REFERENCE SHEET:

Inositol

Pronunciation

Inositol (in-o-sĭ-tol)

Summary

Essential for the growth of tissues, inositol is found in nine different forms (isomers), including myo-, d-chiro-, scyllo-, muco-, epi-, neo-, allo-, l-chiro-, and the synthetic cis-inositol. Myo-inositol (MI) and D-chiro-inositol (DCI) are the two main forms in our bodies and most commonly used as supplements. Previously considered an essential B vitamin (vitamin B8), it is now known that the human body can synthesize four grams of inositol per day, whereas approximately one gram per day can be obtained from the diet. For this reason, inositol is now mainly referred to as an essential pseudovitamin. Inositol is a constituent of phospholipids in cellular membranes, a precursor of secondary messengers in metabolic pathways, and a component of reproductive fluids. It may play an important role in conditions related to insulin resistance, such as polycystic ovarian syndrome, metabolic syndrome, gestational diabetes, and other diabetic complications. Additionally, since MI can cross the blood-brain barrier, it may be beneficial in treating symptoms of affective disorders. Dietary sources of inositol are primarily found in fruits, beans, grains, and nuts.

Forms

Initially, the name “inositol” was given to the most abundant isomer found naturally. However, to distinguish it from the other eight forms, it was re-labeled as “myo-inositol”. The term “inositol” now encompasses all nine isomers, but MI remains the form that is often assumed when referring to inositol.

Isoforms of inositol take on differential physiological roles. Both MI and DCI are involved in insulin signaling; DCI is more involved in glycogenesis, while MI decreases intestinal absorption of glucose and increases glucose uptake through glucose transporter activation and utilization. Each isomer has differences in tissue distribution and treatments combining MI and DCI have been based on an observed plasma ratio of 40:1.

Form	Distribution	Comparison
Myo-inositol (MI)	Seminal fluids, prostate, epididymis, seminal vesicles High in follicular fluid of healthy patients, low in PCOS patients Cerebrospinal fluid, brain	↑ mature oocytes, embryo quality & ↓ immature oocytes by MI compared with DCI supplements in PCOS patients ↓ LH/FSH ratio, total testosterone, HOMA index; ↑ SHBG compared with DCI supplements in PCOS May be synthesized from glucose-6-phosphate in the body to produce up to 4-5g per day ↑ concentration excreted in urine with insulin resistance, due to impaired epimerase activity
D-chiro-inositol (DCI)	High in fat, muscle, & liver, low in brain and heart High in follicular fluid of PCOS patients, low in healthy patients	↑ r-FSH units, immature oocytes; ↓ mature oocytes, grade I embryos in PCOS receiving supplements ↑ 50-100x activity in glycogenesis than MI Can be synthesized from MI by an epimerase enzyme ↓ concentration excreted in urine with insulin resistance, due to impaired epimerase activity

Main Medical Uses

Polycystic ovarian syndrome (PCOS) may be treated with supplements containing inositol, including MI, DCI, or their combination. Supplementation with MI is effective in reducing gonadotropin doses and the length of ovarian hyperstimulation in women with PCOS undergoing in vitro fertilization. It can similarly reduce gonadotropin doses in non-PCOS women leading to a trend of increased implantation frequency. MI may lower birth weight and reduce the risk of gestational diabetes. It may also reduce the risk of preterm delivery and neonatal/infant death, retinopathy, and hemorrhage in respiratory distress syndrome. MI can also improve outcomes related to male fertility. Inositol may be effective in treating panic disorder. Metabolic syndrome can also be treated with inositol or MI. There is some evidence to suggest that inositol supplementation may be effective in OCD, though it may not provide further benefits beyond those of serotonin reuptake inhibitors.

Dosing and Administration

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
PCOS	1.0-4.0 g (MI) + 400 µg folic acid for 12-24 weeks; divided doses, twice per day	↓ fasting serum insulin, HOMA index, leptin, LH, prolactin, testosterone, androstenedione LH/FSH, TGs, SBP, DBP, 1st ovulation time, immature oocytes, & associated erythrocyte oxidative stress; ↑ insulin sensitivity, plasma sex hormone binding globulin (SHBG) after 24 weeks, estradiol, HDL, ovulation frequency, follicles > 15 mm diameter & visibility during stimulation, recovered oocytes, embryos transferred & embryo Score S1, & weight loss. Restores menstrual cycle regularity	A, B, C	**MI:** ↓ serum insulin, insulin resistance, weight ↓ LH, LH/FSH, prolactin, free and total testosterone, androstenedione; ↑ SHBG, estradiol ↓ hs-CRP, IL-1 gene expression in peripheral blood mononuclear cells, leptin, TGs, SBP, DBP; ↑ HDL ↑ menstrual cycle regularity, ovulation frequency; ↓ 1st ovulation time, ovulation failure frequency ↑ follicles > 15 mm diameter, recovered oocytes, embryos transferred & embryo Score S1; ↓ immature oocytes
	100 mg (inositol) twice per day for 14 weeks	↑ ovulation frequency (23%), estradiol, weight loss, HDL; ↓ 1st ovulation time (23.6 days), ovulation failure frequency, leptin	B	**Inositol:** ↑ estradiol, HDL, ovulation frequency, weight loss; ↓ leptin, 1st ovulation time, ovulation failure frequency
	1200 mg (DCI) daily for 6-8 weeks	↓ insulin, free testosterone, SBP & DBP, TGs. Induced ovulation.	C	**DCI:** ↓ insulin, insulin resistance ↓ free testosterone, SBP & DBP, TGs ↑ menstrual cycle regularity; Induces ovulation
	550 mg (MI) + 13.8 mg (DCI) twice per day for 6 months	↓ LH, free testosterone, fasting insulin, HOMA index; ↑ 17-beta-Estradiol	C	**MI + DCI:** ↓ insulin, insulin resistance, glucose, LH, FSH, free testosterone, body weight; ↑ 17-beta-estradiol, SHBG

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Gestational diabetes (GDB)	2000 mg (MI) twice per day	↓ rate of GDB & preterm delivery	A	↓ fasting, 1-h, 2-h oral glucose tolerance tests, birth weight & preterm delivery rate
	4000 mg (MI) + 400 µg folic acid per day for 8 weeks	↓ fasting glucose & insulin, HOMA-IR; ↑ adiponectin	B	↓ fasting glucose & insulin, insulin resistance; ↑ adiponectin
	4000 mg (MI) + 400 µg folic acid per day over pregnancy duration	↓ GDB incidence, insulin therapy requirements, baby size with decreased rate of neonatal hypoglycemia; ↑ gestational age of delivery	B	
	2000 mg (MI) + 200 µg folic acid per day from 1st trimester to delivery	↓ rate of GDB, HOMA-IR	B	
Respiratory distress syndrome in preterm infants	120-160 mg/kg (MI, intravenously) for the first 10 days of life	↓ ventilation support, deaths, bronchopulmonary dysplasia; ↑ ductus arteriosus closure	B	↓ ventilation support (requirements for inspiratory O2 & airway pressure), bronchopulmonary dysplasia; ↑ ductus arteriosus closure, saturated phosphatidylcholine/ sphingomyelin ratio
	80 mg/kg (MI intravenously) for first 5 days of life	↓ requirements for inspiratory O2 & airway pressure, bronchopulmonary dysplasia, premature retinopathy	B	
Metabolic syndrome in post-menopausal women	2000 mg (MI) twice per day for 1 year	↓ number of px with metabolic syndrome via: ↓ serum glucose, insulin, TGs, total cholesterol, BP, HOMA-IR; ↑ HDL-C	B	↓ serum glucose, insulin, insulin resistance, TGs, total cholesterol, BP; ↑ HDL-C ↓ sdLDL, hsCRP, & glucose; ↑ plasmalogens
	2000 mg (MI) twice per day for 6 months	↓ DBP (11%), TGs (20%), HOMA-IR (75%); ↑ HDL-C (22%)	B	

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Male infertility	2000 mg (MI) + 200 µg folic acid twice per day for 3 months	↑ serum inhibin B, acrosome-reacted spermatozoa, sperm concentration, total sperm count & motility; ↓ FSH & LH	B	↑ serum inhibin B, acrosome-reacted spermatozoa, sperm concentration, total sperm count & motility; ↓ FSH & LH ↑ spermatozoa concentration in healthy & oligo-asthenospermia
Female infertility under IVF or ICSI	2000 mg (MI) + 200 µg folic acid twice per day for 3 months in non-PCOS women undergoing IVF or ICSI	↓ r-FSH to form mature follicles, number of retrieved oocytes, metaphase II eggs, inseminated eggs, 2PN oocytes & embryos; ↑ LH	B	Non-PCOS: ↓ r-FSH to form mature follicles, number of retrieved oocytes, metaphase II eggs, inseminated eggs, 2PN oocytes & embryos; ↑ LH IVF poor-responders: ↓ r-FSH, low-quality oocytes (M1, Germinal Vesicle, only zona and degenerated oocytes); ↑ mature oocytes retrieved, ovarian sensitivity index
	4000 mg (MI) + 400 µg folic acid for 3 months in IVF poor-responders	↓ r-FSH, low-quality oocytes (M1, Germinal Vesicle, only zona and degenerated oocytes); ↑ mature oocytes retrieved, ovarian sensitivity index. Trended towards increased fertilization, implantation, grade 1 embryo, & pregnancy rates	B	
Panic disorder	1200 mg (inositol) per day for 1 month	↓ panic attack frequency & agoraphobia severity	C	↓ serotonin-2A receptor and muscarinic acetylcholine receptor function ↑ striatal D2 receptor density

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Adverse Effects

At doses greater than 12g per day, gastrointestinal effects, such as nausea, flatulence, and diarrhea, may occur. However, the incidence of these events are considered mild and do not increase in severity as the dose increases. The use of MI in treating PCOS is associated with fewer adverse effects than metformin. Intravenous administration up to 80mg/kg/day of MI in infants did not increase the incidence of adverse events compared with placebo. Increasing doses (300-2400 mg) of DCI has been shown to negatively impact oocyte quality in patients with PCOS.

Associated Depletions and Interactions

Classification	Pharmaceutical	Effect	Class of Evidence
Hormone	Melatonin	↑ oocyte and embryo quality synergistically	B
		↑ mature oocytes, embryo quality; ↓ immature oocytes	D
Thymoleptic agents	Lithium	↓ psoriasis associated with lithium treatment; ↓ brain myo-inositol	C
	Ebselen (a lithium mimetic)	↓ brain myo-inositol	C
Omega-3 fatty acids	High EPA/DHA omega-3 fatty acids	↓ more greatly in Young Mania and Children's Depression Rating Scales in the combined therapy group	C
Selective estrogen receptor modulator (SERM)	Clomiphene citrate	↑ ovulation rate compared to drug alone in PCOS	C
		↑ ovulation and pregnancy rate when myo-inositol alone did not achieve these effects with prior treatment in PCOS	D
Protein	Alpha-lactalbumin	↑ ovulation and plasma myo-inositol when myo-inositol alone did not achieve these effects with prior treatment in PCOS	D
		↑ myo-inositol plasma concentration via an associated increase in tight junction permeability	D
Dietary fiber	Glucomannan	↓ blood glucose and insulin with greater significance in combination	D
Coffee	Coffee (caffeine 100 mg)	↓ MI bioavailability in powdered form, but not MI soft gels	D
Oral contraceptives	Drospirenone 3 mg/ethinyl estradiol 30 µg	↓ total testosterone, C-peptide, insulin, HOMA-IR compared to drug alone. Counteracts weight gain and BMI by drug	D
	Estradiol (30µg)/gestodene 75 (µg)	↓ fasting insulin, glucose levels & HOMA-IR, hirsutism score, serum testosterone, androstenedione, & DHEAS, LDL-C; ↑ SHBG, HDL-C in the combination group	D

Pharmacokinetics

Absorption

Softgel capsules of MI (0.6g) are equally as bioavailable as powdered MI (2g) in healthy subjects. Intestinal transportation of MI across the apical membrane is accomplished by the sodium/inositol symporter 2 (SMIT2). SMIT1/SMIT2 and the H+ myo-inositol transporter are responsible for inositol uptake throughout the body and brain. MI can pass the blood-brain barrier.

Metabolism

MI oxygenase metabolizes MI to D-glucuronic acid in the renal cortical tubules. D-glucuronic acid is then converted by aldehyde reductase to L-gluconate. Metabolism of L-gluconate results in xylulose and ribulose, which both can be degraded through glycolysis.

Excretion

If not reabsorbed by the SMT2 transporters on the apical membrane of the proximal convoluted tubules, both MI and DCI are excreted in the urine.