

Review Article

Myo-Inositol and D-Chiro-Inositol in Polycystic Ovarian Syndrome

Divya Vishwanatha Kini¹, Ashwini Nayak U²¹2nd Year MBBS, ²Associate Professor, Obstetrics and Gynaecology,
M S Ramaiah Medical College, Bangalore, Karnataka, India

Corresponding Author: Divya Vishwanatha Kini

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ABSTRACT

PCOS is an endocrine disorder seen in a large number of females of the reproductive age group. The diverse clinical implications of PCOS such as obesity, hirsutism, acne, irregular menstrual cycles, infertility and hence the impact on daily life of suffering women is immense. Furthermore, given that the cause behind this metabolic disturbance being the underlying insulin resistance, therapy should lay stress on the long term and short term benefits of the same.

Two major compounds, namely Myo Inositol and D-Chiro Inositol, which are forms of Inositol, a crucial component of the insulin signalling and release pathway, has shown to be of extreme benefit in decreasing the insulin resistance. Being a naturally occurring substance in the human body as well as in plants, administration as well as compliance is found to be easier and better tolerated. Treatment of the insulin resistance with these will thus curtail the associated irregularities associated with PCOS as well. Educating the patient about the lifestyle to be maintained is also a necessary point to be noted when it comes to therapy for PCOS especially of those patients in the younger age groups.

Through this article, a compilation of various studies with an aim of easy understanding of the mechanism and benefits of Inositol and its various forms in treatment of PCOS has been made.

Keywords: Myo-Inositol, D Chiro Inositol, Poly Cystic Ovarian Syndrome, Menstrual Irregularities, Ovary, Follicles.

INTRODUCTION

According to a study by Nidhi et al, the prevalence of PCOS is about 9.13% in Indian adolescents. ^[1] Around 6-10% women in the child bearing age are found to be affected. ^[2] In another study by Pratik Kumar Chatterjee et al, in a study on 100 people diagnosed with PCOS, 40% of them were known cases of diabetes while 28% had a family history of PCOS thus showing the relation between Diabetes Mellitus as well as occurrence of PCOS. ^[3] As per the Rotterdam (2003) Diagnostic criteria for PCOS- two out of any three of the following is diagnostic of PCOS:

- Clinical Hyperandrogenism (Ferriman-Gallwey score >8) ^[1] or Biochemical Hyperandrogenism (Elevated Total/Free Testosterone) or
- Oligomenorrhea (Less than 6-9 Menses per year) or Oligo-Ovulation or
- Polycystic Ovaries on Ultrasound (>=12 Antral Follicles in One Ovary or Ovarian Volume >=10 cm³) ^[4-6]

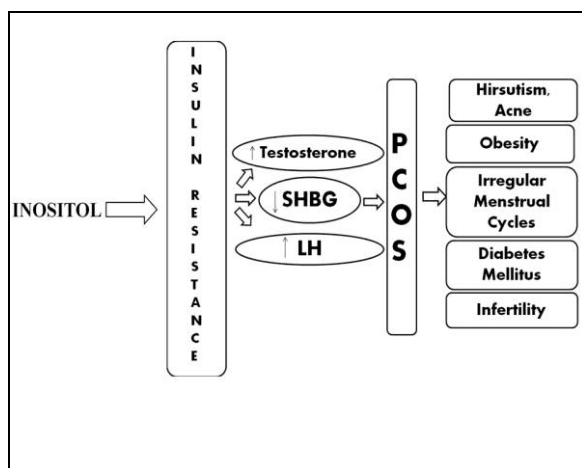


Figure 1

Earlier, the treatment for PCOS was symptomatic. Insulin sensitising drugs and glucophages such as Metformin, contraceptives to regulate the menstrual cycles, androgen lowering Spironolactone, Clomiphene for fertility and Gonadotropin injections were used. But recent studies have shed light on the underlying mechanisms of PCOS and seen that decrease in the INOSITOL level is involved and supplementation of adequate doses of this will thus help treat PCOS. For this, derivatives of Inositol namely Myo-inositol and D-chiro Inositol, as these are the only forms of Inositol involved in insulin metabolism, are used to overcome the insulin resistance as a combination to produce maximal beneficial effects. [7]

Mechanism of Myo-Inositol & D-Chiro Inositol Action

Inositol has 9 stereoisomers of which only i.e. Myo Inositol and D-chiro Inositol are involved in Insulin regulation and hence given prime importance in this study. [8]

Myo-Inositol (MI)

It is an Inositol stereoisomer first identified in the muscle and consists of a carbohydrate ring along with 6 hydroxy groups. Myo-Inositol has effects on Follicle Stimulating Hormone (FSH) and Thyroid Stimulating Hormone (TSH) as well and thus is an important factor when it comes to regulating hormone levels. It is normally found in animals as a component

of phospholipids and in plants as phytic acid. Beans, Cantaloupe and Citrus Fruits (except Lemons) were found to contain high content of Myo-Inositol in them. [9] Phytic acid can increase insulin sensitivity, enhance glucose uptake and reduce lipolysis. It also has actions in the nucleus and cytoplasm of the oocytes and affects their development. [1] There is an increase in the ovulation rate and also a rise in the estradiol levels. [7]

D-Chiro Inositol (DCI)

It is also one of the 9 stereoisomers of inositol. It shows additional actions such as increasing the insulin receptor sensitivity along with Myo Inositol and thus maintains a euglycemic state.

Combination of MI and DCI

The action of these substances is mainly on the ovarian thecal cells and adipocytes. Inositol is easily transported in and out of cells as it is a natural component of the cell membrane.

Inositol is found in the cell membranes as phosphatidyl-myoinositol, the precursor for inositol triphosphate (IP₃). Both Myo-Inositol and D-chiro Inositol act as second messengers in the cells. Whenever there is a need for more of DCI, MI converts to DCI with the help of insulin and NAD-dependent epimerase. [7-8,10-12]

A higher DCI level, though lower than MI as always, is seen in more glycogen storing tissues such as the liver while it is lower in high glucose consuming tissues such as brain and heart. [10]

In PCOS, studies on follicular fluid contents have shown that there is almost a 500-fold decrease in the MI levels of the ovary. This is attributed to the fact that the ovary does not display the insulin resistance as seen in other cells in PCOS and hence an enhanced conversion of MI to DCI with the help of the insulin dependent epimerase. Hence the ovarian MI: DCI ratio falls (decreased MI and increased DCI). Follicular development is

impaired owing to the reduced MI levels in the ovaries. [8,12]

Studies have also shown that a combination of Myo-inositol along with folic acid to be efficient. [7] But a better outcome is seen when a combined dose of MI and DCI is administered which is found to be extremely beneficial in treatment of PCOS. They are found to improve ovarian functioning as well as reduce the metabolic disturbances.

The follicular fluid is found to have MI: DCI in the ratio of 100:1, MI always being higher in all cells. But the physiological ratio is 40:1 in seen in all other cells and dosage given to the patients in this ratio is found to be most effective. [10,13]

Specific Actions of Inositol - MI and DCI

Glucose Metabolism

Insulin action occurs through the insulin receptors which consist of two subunits, α and β . The α subunit is present extracellularly and it is this which binds to the insulin. The intracellular β subunit undergoes autophosphorylation of its tyrosine residues which further phosphorylates the intracellular endogenous substrates like insulin receptor substrate-1 (IRS-1) which leads to a set of events in the cell. Studies done on cultured fibroblasts and skeletal muscle tissues by Dunaif et al [14] in PCOS have shown that the phosphorylation of the serine residues takes place instead and that of tyrosine residues reduces thus leading to reduced cellular metabolism of glucose in the tissue and reduced energy available for utilisation. The serine auto-phosphorylation of the β subunit is linked to probable genetic mutations. [14-16]

a) Glucose metabolism occurs through inositol phosphoglycans (IP) which are of two types

- P type (Phosphatase simulator): which is DCI bound to galactosamine

- A type which is an AMP (5'-Adenosine monophosphate) kinase inhibitor [10-11]

Inositol phosphoglycans (IPG) in our body act by stimulating glucose uptake. Pyruvate dehydrogenase complex (PDHC) is an important enzyme complex in glucose metabolism. P type inositol phosphoglycans (P-IPG) activate the pyruvate dehydrogenase complex by a positive effect on PDHC phosphatases which thereby enhance PDHC activity. In insulin resistance, studies have shown that there is an increased P-IPG in urine and thus a relative increase in levels of A-IPG in the body. A-IPG has a negative effect on PDHC and thus glucose metabolism reduces. [10-11]

b) The actions of insulin is carried out mainly by PI3K (Phosphatidylinositol 3 kinase) pathway.

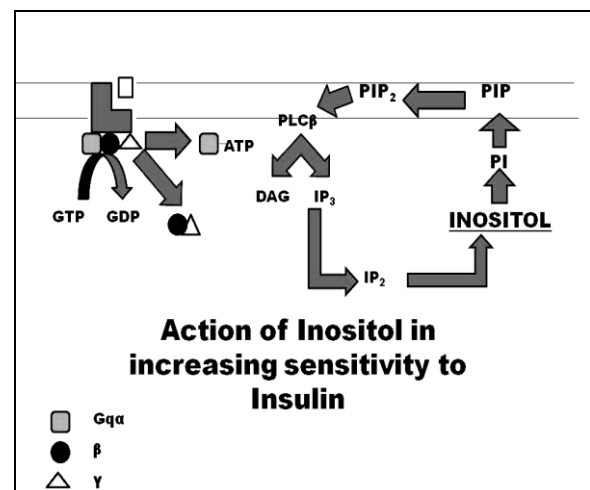


Figure 2

Inositol is acted upon by various kinases (such as phospho inositol-3-kinase) in a step wise manner as shown above and converted to phosphate derivatives. Phosphoinositol-4, 5-bisphosphate (PIP₂), one of the intermediates formed, is acted upon by phospholipase c β (PLC β) and split into Inositol triphosphate (IP₃) and Di-acetyl glycerol (DAG) which are second messengers and bring about calcium level rise in cells.

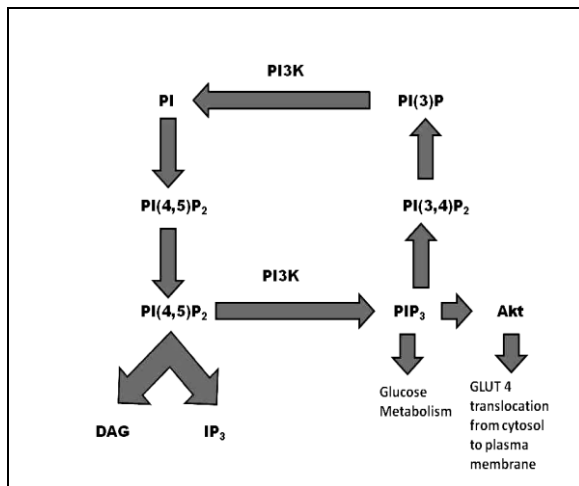


Figure 3

By acting on receptors known as IP_3 -R, Inositol-1,4,5-triphosphate increases the intracellular levels of calcium by stimulating its release from the mitochondria. In the oocytes, a specific IP_3 -R1 receptor is present which plays a vital role in oocyte maturation during the final stages when it is most sensitive to calcium level fluctuations. [10]

The cycle finally culminates in a compound phospho inositol triphosphate (PIP_3) which undergoes another signalling pathway known as the Akt pathway wherein the GLUT4 (glucose transporter 4) molecules are translocated from the cytoplasm to the plasma membrane in order to enhance the uptake of glucose. The GLUT4 are more expressed in peripheral insulin sensitive tissues such as the adipose and skeletal muscles. [16] This glucose is metabolised by the PDHC as mentioned above.

Inositol has many derivatives in the PI3K pathway and administration of inositol thereby increases their production, potentiates the functioning of the cell and thus insulin receptor sensitivity increases. In this way, Inositol supplements help treat the insulin resistance in PCOS.

c) In cases of type 2 diabetes mellitus, where insulin resistance is marked as seen in PCOS, the decreased insulin sensitivity leads to decreased epimerase activity as it is insulin

dependent and hence reduced DCI synthesis. But the ovary never displays this type of insulin resistance and hence when insulin levels rise in insulin-resistant patients, the raised insulin levels act on the ovarian epimerase and leads to increased DCI synthesis which further stimulates testosterone and glycogen synthesis in the ovaries. This is the major mechanism of PCOS at the cellular level known as the 'DCI paradox in the ovary'. [10]

Women with PCOS with abnormal glucose metabolism tend to have early development of Impaired Glucose Tolerance (IGT) and faster conversion to Diabetes Mellitus (DM). [6]

LH Induced Androgenesis

The theca cells are the cells surrounding the granulosa cells in an ovarian follicle. These are thought to have been produced from the ovarian stromal fibroblasts. Theca cells, under the influence of LH and further followed by cAMP dependent signal transduction pathways, [17] produce androgens which are sent to the granulosa cells for further conversion to sex hormones such as estradiol. [18,19]

- The increased theca cell androgen production in PCOS has been linked to
- Increased activity of enzymes such as 17α hydroxylase/ $17, 20$ lyase (CYP17) and 3β hydroxysteroid dehydrogenase.

Increased expression of the P450 side chain cleavage and CYP17 mRNAs [17] which are involved in the production of androgens (from cholesterol) and hence the increased activity of these enzymes leads to increased production of androgens.

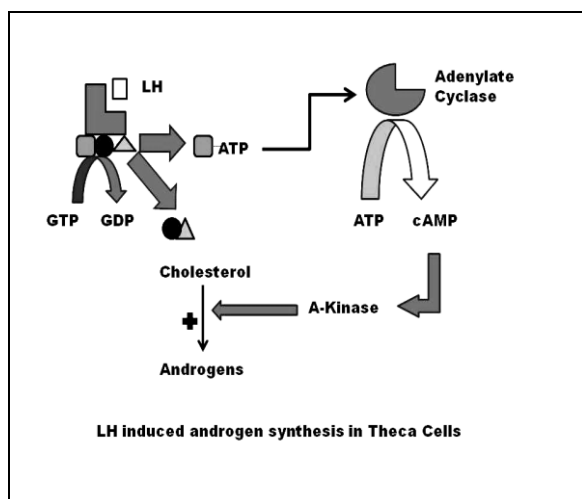


Fig. 4

Insulin acts through the PI3K pathway causing LH driven cAMP accumulation in the theca cells. LH enhances steroidogenesis by cAMP protein kinase pathway as shown in the diagram above. Androgen hypersensitivity to insulin could result from

- upregulation of androgenic insulin signalling pathway
- upregulation of IGF-1 (insulin like growth factor-1) receptors
- Decreased ovarian IGF binding protein-1 or sex hormone binding globulin (SHBG) [2,6,18,20]

Thus, in insulin resistance as seen in PCOS, the LH activity is enhanced and laboratory findings confirm this as well.

Inositol is also required for other processes such as blastogenesis, cytoskeletal development, oocyte transport through oviducts in females and for anti-mullerian hormone (AMH) serum level regulation in males. [10]

In the developing foetus, it is needed for lung development and in preventing neural tube defects.

Leptin level Disarray in PCOS

Leptin, a satiety hormone, is a cytokine receptor of tumour necrosis factor group and acts on single transmembrane cytokine receptors called leptin receptors. Leptin release is normally under the control of insulin. In cases of obesity, Insulin acts on the insulin receptors on the

adipocytes and brings about release of leptin. This control is lost in PCOS due to the insulin resistance that has developed. But in the ovaries where insulin resistance is absent, as mentioned above in case of the excessive insulin mediated DCI production, excessive leptin leads to reduced sensitivity to the released gonadotropins. [20]

Other Benefits of Inositol

Endometrial Carcinoma

Endometrial carcinoma is the second most common malignancy in women. Some of the known risk factors are Obesity, use of unopposed use of estrogens, infertility and nulliparity. [21]

The risk of endometrial carcinoma is found to be higher in patients with PCOS. This is attributed to the unopposed estrogen exposure in these patients. Normally, the proliferation of the epithelial tissue and stromal fibroblasts of the endometrium takes place in the follicular phase and early luteal phase of the menstrual cycle when the estrogen levels are high and progesterone is low. Due to anovulatory cycles (absence of Progesterone) seen in PCOS, there is chronic unopposed exposure to estrogen without the usual counter action provided by progesterone and hence proliferation of the endometrial cells. This uncontrolled proliferation is what makes the endometrium prone to malignancy. [22]

Thus by administration of INOSITOL and regularization of the menstrual cycles, there is no unopposed estrogen exposure and hence the risk of endometrial carcinoma reduces.

Thyroid Disorders

Hypothyroidism is an endocrine disorder also found to be associated with PCOS. Studies have shown that obesity is a common entity seen in most PCOS patients as well as those with hypothyroidism. A correlation between these two endocrine disorders was made wherein the increased leptin levels as seen in obesity has been found to be the

causative factor. Leptin has actions in promoting autoimmunity by increasing the effector T cells and down regulating regulator T cells. Leptin is also found to act on the hypothalamus and increase the production of Thyrotropin releasing hormone (TRH) via the Janus activating kinase-2/signal transducer and activator of transcription 3 factor. This acts on the pituitary and thereby increases Thyroid stimulating hormone (TSH). Adipocytes have TSH receptors on which this TSH acts and increase their proliferation. But the fact as to which, i.e. PCOS or the Thyroid disorder, is the predecessor is yet not fully ascertained. [23]

Hence, INOSITOL supplementation increases insulin sensitivity of all cells including the adipocytes and hence leptin levels are maintained. The TSH stimulation by leptin is absent and hence thyroid hormone levels maintained.

Other Drug Combinations in PCOS

Melatonin

It is a hormone secreted by the pineal gland in a circadian manner seen to attain high levels in the nights. Melatonin is shown to have anti oxidant action; reduces nitrogen and reactive oxygen species (ROS). ROS are involved in follicular, oocyte and corpus luteum development in the ovaries. Thus melatonin has a direct action on the ovaries. In oocytes, it prevents damage caused by reactive oxygen species, improves oocyte quality and is a cell protector. [24] A study by R.Prizzo et al has shown that effect of melatonin along with the conventional Myo-Inositol and Folic acid combination on oocyte quality and pregnancy outcome in IVF cycle was found to yield reduced number of oocytes with germinal vesicles, decreased degenerated oocytes, increased the number of mature oocytes and good quality embryo formation. [24] Studies have also shown genetic alterations in genes coding

for melatonin in PCOS such as the MTNR1A gene which has been found to be coupled to G protein Gq which activates PLC. This PLC, as explained earlier, further breaks down PIP₂ into DAG and IP₃ leading to calcium release and insulin secretion. Defects in this gene thus lead to dysregulation of insulin secretion. [25]

Hence, when combined when MI, Folic acid and Melatonin are combined the development and growth of an oocyte is safe guarded and excellent quality ones are thus produced.

Chromium Picolinate

Chromium is a trivalent cation found in trace amounts in normal diet. It is combined with Picolinate in order to increase gut absorption. [26] When given in PCOS, it was found to reduce the hyperinsulinemia and also the hyperandrogenism to certain extent but not the hormonal imbalances. It acts by enhancing insulin signalling and increasing the sensitivity of its receptors. [26]

In the body, after chromium dissociates from Picolinate it is transported by Transferrin and then Chromodulin which is its specific binding protein. This complex binds to the insulin receptors and increases glucose transport. [27]

The combined action of both Inositol and Chromium Picolinate on Insulin Regulation will help treat the underlying cause in PCOS.

Vitamin D

It is a fat soluble vitamin found to be reduced in PCOS. This has been thought to be due to the obesity present in PCOS wherein more of this fat soluble vitamin is sequestered into the adipose tissues. [9] Also, Vit D is found to be involved in direct regulation of the Aromatase gene. Hence when Vitamin D is reduced, there is presence of reduced activity of the aromatase enzyme and thus ovarian environment changes to a hyperluteinised (ie. increased LH) with a

decreases level of progesterone and estrogen secretion by the preovulatory follicles. [9] 1, 25-DihydroxyVitamin D is the active form of Vitamin D found to be involved in regulating insulin receptor sensitivity, expression, release and suppression of pro-inflammatory cytokines. The associated calcium decrease leads to follicular arrest in the ovaries and hence menstrual irregularities and infertility. [9] Thus, when both Inositol and Vitamin D are supplemented in patients suffering from PCOS, follicular development will be benefitted.

DISCUSSION

MI and DCI are the finest current developments in the subject of PCOS. This combination though proven to be favourable, has to still be administered in the right dosage to the patients or untoward effects may be observed.

Studies by Gerli et al on Myo Inositol per se in 2007 has shown that when around 92 patients were given either Myo Inositol - folic acid combination 2g per day continuously and the controls given folic acid only, the patients administered MI showed higher ovulation rates and increased levels of circulating estradiol signifying follicular maturation within first 8 days of treatment. [28]

Jean-Patrice Baillargeon et al in their studies on Urinary clearance of DCI have shown that the marked increase in urinary clearance of DCI is inversely related to the insulin sensitivity. A genetically or environmentally induced defect leads to the decreased insulin sensitivity. The compensatory hyper-insulinemic state thus developed causes the increased clearance of DCI but no effect on clearance of MI. Hence, the reduced intracellular levels of DCI leads to diminished release of DCI-IPG in response to insulin at the receptor and hence the insulin resistance aggravates. [29]

Follicles with good quality oocytes have a higher quantity of MI in their

follicular fluid. When doses of DCI alone are above 600mg/dL, decremental effect is seen on oocyte growth and development. [4] Hence, the proportion of 40:1 should always be maintained. [5]

MI in doses of about 2-4 g has proven to be effective but combination of both MI and DCI is the most beneficial. MI is said to normalise the metabolic profile of PCOS patients while DCI acts on more the hormonal imbalance i.e. hyperandrogenism. [4]

Studies by Colazingari s et al have shown that when MI and DI were administered to PCOS women undergoing IVF-ET in the physiological ratio (MI 1.1g and DCI 27.6mg along with folic acid) and some with DCI alone, the results undoubtedly proved that the combined therapy was more effective in improving the oocyte and embryo quality and also increased pregnancy rates. [30]

CONCLUSION

Myo Inositol and D Chiro Inositol are crucial components of the ovarian milieu. As proven in the various studies done, supplementing these will be extremely beneficial if taken at the right dose at the right time thereby maintaining and aiding in the reproductive cycles of affected women. The treatment should be supportive as well and patients must be made to understand the importance of the long term complications, available treatment options and explained as to which the safest is and best one to be considered. If carried out efficiently, this combination is sure to be convincing and one of the best treatment choices.

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