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Uses of Myo-inositol and D-chiro-inositol for Management of PCOD

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ABSTRACT: Polycystic ovarian disease, when diagnosed among women has been demonstrated to be associated with resistance to insulin with hyper-insulinemia. It is mainly due to deficiencies of Myo-inositol and D-*chiro*-inositol enriched Phosphoglycans which act as a mediator for insulin functioning. These medicinal agents normalize ovarian functioning, improvement of oocytes along with the quality of embryo in PCOD patients. The main challenge to the treatment of PCOS lies in its early detection in the young females. This can be overcome by conducting regular checkups and monitoring biochemical test results of LH/FSH ratio and fasting blood glucose in teenage females so classifying early symptoms can help in timely treatment of the disorder.

This review article presents an overview of various published articles on the pathogenesis of PCOD, roles of Myo-inositol and D-chiro-inositol in regulating the pathophysiology and treating the condition without any hormone based intervention in both obese and non-obese female patients.

Keywords: PCOD, young females, Myo-inositol, D-chiro-inositol, insulin, obesity.

INTRODUCTION

Polycystic ovarian disease (PCOD) is a chronic disease that has multiple systemic involvements affecting metabolism and diseases of endocrinal system, which can affect health of reproductive system. This disease also increases the likelihood of neoplasms of female origin. Typically, this disease has main clinical features of biochemical hyperandrogenism as well as an ovulation. The prevalence of polycystic ovarian disease is extremely variable and may range between 4.5 % and 11.2 % among adult females (Cheung and Cog 2010).

As per the 2003 Rotterdam's criteria for diagnosing polycystic ovarian disease, minimum of 2 out of 3 main characteristics should be met. These characteristics are- a) hyper-androgenism, b) persistent type of oligo- or an-ovulation (skipped or irregular periods) along with c) poly-cystic ovaries (ovaries containing small, fluid-filled sacs grow inside them) that must exhibit precise ultrasonography features (Rotterdam ESHRE/ASRM Criteria 2004).

Rotterdam criteria are valid till date and have been frequently employed in differentials of a variety of clinical medical conditions apart from PCOD. However, there is a requirement of newer consensus, since existing criteria does not include resistance towards insulin and/or hyper-insulinemia. Both of these conditions are seen in significantly large percentage of women diagnosed with PCOD. Additionally, newer equipment used for ultrasonography helps in better quality characterization of morphology of affected ovaries (Dewailly, 2016). Most ovaries that are considered to be clinically polycystic when visualized using ultra-sonography do not show any polycystic ovarian disease (PCOD) (Barber *et al*., 2016).

The underlying etiopathology of PCOS still remains an enigma, and the disease itself has been linked with notable consequences over health which includes- type II diabetes or Diabetes Mellitus and endometrial/ovarian carcinomain the long run (March *et al.*, 2010).

Studies have revealed the association of PCOD with obesity and risk of cardiovascular disease (Barber *et al*., 2016), even though obesity and cardiovascular disease are not considered to be one of the classical diagnosis related criteria in PCOD. Irrespective of one's body mass index (BMI) and proportion of fat mass, PCOD has been linked with insulin based resistance and presence of hyper-insulinemia along with a high risk of alterations in glycemics profile on comparison with observations in controls having identical bodily weight. Overall prevalence of early stage of glucose intolerance can rise up to 40 % in PCOD (Barber *et al*., 2016).

Pathogenesis of polycystic ovarian disease. Numerous theories have been advocated for explaining pathogenesis of PCOD. Most important and widely

accepted theory suggests an excessive secretion of Gonadotropin releasing hormone or GnRH from hypothalamus. The increase in GnRH (Gonadotropin Releasing Hormone) causes excess production of Luteinising hormone (LH). This sequence of events leads to increased stimulation of ovaries for producing increased quantities of testosterone (Goodarzi *et al.*, 2011; Tsilchorozidou *et al.*, 2004).

According to a second theory, there is an endocrinal disturbance of insulin based axis such as hyper-insulinemia in conjunction with development of resistance against insulin. The higher circulating level of insulin undergoes reduced sex hormone-binding globulin (SHBG) secretion from hepatic tissues. This decrease in SHBG level causes an increase in level of freely circulating testosterone which results in hyper-androgenemia (Wallace *et al.*, 2013).

The state of hyperinsulinemia also increases the frequency of GnRH release pulse, although, Luteinizing Hormone (LH) levels rises more predominantly than increase in Follicle Stimulating Hormone (FSH) level. This causes a decrease in maturation of ovarian follicles, an increase in production of ovary derived androgens and a decrease in levels of SHBG (Sanchez-Garrido and Tena-Sempere 2020).

Tissue-specific Myo-inositol (MI):D-Chiro-inositol (DCI) ratio undergoes modulation via insulin through the enzyme known as 'aromatase'. This particular enzyme has been reported to undergo alteration in conditions leading to development of resistance towards insulin (IR) along with reduction in epimerization of MI to DCI in insulin-sensitive tissues. In ovaries, the MI/DCI ratio is 100:1, but it is dramatically reduced by insulin-stimulated epimerase in hyperinsulinemic women with polycystic ovary syndrome (PCOS) (Bizzarri *et al.*, 2023).

Effect of Myo-inositol and D-chiro-inositol therapy in polycystic ovarian disease (PCOD). Inositol, a member of the vitamin B family, is one of the 9 types of inositol. Inositol plays an important role in maturation of oocytes via calcium-mediated signalling pathways (Artini *et al.*, 2013). It has been demonstrated that ovarian follicles containing high Myo-inositol levels produce better quality of oocytes and aid in finer maturation of ovarian follicles (Artini *et al.*, 2013; Barriga *et al.*, 2020). Myo-inositol, and its stereoisomer, D-chiro-inositol are main members of this family that have demonstrated beneficial results in the treatment of PCOD (Bizzarri *et al.*, 2023).

Myo-inositol plays an important function in cytogenesis, growth of cells, synthesis of cellular membrane and its structure. It functions as a precursor of phosphoinositides, which take part in the regulation of proliferation of cells, among other variety of functions (Papaleo *et al.*, 2009).

The primary cause of manifestation of PCOD is defective secondary messenger. The circulating free inositol gets captured in tissues by sodium-dependent co-transporter which is localized within cell membranes. Myo-inositol plays a key role by acting as a secondary messenger in inositol-phospholipids-calcium system for reducing disturbances in the underlying signaling pathway of this disease (Pasquali *et al.*, 2016).

It has also been observed that women affected by PCOD demonstrate lower levels of D-chiro-inositol and so external administration D-chiro-inositol results in restoring the gonadal functions and lowering of free testosterone and triglycerides levels. In addition, there is an improvement in insulin sensitivity (Cheang *et al.*, 2008).

Wang *et al.* (2018) observed that 42% of females with PCOD had normal Body Mass Index (BMI) although their clinical as well as hormonal profiles had similarity with those of PCOD patients having elevated BMIs i.e., over-weight or obese individuals (Wang *et al*., 2011).

Intra-cellular conversion of Myo-inositol mediated by specific enzyme, 'Epimerase' produces D-chiro-inositol. An inositol phosphoglycan molecule which contains D-chiro-inositol as well as galactosamine plays an important role in activation of key enzymes which regulate both oxidative as well as non-oxidative glucose metabolism (Bizzarri *et al*., 2023).

Combination drug supplement containing Myo-inositol and D-chiro-inositol in physiological ratio as that present in plasma i.e., 40:1 has shown to improve overall the endocrine profile, ovarian functions and resistance towards insulin in PCOD patients (Malvi *et al*., 2019). This brings us to Nordio *et al*. (2019) who reported that administering a combination of Myo-inositol and D-chiro-inositol in physiological plasma ratio of 40:1 must be the 'first line' of treatment in PCOD patients as it reduces metabolic rate and clinically alters PCOD thereby reducing risk of development of metabolic syndrome (Nordio *et al.*, 2019).

Bevilacqua and Bizzarri (2018) gave clinical study data that supported useful effects of inositol by means of lowering levels of glycemia and hyper-insulinemia, and down-regulating the negative impact of sustained stimulation by insulin on adipocytic tissues along with endocrine system. Thus, owing to its benefits, Myo-inositol is now considered an effective option for treating PCOD when compared with hormonal regulation in patients' insulin-resistance of Polcystic Ovarian Disease (Bevilacqua and Bizzarri 2018).

Nas and Tûû (2017) showed a significant improvement ($p<0.05$) in the levels of two hormones- progesterone and prolactin following treatment with Myo-inositol. Additionally, the treatment groups demonstrated significant level of improvement ($P = 0.01$) in disorders affecting the menstrual cycle. Myo-inositol was also observed to reduce incidence of hirsutism from 73% to 36.6%. On the other hand, the incidence of acne was found to decrease to 84% from 94.3% following treatment with Myo-inositol (Nas and Tûû 2017).

Advani *et al*. (2019) evaluated efficacy as well as and safety profile of Myo-inositol. They opined that a combination of therapies may be useful in management of PCOD. Combining the administration of insulin-sensitizing drugs i.e, Myo-inositol, D-chiro-inositol, chromium picolinate along with antioxidants such as-N-acetylcysteine with lycopene and vitamins D, biotin and folic acid has been demonstrated to have safety as

well as show effectiveness among women with obesity and also, among non-obese women diagnosed with PCOD (Advani *et al.,* 2019). After 12 weeks of combination drug therapy, noticeable improvement in menstrual cyclicity was observed in 63% lean and 69% obese patients (Advani *et al.,* 2019).

According to a study done by McBreairty *et al.* (2020), use of dietary control along with exercise increases the efficacy of Myo-inositol as secondary messenger for increasing sensitivity towards insulin. This causes reduction in disruptions in balance between different hormones which can result in development of obesity. Therefore, these investigators concluded that balance in one's lifestyle can increase sensitivity towards insulin. Also, lowering of Body Mass Index maintains homeostasis in body's physiological functions (McBreairty *et al.,* 2020).

Similarly, Qamar and Mustafa (2020) demonstrated a statistically significant correlation (P = 0.01) between intervention therapy by using Myo-inositol and PCOD with its associated symptoms (Qamar and Mustafa 2020).

Gerli *et al*. (2007) randomized study observed improvement in ovulation frequency and timing for first ovulation with an early effectiveness over maturation of follicles in the group treated with Myo-inositol and folic acid. More than 7/10th of the patients reported normal ovarian rhythm (three or more ovulations) through the 16-week treatment period. Also, a rise in circulating estradiol levels was observed during first week of therapy. Additionally, positive metabolic alterations were noted in patients treated with MYO for example, increase in high-density lipoproteins and weight loss. However, no alterations were observed in levels of fasting blood glucose or in insulin response in oral glucose tolerance test (Gerli *et al.*, 2007).

Closer home, data collected from 50 healthcare centers across India revealed that treatment with Myo-inositol and D- chiro-inositol resulted in a remarkable improvement in HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) score, insulin levels, fasting and post-prandial plasma glucose (FPG, PPG), weight and lipid profile. The therapy restored menstruation and spontaneous ovulation and there was a noteworthy decrease in LH/FSH ratio. The treatment indicated multidimensional benefits in improving the hormonal, glycemic, and lipid profile of women with PCOS with considerable efficacy and tolerability (Vyas *et al.,* 2022).

Hence, based upon the various findings regarding the use of Myo-inositol and D- chiro-inositol, it can be said that these drugs can successfully improve the androgenic as well as metabolism related symptoms in PCOD. It has been suggested that restoration of insulin sensitivity should be the treatment approach for all women with PCOS.

Better compliance in usage by the patient results in significantly better outcome in managing irregularities in menstruation, hyper-androgenism and also, results in improved parameters related with metabolism (William *et al.,* 201s6).

CONCLUSIONS

Both Myo-inositol and D-chiro-inositol are insulin based secondary messengers. Myo-inositol influences the follicular gonadotropin pathway which assists ovulation. D-chiro-Inositol modulates release of androgen and helps in insulin signal transduction, while inhibiting ovarian aromatase synthesis. Inositols have proven to be effective in PCOS by improving metabolic and hormonal state, and restoring spontaneous ovulation. In assisted reproductive technology, inositols have revealed improvement of ovarian stimulation parameters, although data concerning fertility outcomes are conflicting. Given their functions, inositols are an attractive treatment option for PCOS, although ingenious studies on spontaneous and non-spontaneous fertility are needed.

FUTURE SCOPE

Early detection of PCOS and studying the effect of Myo-inositol and D-chiro-inositol in PCOS (that is currently restricted due to complexity of inositol metabolism) will enhance future treatment modalities in an effective manner in the coming years.

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Conflict of Interest. None

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