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Role of Inositol in Management of PCOS

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Abstract:

Polycystic ovary syndrome (PCOS) is a common metabolic and reproductive condition affecting females of reproductive age. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and/or polycystic ovarian morphology. Obesity is more common in women with PCOS compared to women without, and women with PCOS are more likely to be affected by insulin resistance irrespective of body mass index (BMI). Insulin resistance is common in women with polycystic ovary syndrome (PCOS). Inositol may have insulin sensitizing effects; however, its efficacy in the management of PCOS remains indeterminate.

Keywords: Inositol, PCOS, myo-inositol.

Introduction:

The inositol stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI), are hexahydroxycyclohexanes, with the same molecular formula as glucose. They are the two most abundant members of a family of nine steroisomeric inositols, and are found widely in nature (**1).**

Present in fruits and beans, the inositols are incorporated into cell membranes as phosphatidyl-MI, which is a precursor of inositol triphosphate (InsP3). InsP3 is a second messenger for many hormones including insulin and follicle-stimulating hormone (FSH). Defects in this pathway can lead to impaired insulin signaling and cause insulin resistance. This is the rationale for the suggested use of inositols in the management of insulin resistance syndromes, including polycystic ovary syndrome (PCOS) (**2).**

Mechanism of action of myo-inositol

Inositol is a polyalcohol of which there are nine stereoisomers (cyclohexane-1,2,3,4,5,6-hexol). Two of them have been shown to mediate the post-receptor effects of insulin: myo-inositol (MI-cis-1,2,3,5-trans-4,6-cyclohexanehexol) and D-chiro-inositol (DCI-cis-1,2,4-trans-3,5,6-cyclohexanehexol) (DCI). The food categories that contain the highest concentration of inositols are fruits, beans, corn and nuts. DCI negatively interferes with MI absorption at the intestinal level. Uptake of free inositol by tissues occurs by a membrane dependant sodium inositol cotransporter, for which MI has 10 times greater affinity than DCI. MI and DCI are mediated by some inositolphosphoglycans (IPGs), already known as second messengers. These mediators are then internalized and modify enzymatic activity and intracellular metabolism, mimicking the action of insulin. When insulin binds to its receptor, these IPGs are generated by hydrolysis of glycosylphosphatidylinositol (GPI) lipids and/or specific

proteins located on the outer part of the cell membrane. Two IPGs are formed: IPG-DCI (or IPG-P) and IPG-MI (or IPG-A). IPG-P will directly activate the glycogen synthase but will also indirectly activate it via the activation of phosphoprotein phosphatase 1 (PP1). IPG-A causes direct glucose uptake and inhibits cAMP protein kinase A and adenylate cyclase, thereby activating PP1. These effects allow a decrease in blood glucose levels (insulin-like effect), regardless of the signal passing through the insulin receptor (**3).**

In women with PCOS, impaired inositol and/or GPI metabolism contributes to insulin resistance, but obesity plays a specific role in abnormal IPG-P production independently of PCOS (**3**).

MI decreases body weight, leptin secretion and increases HDL cholesterol, but this author have noted that metabolic risk factor benefits of inositol treatment were not observed in the morbidly obese subgroup of women. Thanks to its antioxidant action (SOD, catalase and GSH increase), MI improves cell morphology and growth, as well as the synthesis of lipids participating in cell membranes. Figure 1 summarizes the different actions of MI in the ovary (**4).**

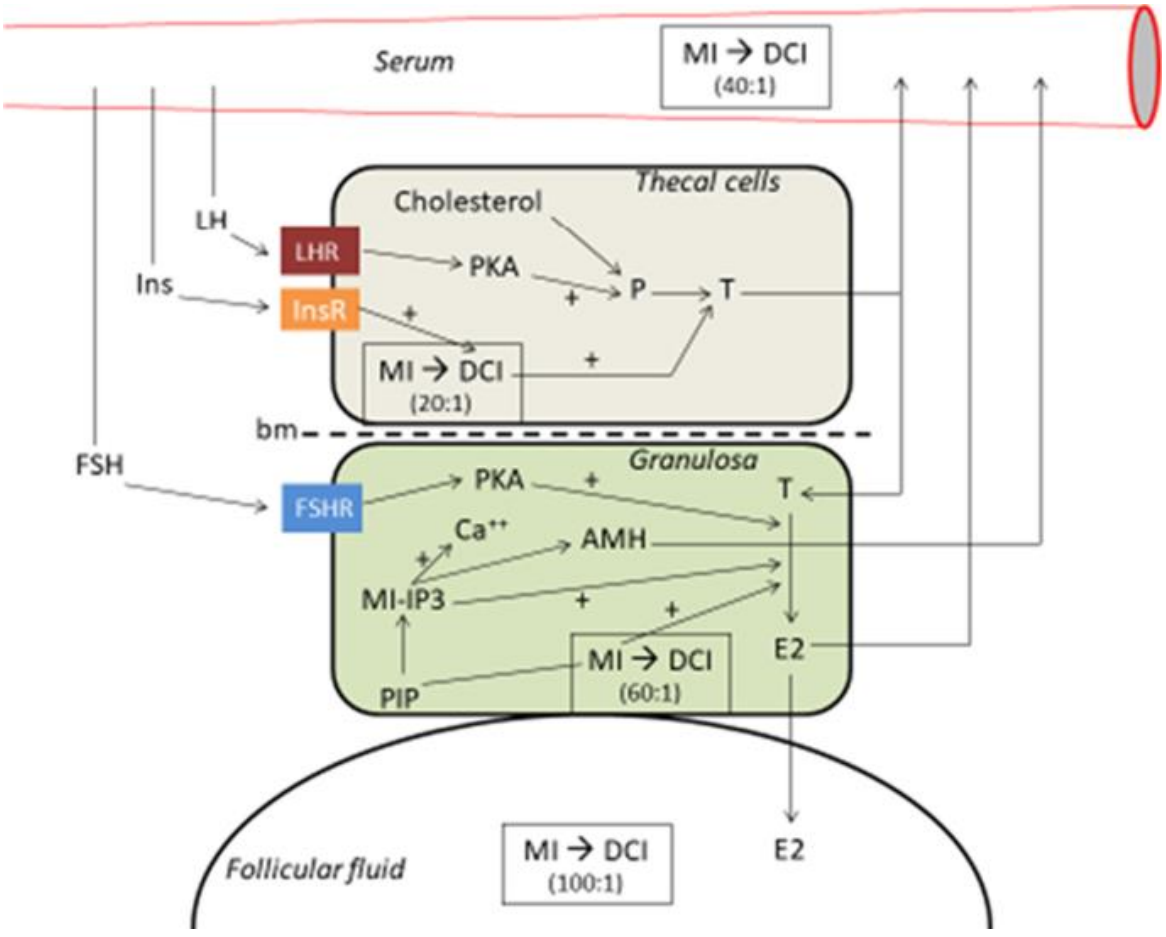

Figure (1): Roles of myo-inositol (MI) in the ovary (original figure from the author, after review of patho-physiologic effects of MI, DCI and others hormones on ovarian cells). MI: myo-inositol; DCI: D-chiro-inositol; (40:1): MI/DCI ratio; LHR: LH receptor; PKA: protein kinase A; P: progesterone; T: testosterone; INs: insulin; InsR: insulin receptor; bm: basalis membrane; PIP: phospho inositide phosphate; IP3: inositide triphosphate; AMH: anti-Müllerian hormone; E2: estradiol; + : stimulating effect (**4).**

Myo-inositol is the most abundant inositol isomer in the human body; DCI is synthesized by an insulin-dependent epimerase that converts MI into DCI. Epimerase activity dysregulation affects MI/DCI ratio, as in PCOS where a defect of MI utilization could impair FSH and insulin signaling. Each organ has a specific MI/DCI ratio related to its function. Therefore, in glycogen storage organs, high levels of DCI have been observed. In the ovary, DCI is responsible for an excess production of insulin-dependent testosterone, whereas MI enhances the action of FSH, via anti-Müllerian hormone (AMH) (**5).**

MI has been found in follicular fluid and appears to improve oocyte and embryo quality. Usually, the MI/DCI ratio is 100:1, whereas in PCOS it is 0.2:1 (**4**).

When the concentration of MI is reduced in the follicular fluid (which is the case of PCOS, where it is reduced by 500 times), epimerase activation is excessive leading to an excess of DCI, an increase in insulin resistance and an increase in LH levels. If DCI concentrations above the MI/DCI limit ratio of 70:1 in follicular fluid, the blastocyst quality was decreased. The adequate MI/DCI ratio for supplementation is 40:1. This ratio is the best (among seven different ratios between MI and DCI) for PCOS therapy aimed at restoring menstrual cycle and ovulation, increasing progesterone and SHBG and decreasing LH, testosterone and insulin levels (**6).**

Effects of MI on menstrual cycle disorders

In PCOS, early follicular growth is excessive, but subsequent progression to a dominant follicle is interrupted (follicular arrest). Intraovarian androgens have been implicated in the excess of follicles and the elevated serum estradiol levels. This increased production of androgens is an inherent property of thecal cells, but it is increased by the surplus of LH and by hyperinsulinism. In women with PCOS, treatment with metformin (MET) ameliorated the insulin sensitivity and decreased the androgens levels, but the limitations to MET use are its gastrointestinal side effects. In this case of PCOS, the place of MI was evaluated. Studies by **Zacché et al. (7)** and **Minozzi et al. (8)** show that MI leads to a decrease in LH and androgen levels, as well as a decrease in insulin resistance. Thus, MI is believed to be able to re-establish ovulatory menstrual cycles (especially in obese women with PCOS) but its effect on pregnancy rates is difficult to determine (different diagnoses, insufficient power of studies, non-comparative studies). The second anomaly is the failure to select a dominant follicle, leading to the accumulation of selectable follicles and the typical aspect of polycystic (multifollicular) ovaries when ultrasonography is performed. This phenomenon called follicular arrest is the result of a lack of FSH action and/or premature LH action. Studies have shown the role played by anti-Müllerian hormone (AMH) in inhibiting the follicular response to FSH. Hyperinsulinism, on the other hand, increases the sensitivity of follicles to LH. MI is responsible for a decrease in LH, in the LH/FSH ratio and in testosterone and androstenedione. When ovulation is induced in PCOS women with hyperinsulinism, MI reduces the risk of multifollicular development (**9).**

Therefore, MI reduces androgen levels (testosterone and androstenedione), corrects the LH/FSH ratio, restores normal menstrual cycles and induces ovulation, thereby facilitating spontaneous pregnancies by adequate luteal phase progesterone production (**10).**

THERAPEUTIC POTENTIAL

It is suggested that the inositols MI and DCI can reduce insulin resistance, improve ovarian function, and reduce androgen levels in women with PCOS. The effect of MI on ovarian function and oocyte quality is independent of its concentration in circulation (**11).**

DCI has been shown to be involved in insulin metabolism. Urinary DCI levels are lower in patients with diabetes or impaired glucose tolerance. Serum levels of DCI are reported to be lower in women with PCOS, both at

baseline and after administration of glucose loads. DCI treatment has been found to reduce insulin levels, lipids, and blood pressure, in women with PCOS (**1).**

CLINICAL EVIDENCE: MYO-INOSITOL

MI has been found to improve the number of good quality oocytes, clinical pregnancies, and delivery rates in overweight women with PCOS. Thus, it modulates the reproductive axis in a beneficial manner. In all these trials, a daily dose of 2 g MI was used over an observation period of 3–6 months. The biochemical, endocrine, and clinical benefits of MI were thought to be due to its insulin-sensitizing action (**1).**

A study used MI 2 g and folic acid as a soluble powder, twice daily, continuously, till the end of study (6 months) or a positive pregnancy test was obtained. Of 25 women with PCOS, 22 (88%) experienced a first menstrual cycle after 34.6–5.5 days. Of these 22, 18 continued to have regular menstruation and documented spontaneous ovulation. The length of successive cycles improved to 31.7 ± 3.2 days, and there was a significant fall in serum testosterone and free testosterone. Two more women showed follicular development on ultrasound, but did not exhibit an elevation of progesterone, thus suggesting anovulation. A total of ten biochemical pregnancies occurred during 6 months, of which one ended in a spontaneous abortion and one was a biochemical abortion. No multiple gestations were noted. MI can, thus, be used as a safe means of induction of ovulation in women with PCOS (**10).**

In a study of fifty women with PCOS, 2 g MI was found to reduce the risk of ovarian hyper stimulation syndrome with ovulation-induction protocols. Concentrations of LH, prolactin, androstenedione, insulin, and LH/FSH ratio were reduced significantly. Insulin sensitivity improved as well. The duration of ovulation induction and dose requirement of recombinant FSH were significantly lower with MI therapy. MI administration achieved lower oocyte retrieval, but had a greater proportion of large dimension (top quality) oocytes, which translated to a higher pregnancy rate. Biochemical pregnancy occurred in 15, clinical pregnancy in 10, and successful delivery in 8 women treated with MI, as compared to 8, 4, and 3 non-MI-treated participants. All these differences were statistically significant (**11).**

An Iraqi study on 95 participants reported that a combination of inositol 500 mg, with choline 500 mg and metformin 850 mg, all administered twice daily for 6 months led to a significant decrease in body mass index (BMI), serum leptin, and serum anti-Mullerian hormone (AMH), as compared to metformin monotherapy and lifestyle management alone. The isomer of inositol was not specified in the study (**12).**

Systematic reviews and meta-analysis have collated data on the efficacy of MI in PCOS, and suggest the need for further studies. Data also support the use of this molecule in gestational diabetes mellitus (GDM), which is also a syndrome characterized by insulin resistance (**13).**

CLINICAL EVIDENCE: D-CHIRO-INOSITOL

Various authors have studied the effect of DCI on endocrine, metabolic, and reproductive parameters in PCOS. Administration of 600 mg DCI/day for 6-8 weeks to lean women with PCOS (BMI 20.0–24.4 kg/m^2) reduces insulin and free testosterone levels, while decreasing systolic blood pressure, diastolic blood pressure, and serum triglycerides. A higher rate of ovulation is noted with DCI, though the difference is not statistically significant (**14**).

In obese PCOS women (BMI >26 kg/m^2) also, DCI is found to improve endocrine parameters including serum testosterone, serum androstenedione, and gonadotropin-releasing hormone-induced LH response. It also reduces BMI and improves insulin sensitivity markers in PCOS patients with diabetic relatives, who exhibit a greater response as compared to those with no family history of diabetes **(15).**

The effect of DCI extends to menstrual regularity, which improves with its supplementation. This regularity is associated with a decrease in serum AMH and in insulin resistance. Low AMH, high homeostatic model of assessment index, and presence of oligomenorrhea at the first visit are the independent predictors of achieving menstrual regularly with DCI **(16).**

This effect may be mediated through a decrease in follicular fluid oxidative stress status. In a study conducted on 68 participants, women with PCOS were pretreated before ovarian stimulation with either DCI 500 mg b.d or metformin 850 mg b.d. or left untreated for 3 months. DCI improved the maturity and quality of oocytes significantly, while reducing oxidative stress (as measured by amino acidic free - SH group labeling). The usage of DCI was not associated with any adverse effect in this study (**17).**

These studies complement a relatively old Cochrane review, which assessed the role of insulin-sensitizing agents in the management of PCOS. A similar Cochrane review, focusing on MI, is in progress for GDM (**18).**

SAFETY/TOLERABILITY

Inositol is generally regarded as safe and can be used in pregnancy. Its excretion in breast milk, and safety in lactation, is unknown. Gastrointestinal symptoms can occur, but are rare (**19).**

PRAGMATIC PRESCRIPTION

Keeping in view the above physiologic and pharmacological evidence, we suggest pragmatic use of inositol therapy in the prevention and management of PCOS. While the 2013 Endocrine Society guidelines for the management of PCOS do not suggest the use of inositols, there is a definite role for this upcoming therapy **(20).**

Currently, PCOS treatment is based on lifestyle modification and metformin for metabolic modulation; clomiphene for the induction of ovulation; and oral contraception for menstrual regularity and management of hyperandrogenism. All these modes of treatment have their advantages and limitations. All of them focus on a single aspect of PCOS pathophysiology, and none is able to address all clinical aspects of the syndrome. While metformin does improve insulin sensitivity, thus alleviating the core defect of insulin resistance, it is not approved as a first line drug for the management of cutaneous or hyperandrogenic features **(21).**

Combination inositol therapy (MI and DCI) has the potential to improve all symptoms, signs, and laboratory anomalies of PCOS. Both inositols, prescribed together, should be able to improve the required inositol concentrations in both systemic circulation and the ovary, thus addressing the ovary inositol paradox. The correction of systemic insulin resistance by MI will treat the metabolic features of PCOS. Simultaneously, adequate DCI levels will create a healthy intra-ovarian milieu, which will correct hyperandrogenism, improve menstrual regularity, and promote ovulation and fertility (**1).**

Myo- + D-chiro-inositol (MDI) therapy can be used in PCOS as monotherapy or as a combination with other treatment modalities. Such usage is based on biomedical as well as psychosocial factors (Table1). The choice of an MDI preparation and MI/DCI ratio should be based on physiological factors. Current evidence is inadequate to provide a definite answer regarding the optimal MI/DCI ratio. While MI is necessary for metabolic management, DCI is equally important for menstrual, ovulatory, and cutaneous hyperandrogenic resolution. Therefore, the ratio may be less important than the absolute concentrations of both inositols. It is clear, therefore, that a high concentration of DCI is necessary to circumvent epimerase deficiency and ensure adequate levels in the ovary. Most pharmaceutical preparations provide very low amounts of DCI, which are insufficient to achieve adequate levels in the ovary. Hence, formulations with relatively higher levels of DCI are preferred (**1).**

Table (1): Pragmatic use of D-chiro-inositol (myo- + D-chiro-inositol) therapy in polycystic ovary syndrome **(1).**

Monotherapy
Inability to follow/inadequacy of lifestyle modification
Contraindication to metformin/OC
Intolerance of metformin/OC
Nonacceptance of metformin/OC (social stigma)*
Combination therapy
Inadequacy of metformin in achieving optimal metabolic control
Inadequacy of clomiphene in achieving ovulation
Inadequacy of OC in achieving eu-androgenemia
Coadjutant therapy in assisted reproductive technology
*In adolescents, unmarried women, and newly married women, who wish to avoid the label of using anti-diabetic and/or contraceptive drugs. OC: Oral contraceptive, OHSS: Ovarian hyper stimulation syndrome, PCOS: Polycystic ovary syndrome

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