) and remained significant when a study including children was excluded. Interestingly, diarrhea risk was most elevated in patients receiving immediate release metformin. Lastly, the risk of nausea was significantly elevated in patients taking metformin versus the control (RR = 1.641, 95% CI [1.169, 2.302], p = 0.0004). Following meta-regression, none of the assessed variables influenced nausea risk; however, nausea was more elevated in patients who were treated with metformin at the start of the study versus those who had been taking metformin prior to study initiation. Lastly, no significant difference was observed between the metformin group and the control in terms of the risk of bloating, constipation, or vomiting.

Metformin when used in T2DM and other conditions such as PCOS is typically given over an extended period. As with all medicines that are prescribed for chronic use, adherence is vital. While persistence (defined as continuation of treatment) is greater with metformin versus other anti-diabetes therapies, only 58.6% of patients continue taking metformin for at least 9 months [86]. Barriers to patient adherence to metformin include difficult to swallow large or roughly coated pills. This is particularly true for T2DM patients who may have dysphagia [87]. Adherence may be further reduced due to the gastrointestinal adverse effects commonly observed in these patients. In particular, while instant release form of metformin is associated with a greater degree of gastrointestinal distress, these effects are reduced in extended-release metformin [88]. Of note, metformin's clinical utility is supported by robust evidence, particularly in the management of T2DM, and extends to other conditions as well, despite its association with adverse effects such as gastrointestinal discomfort.

Use of Metformin in Pregnancy

As part of a routine pregnancy, maternal insulin resistance is developed to maintain proper placental glucose transport; however, further insulin resistance can lead to the development of GDM [89] and to numerous pregnancy complications including miscarriage, preterm delivery, and congenital anomalies [90]. In patients with/at risk of developing GDM, lifestyle changes are recommended to maintain glycemic control. If this is deemed insufficient, insulin therapy is routinely recommended; however, metformin may be given as a supplementary therapy [91]. Some concerns have been raised about the use of metformin in pregnancy, as it is able to cross the placenta; thus, the effect of metformin treatment on both the mother and the fetus must be considered. In a meta-analysis of 35 studies incorporating 8,033 pregnancies, metformin use significantly reduced gestational weight gain and demonstrated a minor reduction in pre-eclampsia risk [92]. In contrast, there was no difference in gestational hypertension, cesarean section, gestational age at delivery, and glycemic control, with an increase in gastrointestinal side effects in the metformin group.

Despite offering an improvement in some pregnancy outcomes in patients with GDM, concerns remain around the long-term effects on the development of the offspring since little evidence is available regarding this subject. In a follow-up GDM study, children of mothers treated with metformin were larger at 2 and 9 years of age, demonstrating increased weight, waist circumference, and waist to hip ratio; however, concerns were raised regarding this study due to an incomplete follow-up cohort [93]. In a Norwegian follow-up study, children of mothers with PCOS who had been treated with metformin were followed for 5–10 years, with higher levels of obesity, elevated BMI, and waist to hip ratio being reported in the metformin group [94].

Myo-Inositol

Gastrointestinal Effects

Myo-inositol is widely used as a dietary supplement in several clinical settings. It shows a favorable short-term safety profile with generally mild, transient, and dose-dependent adverse effects reported in the literature.

Gastrointestinal complaints such as nausea, flatulence, or diarrhea are the most frequently reported, typically at doses ≥12 g/day, whereas standard clinical doses (2–4 g/day) are very well tolerated [95]. In women with PCOS, myo-inositol supplementation (commonly 2 g twice daily) is associated with a low incidence of adverse reactions and rare discontinuations due to intolerance. Randomized trials report adverse event rates between 0% and approximately 30%, mostly mild gastrointestinal discomforts without serious consequences and without leading to discontinuation [96]. Large systematic reviews confirm good tolerability and overall minimal side effects of myo-inositol use in PCOS populations, though heterogeneity in adverse events reporting limits precise pooled estimates [97, 98].

Use of Myo-Inositol in Pregnancy

During pregnancy, where myo-inositol has been studied for prevention of gestational diabetes and other complications, daily doses of 4 g are generally well tolerated. Large RCTs and meta-analyses have not identified major maternal or fetal safety concerns attributable to myo-inositol, nor serious adverse events. [99]. A recent Cochrane review of eight RCTs (n = 1,361) reported only a single case of mild headache as an adverse event, and no other serious events were described following myo-inositol supplementation [100]. Nevertheless, side effects reporting is often incomplete (minor maternal symptoms such as nausea or vomiting are variably captured), sample sizes for some outcomes are limited, and overall certainty of long-term safety in pregnancy remains poor [101].

Other Clinical Fields

Outside reproductive medicine, myo-inositol has been investigated in metabolic and psychiatric conditions at higher doses, specifically ≥12 g/day and up to 18–30 g/day in some psychiatric trials. Across these studies, transient gastrointestinal disturbances, mild headache, dizziness, or sleep changes are the most common adverse events, with no consistent laboratory or clinical evidence of hepatic, renal, or metabolic toxicity [95, 102].

Strengths and Limitations

The primary strength of this review is that, to the best of our knowledge, it is the first review of its kind to investigate metformin and myo-inositol across a variety of applications outside the field of PCOS. Furthermore, the narrative nature of this review allows for a wider scope than would have been possible with a specific systematic approach. As with all narrative reviews, the non-systematic approach of this paper leads to several weaknesses. This nonevidence-based approach does not allow for clear conclusions to be drawn and allows for different interpretations of the literature, introducing potential sources of bias. Of note, while metformin has received great attention from researchers over the years, myo-inositol has gathered scientific interest only recently so that fewer large-scale RCTs are available to date. Also, more long-term population studies are required to deeply investigate the potential of myo-inositol use both in brief and long periods. Moreover, there are incomplete and non-standardized reports regarding adverse events related to myo-inositol use. Accordingly, there is a need to collect side effects using validated instruments, report absolute rates by type and severity, and include biochemical monitoring of organ function when relevant to better characterize safety.

Conclusion

Although both metformin and myo-inositol act on the metabolic axis, they do so through distinct mechanisms of action. Metformin remains the most established insulin sensitizer, particularly in the treatment of T2DM, even though its clinical utility may be limited by gastrointestinal side effects that reduce patient adherence. In contrast, myo-inositol is an endogenously occurring compound with a favorable tolerability profile and a physiological role in various biochemical pathways, making it worth investigating alternative to metformin, even with current limited literature endorsement.

Myo-inositol has demonstrated good efficacy and safety in improving ovulatory function, fertility outcomes, and metabolic parameters. However, metformin may be indicated in specific patient populations, such as those with pronounced insulin resistance, elevated BMI, high-risk IVF procedures, or systemic hyperandrogenic phenotypes. Therefore, therapeutic decisions should be personalized, balancing the metabolic benefits, tolerability, and overall clinical profile of each patient.

Both compounds have been investigated in a wide range of clinical contexts, including fertility care, endocrinological disorders such as hypothyroidism, mental

health, and oncology. Nonetheless, further high-quality research is needed to clarify and expand their potential roles, particularly in underexplored areas like psychiatric disorders and cancer therapy.

Conflict of Interest Statement

V.U. is the owner of Lo.Li. Pharma s.r.l., while M.R. is an employee at Lo.Li Pharma s.r.l. M.M.O., M.N., G.P., and V.U. are affiliated with EGOI-PCOS which receives unconditional support from Lo.Li. Pharma s.r.l.

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Author Contributions

Conceptualization and writing – original draft: M.R. and V.U; writing – review and editing: M.R., M.M.O., M.N., G.P., and V.U.; and supervision: V.U.

References

1 Maffetone PB, Rivera-Dominguez I, Laursen PB. Overfat and underfat: new terms and definitions long overdue. Front Public Health. 2016;4:279. https://doi.org/10.3389/fpubh.2016.00279
2 Naseri A, Sanaie S, Hamzehzadeh S, Seyedi-Sahebari S, Hosseini M-S, Gholipour-khalili E, et al. Metformin: new applications for an old drug. J Basic Clin Physiol Pharmacol. 2023;34(2):151–60. https://doi.org/10.1515/jbcpp-2022-0252
3 McCreight LJ, Stage TB, Connelly P, Lonergan M, Nielsen F, Prehn C, et al. Pharmacokinetics of metformin in patients with gastrointestinal intolerance. Diabetes Obes Metab. 2018;20(7):1593–601. https://doi.org/10.1111/dom.13264
4 McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia. 2016;59(3):426–35. https://doi.org/10.1007/s00125-015-3844-9
5 Kinaan M, Ding H, Triggle CR. Metformin: an old drug for the treatment of diabetes but a new drug for the protection of the endothelium. Med Princ Pract. 2015;24(5):401–15. https://doi.org/10.1159/000381643
6 Perazza F, Leoni L, Colosimo S, Musio A, Bocedi G, D'Avino M, et al. Metformin and the liver: unlocking the full therapeutic potential. Metabolites. 2024;14(4):186. https://doi.org/10.3390/metabo14040186
7 Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577–85. https://doi.org/10.1007/s00125-017-4342-z
8 Chai J, Wang Y, Guo S, Wang Z, Chen H, Wang X, et al. Proteomics exploration of metformin hydrochloride for diabetic kidney disease treatment via the butanoate metabolism pathway. J Pharm Biomed Anal. 2025;254:116584. https://doi.org/10.1016/j.jpba.2024.116584
9 Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23(7):850–8. https://doi.org/10.1038/nm.4345
10 Alvarez-Silva C, Kashani A, Hansen TH, Pinna NK, Anjana RM, Dutta A, et al. Trans-ethnic gut microbiota signatures of type 2 diabetes in Denmark and India. Genome Med. 2021;13(1):37. https://doi.org/10.1186/s13073-021-00856-4
11 Bryrup T, Thomsen CW, Kern T, Allin KH, Brandslund I, Jørgensen NR, et al. Metformin-induced changes of the gut microbiota in healthy young men: results of a non-blinded, one-armed intervention study. Diabetologia. 2019;62(6):1024–35. https://doi.org/10.1007/s00125-019-4848-7
12 Lee H, Ko G. Effect of metformin on metabolic improvement and gut microbiota. Appl Environ Microbiol. 2014;80(19):5935–43. https://doi.org/10.1128/AEM.01357-14
13 Silamiķele L, Silamiķelis I, Ustinova M, Kalniņa Z, Elbere I, Petrovska R, et al. Metformin strongly affects gut microbiome composition in high-fat diet-induced type 2 diabetes mouse model of both sexes. Front Endocrinol. 2021;12:626359. https://doi.org/10.3389/fendo.2021.626359
14 Bauer PV, Duca FA, Waise TMZ, Rasmussen BA, Abraham MA, Dranse HJ, et al. Metformin alters upper small intestinal microbiota that impact a Glucose-SGLT1-Sensing glucoregulatory pathway. Cell Metab. 2018;27(1):101–7.e5. https://doi.org/10.1016/j.cmet.2017.09.019
15 Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, et al. An increase in the akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut. 2014;63(5):727–35. https://doi.org/10.1136/gutjnl-2012-303839
16 Adeshirlarijaney A, Zou J, Tran HQ, Chassaing B, Gewirtz AT. Amelioration of metabolic syndrome by metformin associates with reduced indices of low-grade inflammation independently of the gut microbiota. Am J Physiol Endocrinol Metab. 2019;317(6):E1121–30. https://doi.org/10.1152/ajpendo.00245.2019
17 Seicaru EM, Popa Ilie IR, Cătinean A, Crăciun AM, Ghervan C. Enhancing metformin effects by adding gut microbiota modulators to ameliorate the metabolic status of obese, insulin-resistant hosts. J Gastrointestin Liver Dis. 2022;31(3):344–54. https://doi.org/10.15403/jgld-4248
18 Díaz-Perdigones CM, Muñoz-Garach A, Álvarez-Bermúdez MD, Moreno-Indias I, Tinahones FJ. Gut microbiota of patients with type 2 diabetes and gastrointestinal intolerance to metformin differs in composition and functionality from tolerant patients. Biomed Pharmacother. 2022;145:112448. https://doi.org/10.1016/j.biopha.2021.112448
19 Suffee N, Le Goff W, Chen J. Editorial: cardiometabolic diseases and inflammatory responses. Front Immunol. 2024;15:1384022. https://doi.org/10.3389/fimmu.2024.1384022
20 Kristófi R, Eriksson JW. Metformin as an anti-inflammatory agent: a short review. J Endocrinol. 20212021;251(2):R11–22. https://doi.org/10.1530/joe-21-0194
21 Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. Nat Rev Endocrinol. 2023 2023;19(8):460–76. https://doi.org/10.1038/s41574-023-00833-4
22 Dinicola S, Unfer V, Facchinetti F, Soulage CO, Greene ND, Bizzarri M, et al. Inositols: from established knowledge to novel approaches. Int J Mol Sci. 2021;22(19):10575. https://doi.org/10.3390/ijms221910575
23 Cabrera-Cruz H, Oróstica L, Plaza-Parrochia F, Torres-Pinto I, Romero C, Vega M. The insulin-sensitizing mechanism of myo-inositol is associated with AMPK activation and GLUT-4 expression in human endometrial cells exposed to a PCOS environment. Am J Physiol Endocrinol Metab. 2020;318(2):E237–48. https://doi.org/10.1152/ajpendo.00162.2019

24 Kiani AK, Paolacci S, Calogero AE, Cannarella R, Di Renzo GC, Gerli S, et al. From Myo-inositol to D-chiro-inositol molecular pathways. Eur Rev Med Pharmacol Sci. 2021;25(5):2390–402. https://doi.org/10.26355/eurrev_202103_25279
25 Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A combined therapy with myo-inositol and D-Chiro-Inositol improves endocrine parameters and insulin resistance in PCOS young overweight women. Int J Endocrinol. 2016;2016:3204083. https://doi.org/10.1155/2016/3204083
26 Bizzarri M, Monti N, Piombarolo A, Angeloni A, Verna R. Myo-inositol and D-Chiro-Inositol as modulators of ovary steroidogenesis: a narrative review. Nutrients. 2023;15(8):1875. https://doi.org/10.3390/nu15081875
27 Bodepudi R, Seher S, Khan SA, Emmanuel S, Shantha Kumar V, Nerella R, et al. Myoinositol versus metformin in the treatment of polycystic ovarian syndrome: a systematic review. Cureus. 2023;15(7):e41748. https://doi.org/10.7759/cureus.41748
28 Lupoli R, Di Minno A, Tortora A, Ambrosino P, Lupoli GA, Di Minno MND. Effects of treatment with metformin on TSH levels: a meta-analysis of literature studies. J Clin Endocrinol Metab. 2014;99(1):E143–8. https://doi.org/10.1210/jc.2013-2965
29 Amirabadizadeh A, Amouzegar A, Mehran L, Azizi F. The effect of metformin therapy on serum thyrotropin and free thyroxine concentrations in patients with type 2 diabetes: a meta-analysis. Sci Rep. 2023;13(1):18757. https://doi.org/10.1038/s41598-023-43266-9
30 Vigersky RA, Filmore-Nassar A, Glass AR. Thyrotropin suppression by metformin. J Clin Endocrinol Metab. 2006;91(1):225–7. https://doi.org/10.1210/jc.2005-1210
31 Cappelli C, Rotondi M, Pirola I, Agosti B, Gandossi E, Valentini U, et al. TSH-lowering effect of metformin in type 2 diabetic patients: differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients. Diabetes Care. 2009;32(9):1589–90. https://doi.org/10.2337/dc09-0273
32 Krysiak R, Okopien B. Thyrotropin-lowering effect of metformin in a patient with resistance to thyroid hormone. Clin Endocrinol. 2011;75(3):404–6. https://doi.org/10.1111/j.1365-2265.2011.04058.x
33 Benvenga S, Nordio M, Laganà AS, Unfer V. The role of inositol in thyroid physiology and in subclinical hypothyroidism management. Front Endocrinol. 2021;12:662582. https://doi.org/10.3389/fendo.2021.662582
34 Nordio M, Pajalich R. Combined treatment with myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. J Thyroid Res. 2013;2013:424163. https://doi.org/10.1155/2013/424163
35 Nordio M, Basciani S. Treatment with myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. Int J Endocrinol. 2017;2017(1):2549491. https://doi.org/10.1155/2017/2549491
36 Porcaro G, Angelozzi P. Myo-inositol and selenium prevent subclinical hypothyroidism during pregnancy: an observational study. IJMDAT. 2018;1(2):e164.
37 Morgante G, Musacchio MC, Orvieto R, Massaro MG, De Leo V. Alterations in thyroid function among the different polycystic ovary syndrome phenotypes. Gynecol Endocrinol. 2013;29(11):967–9. https://doi.org/10.3109/09513590.2013.829445
38 Elia EM, Quintana R, Carrere C, Bazzano MV, Rey-Valzacchi G, Paz DA, et al. Metformin decreases the incidence of ovarian hyperstimulation syndrome: an experimental study. J Ovarian Res. 2013;6(1):62. https://doi.org/10.1186/1757-2215-6-62
39 Niu J, Lu M, Liu B. Association between insulin resistance and abnormal menstrual cycle in Chinese patients with polycystic ovary syndrome. J Ovarian Res. 2023;16(1):45. https://doi.org/10.1186/s13048-023-01122-4
40 Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356(6):551–66. https://doi.org/10.1056/NEJMoa063971
41 Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2020;12(12). https://doi.org/10.1002/14651858.CD006105.pub4
42 Kamenov Z, Kolarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. Gynecol Endocrinol. 2015;31(2):131–5. https://doi.org/10.3109/09513590.2014.964640
43 Zheng X, Lin D, Zhang Y, Lin Y, Song J, Li S, et al. Inositol supplement improves clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET. Medicine. 2017;96(49):e8842. https://doi.org/10.1097/md.0000000000008842
44 Ferrari F, Facchinetti F, Ontiveros AE, Roberts RP, Saade MM, Blackwell SC, et al. The effect of combined inositol supplementation on maternal metabolic profile in pregnancies complicated by metabolic syndrome and obesity. Am J Obstet Gynecol. 2016;215(4):503.e1–38. https://doi.org/10.1016/j.ajog.2016.05.038
45 Longo M, Alrais M, Tamayo EH, Ferrari F, Facchinetti F, Refuerzo JS, et al. Vascular and metabolic profiles in offspring born to pregnant mice with metabolic syndrome treated with inositols. Am J Obstet Gynecol. 2019;220(3):279.e1–9. https://doi.org/10.1016/j.ajog.2018.11.1101
46 Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Mindlis I, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update. 2017;23(6):646–59. https://doi.org/10.1093/humupd/dmx022
47 Rubino P, Palini S, Chigioni S, Carlomagno G, Quagliariello A, De Stefani S, et al. Improving fertilization rate in ICSI cycles by adding myoinositol to the semen preparation procedures: a prospective, bicentric, randomized trial on sibling oocytes. J Assist Reprod Genet. 2015;32(3):387–94. https://doi.org/10.1007/s10815-014-0401-2
48 Montanino Oliva M, Minutolo E, Lippa A, Iaconianni P, Vaiarelli A. Effect of myo-inositol and antioxidants on sperm quality in men with metabolic syndrome. Int J Endocrinol. 2016;2016:1674950. https://doi.org/10.1155/2016/1674950
49 Mohammadi F, Varanloo N, Heydari Nasrabadi M, Vatannejad A, Amjadi FS, Javedani Masroor M, et al. Supplementation of sperm freezing medium with myoinositol improve human sperm parameters and protects it against DNA fragmentation and apoptosis. Cell Tissue Bank. 2019;20(1):77–86. https://doi.org/10.1007/s10561-018-9731-0
50 Calogero AE, Gullo G, La Vignera S, Condorelli RA, Vaiarelli A. Myoinositol improves sperm parameters and serum reproductive hormones in patients with idiopathic infertility: a prospective double-blind randomized placebo-controlled study. Andrology. 2015;3(3):491–5. https://doi.org/10.1111/andr.12025
51 Etrusco A, Laganà AS, Chiantera V, Buzzaccarini G, Unfer V. Myo-inositol in assisted reproductive technology from bench to bedside. Trends Endocrinol Metab. 2024;35(1):74–83. https://doi.org/10.1016/j.tem.2023.09.005
52 Service CA, Puri D, Al Azzawi S, Hsieh TC, Patel DP. The impact of obesity and metabolic health on male fertility: a systematic review. Fertil Steril. 2023;120(6):1098–111. https://doi.org/10.1016/j.fertnstert.2023.10.017
53 Ghasemnejad-Berenji M, Ghazi-Khansari M, Yazdani I, Nobakht M, Abdollahi A, Ghasemnejad-Berenji H, et al. Effect of metformin on germ cell-specific apoptosis, oxidative stress and epididymal sperm quality after testicular torsion/detorsion in rats. Andrologia. 2018;50(2):e12846. https://doi.org/10.1111/and.12846

54 Wang M, Zeng L, Su P, Ma L, Zhang M, Zhang YZ. Autophagy: a multifaceted player in the fate of sperm. Hum Reprod Update. 2022;28(2):200–31. https://doi.org/10.1093/humupd/dmab043
55 Yang Y, Chen H, Weng S, Pan T, Chen W, Wang F, et al. In vitro exposure to metformin activates human spermatozoa at therapeutically relevant concentrations. Andrology. 2020;8(3):663–70. https://doi.org/10.1111/andr.12755
56 Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012;142(Suppl l):S8–21. https://doi.org/10.1016/S0165-0327(12)70004-6
57 Dodd S, Sominsky L, Siskind D, Bortolasci CC, Carvalho AF, Maes M, et al. The role of metformin as a treatment for neuropsychiatric illness. Eur Neuropsychopharmacol. 2022;64:32–43. https://doi.org/10.1016/j.euroneuro.2022.09.002
58 Kessing LV, Rytgaard HC, Ekstrøm CT, Knop FK, Berk M, Gerds TA. Antidiabetes agents and incident depression: a nationwide population-based study. Diabetes Care. 2020;43(12):3050–60. https://doi.org/10.2337/dc20-1561
59 Lake J, Bortolasci CC, Stuart AL, Pasco JA, Kidnapillai S, Spolding B, et al. Metformin is protective against the development of mood disorders. Pharmacopsychiatry. 2023;56(1):25–31. https://doi.org/10.1055/a-1936-3580
60 Samaras K, Makkar S, Crawford JD, Kochan NA, Wen W, Draper B, et al. Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with type 2 diabetes: the Sydney memory and ageing study. Diabetes Care. 2020;43(11):2691–701. https://doi.org/10.2337/dc20-0892
61 Calkin CV, Chengappa KNR, Cairns K, Cookey J, Gannon J, Alda M, et al. Treating insulin resistance with metformin as a strategy to improve clinical outcomes in treatment-resistant bipolar depression (the TRIO-BD Study): a randomized, quadruple-masked, placebo-controlled clinical trial. J Clin Psychiatry. 2022;83(2):21m14022. https://doi.org/10.4088/JCP.21m14022
62 Lv WS, Wen JP, Li L, Sun RX, Wang J, Xian YX, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. Brain Res. 2012;1444:11–9. https://doi.org/10.1016/j.brainres.2012.01.028
63 Barkai AI, Dunner DL, Gross HA, Mayo P, Fieve RR. Reduced myo-inositol levels in cerebrospinal fluid from patients with affective disorder. Biol Psychiatry. 1978;13(1):65–72.
64 Frey R, Metzler D, Fischer P, Heiden A, Scharfetter J, Moser E, et al. Myo-inositol in depressive and healthy subjects determined by frontal 1H-magnetic resonance spectroscopy at 1.5 tesla. J Psychiatr Res. 1998;32(6):411–20. https://doi.org/10.1016/s0022-3956(98)00033-8
65 Coupland NJ, Ogilvie CJ, Hegadoren KM, Seres P, Hanstock CC, Allen PS. Decreased prefrontal Myo-inositol in major depressive disorder. Biol Psychiatry. 2005;57(12):1526–34. https://doi.org/10.1016/j.biopsych.2005.02.027
66 Moore CM, Breeze JL, Gruber SA, Babb SM, Frederick BB, Villafuerte RA, et al. Choline, myo-inositol and mood in bipolar disorder: a proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. Bipolar Disord. 2000;2(3 Pt 2):207–16. https://doi.org/10.1034/j.1399-5618.2000.20302.x
67 Yu W, Greenberg ML. Inositol depletion, GSK3 inhibition and bipolar disorder. Future Neurol. 2016;11(2):135–48. https://doi.org/10.2217/fnl-2016-0003
68 Concerto C, Chiarenza C, Di Francesco A, Natale A, Privitera I, Rodolico A, et al. Neurobiology and applications of inositol in psychiatry: a narrative review. Curr Issues Mol Biol. 2023;45(2):1762–78. https://doi.org/10.3390/cimb45020113
69 Harwood AJ. Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. Mol Psychiatry. 2005;10(1):117–26. https://doi.org/10.1038/sj.mp.4001618
70 Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord. 2016;4(1):27. https://doi.org/10.1186/s40345-016-0068-y
71 Cantelmi T, Lepore E, Unfer VR, Unfer V. Safety of inositol supplementation in patients taking lithium or valproic acid: a pilot clinical study. Eur Rev Med Pharmacol Sci. 2022;26(19):7269–76. https://doi.org/10.26355/eurrev_202210_29920
72 Benjamin J, Levine J, Fux M, Aviv A, Levy D, Belmaker RH. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. Am J Psychiatry. 1995;152(7):1084–6. https://doi.org/10.1176/ajp.152.7.1084
73 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. https://doi.org/10.1097/00004714-200106000-00014
74 Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J. 2000;348(Pt 3):607–14. https://doi.org/10.1042/bj3480607
75 Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. Bmj. 2005;330(7503):1304–5. https://doi.org/10.1136/bmj.38415.708634.F7
76 Zakikhani M, Blouin MJ, Piura E, Pollak MN. Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. Breast Cancer Res Treat. 2010;123(1):271–9. https://doi.org/10.1007/s10549-010-0763-9
77 Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 2018;560(7719):499–503. https://doi.org/10.1038/s41586-018-0343-4
78 Lord SR, Harris AL. Is it still worth pursuing the repurposing of metformin as a cancer therapeutic? Br J Cancer. 2023;128(6):958–66. https://doi.org/10.1038/s41416-023-02204-2
79 Liu G, Song Y, Cui L, Wen Z, Lu X. Inositol hexaphosphate suppresses growth and induces apoptosis in HT-29 colorectal cancer cells in culture: PI3K/Akt pathway as a potential target. Int J Clin Exp Pathol. 2015;8(2):1402–10.
80 Bizzarri M, Dinicola S, Bevilacqua A, Cucina A. Broad spectrum anticancer activity of myo-inositol and inositol hexakisphosphate. Int J Endocrinol. 2016;2016:5616807. https://doi.org/10.1155/2016/5616807
81 Liu X, Liu C, Chen C, Sun W, Ci Y, Li Q, et al. Combination of inositol hexaphosphate and inositol inhibits liver metastasis of colorectal cancer in mice through the Wnt/β-Catenin pathway. Onco Targets Ther. 2020;13:3223–35. https://doi.org/10.2147/OTT.S247646
82 DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism. 2016;65(2):20–9. https://doi.org/10.1016/j.metabol.2015.10.014
83 Du Y, Zhu J, Guo Z, Wang Z, Wang Y, Hu M, et al. Metformin adverse event profile: a pharmacovigilance study based on the FDA Adverse Event Reporting System (FAERS) from 2004 to 2022. Expert Rev Clin Pharmacol. 2024;17(2):189–201. https://doi.org/10.1080/17512433.2024.2306223
84 Hur KY, Kim MK, Ko SH, Han M, Lee DW, Kwon HS, et al. Metformin treatment for patients with diabetes and chronic kidney disease: a Korean diabetes Association and Korean Society of nephrology consensus statement. Diabetes Metab J. 2020;44(1):3–10. https://doi.org/10.4093/dmj.2020.0004
85 Nabrdalik K, Skonieczna-Żydecka K, Irlik K, Hendel M, Kwiendacz H, Łoniewski I, et al. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: a systematic review, meta-analysis and meta-regression of randomized controlled trials. Front Endocrinol. 2022;13:975912. https://doi.org/10.3389/fendo.2022.975912
86 Shani M, Lustman A, Vinker S. Diabetes medication persistence, different medications have different persistence rates. Prim Care Diabetes. 2017;11(4):360–4. https://doi.org/10.1016/j.pcd.2017.03.006

87 Christofides EA. Practical insights into improving adherence to metformin therapy in patients with type 2 diabetes. Clin Diabetes. 2019;37(3):234–41. https://doi.org/10.2337/cd18-0063
88 Tarry-Adkins JL, Grant ID, Ozanne SE, Reynolds RM, Aiken CE. Efficacy and side effect profile of different formulations of metformin: a systematic review and meta-analysis. Diabetes Ther. 2021;12(7):1901–14. https://doi.org/10.1007/s13300-021-01058-2
89 Lin J, Jin H, Chen L. Associations between insulin resistance and adverse pregnancy outcomes in women with gestational diabetes mellitus: a retrospective study. BMC Pregnancy Childbirth. 2021;21(1):526. https://doi.org/10.1186/s12884-021-04006-x
90 Ornoy A, Becker M, Weinstein-Fudim L, Ergaz Z. Diabetes during pregnancy: a maternal disease complicating the course of pregnancy with long-term deleterious effects on the offspring. A clinical review. Int J Mol Sci. 2021;22(6):2965. https://doi.org/10.3390/ijms22062965
91 Feng Y, Yang H. Metformin: a potentially effective drug for gestational diabetes mellitus: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2017;30(15):1874–81. https://doi.org/10.1080/14767058.2016.1228061
92 Tarry-Adkins JL, Ozanne SE, Aiken CE. Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis. Sci Rep. 2021;11(1):9240. https://doi.org/10.1038/s41598-021-88650-5
93 Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care. 2018;6(1):e000456. https://doi.org/10.1136/bmjdrc-2017-000456
94 Hanem LGE, Salvesen Ø, Juliusson PB, Carlsen SM, Nossum MCF, Vaage M, et al. Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5-10 year follow-up of the PregMet randomised controlled trial. Lancet Child Adolesc Health. 2019;3(3):166–74. https://doi.org/10.1016/S2352-4642(18)30385-7
95 Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci. 2011;15(8):931–6.
96 Le NSV, Le MT, Cao TN. Myo-inositol versus metformin effects on clinical features, endocrine and metabolic profiles in infertile women with polycystic ovary syndrome: a randomized controlled trial. Asian Pac J Reprod. 2023;12(6):256–65. https://doi.org/10.4103/2305-0500.390300
97 Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with Polycystic Ovarian Syndrome (PCOS): a meta-analysis of randomized clinical trials. Gynecol Endocrinol. 2019;35(3):198–206. https://doi.org/10.1080/09513590.2018.1540578
98 Greff D, Juhász AE, Váncsa S, Váradi A, Sipos Z, Szinte J, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2023;21(1):10. https://doi.org/10.1186/s12958-023-01055-z
99 D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, et al. Myo-inositol supplementation for prevention of gestational diabetes in Obese pregnant women: a randomized controlled trial. Obstet Gynecol. 2015;126(2):310–5. https://doi.org/10.1097/AOG.0000000000000958
100 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. https://doi.org/10.1002/14651858.CD011507.pub3
101 Mashayekh-Amiri S, Mohammad-Alizadeh-Charandabi S, Abdolalipour S, Mirghafourvand M. Myo-inositol supplementation for prevention of gestational diabetes mellitus in overweight and obese pregnant women: a systematic review and meta-analysis. Diabetol Metab Syndr. 2022;14(1):93. https://doi.org/10.1186/s13098-022-00862-5
102 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. https://doi.org/10.1136/openhrt-2022-001989