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# D-Chiro-inositol in PCOS: the myths and what we know about the reality

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LETTER TO THE EDITOR



# D-Chiro-inositol in PCOS: the myths and what we know about the reality

Dear Editor,

I read with extreme interest and curiosity the recent overview of the use of inositols – D-chiro-inositol, in particular – as treatment for women with polycystic ovary syndrome (PCOS) (Cianci and Vitale 2022). After remaining dormant for many years, a keen interest towards the physiological roles of D-chiro-inositol has recently resurfaced, fuelling clinical and pre-clinical studies that evaluated the potential benefits of supplementation regimens (Dinicola et al. 2021; Gambioli, Montanino Oliva, et al. 2021). In particular, applications for gynecological conditions have received special attention (Bevilacqua et al. 2019; Nordio et al. 2019), despite some of the available investigations produced inconclusive results (mostly due to heterogeneous selection of the study population) that led to biased conclusions and illogical indications for treatments. Although I mostly agree with Cianci and Vitale on their conclusions (Cianci and Vitale 2022), there are aspects that I deem worthy of further discussion in order to better define the therapeutic applications and limits of D-chiro-inositol supplementation.

Unquestionably, the effect of D-chiro-inositol supplementation on insulin sensitivity accounts for most of the clinical effects observed also in women with PCOS, albeit in very limited and specific cases as Cianci and Vitale discuss. Indeed, when insulin resistance in PCOS results in compensatory hyperinsulinemia, treatment with D-chiro-inositol may decrease the systemic levels of insulin and thus reduce the associated cardiometabolic risk. On the contrary, D-chiro-inositol may induce overproduction of testosterone in women with PCOS when insulin levels are within the physiologic range, as in-vitro experiments on thecal cells from women with PCOS seem to suggest (Nestler et al. 1998). Considering that hyperandrogenism is often a feature of the syndrome, and one of the three diagnostic criteria, the available evidence fails to clearly support any kind of beneficial effect from D-chiro-inositol for women with PCOS without hyperinsulinemia. The following question naturally arises, *do all women with PCOS and hyperinsulinemia always benefit from supplementation with D-chiro-inositol?*

To properly address this point, we should consider that D-chiro-inositol participates in the biosynthesis of steroids also as regulator of gene expression of key enzymes. Indeed, as Cianci and Vitale mention in their brief communication, Sacchi et al. first demonstrated in vitro that D-chiro-inositol inhibits the gene expression of aromatase enzyme in a dose-dependent manner (Sacchi et al. 2016). Bevilacqua et al. recently confirmed this finding in animal studies (Bevilacqua et al. 2021). They also observed that high dosages of D-chiro-inositol have similar effects to Letrozole on ovarian morphology and functionality, inducing a PCO-like syndrome, and produce ovarian lesions typical of aged mice when the dose is further increased. These results suggest that D-chiro-inositol administration should reduce circulating oestrogens by down-regulating the expression of aromatase, while allowing accumulation of testosterone produced in the thecal cells. Even though we made parallelisms with the effects of aromatase inhibitors in the past (Laganà and Unfer 2019), it is important to keep in mind that there is no available report that D-chiro-inositol directly inhibits the enzyme. Some preliminary, still unpublished, experiments that we carried out on the isolated enzyme indicate, however, that D-chiro-inositol has no interference with the aromatase activity. Clinical investigations of the effect on steroid status of women with and without PCOS are currently underway, but the first experiments in men confirmed the expected outcome on steroid biosynthesis. Indeed, two pilot studies demonstrated that oral treatment with D-chiro-inositol for 30 days significantly increased androgens and reduced oestrogens in healthy male volunteers and in hypogonadal men (Monastra et al. 2021; Nordio et al. 2021).

All these clinical and preclinical indications suggest that, once absorbed, D-chiro-inositol reaches peripheral tissues, even though quantitative *in-vivo* data on its distribution in human ovaries would be impossible to acquire. Moreover, gynecological outcomes observed with myo-inositol prove that oral supplementation affects the ovarian content of inositols; as myo-inositol and D-chiro-inositol share the same transporter (Schneider 2015), there is no reason to believe that they have a different fate in the body. The two inositols have specific ratios in different tissues and organs, and excess ovarian D-chiro-inositol seems to correlate with negative reproductive outcomes (Ravanos et al. 2017). Alarmingly, unbalanced inositol ratios with increased content of D-chiro-inositol characterise the ovaries of women with PCOS (Heimark et al. 2014; Unfer and Porcaro 2014). Therefore, supplementation with myo-inositol seems to be indicated for women with PCOS. However, depending on the specific situation, the association of myo-inositol

and D-chiro-inositol may be advisable. Supplementation with the physiological plasma ratio of the two inositols, indeed, yielded the best results in terms of gynecological outcomes for overweight/obese women with PCOS (Minozzi et al. 2013; Benelli et al. 2016; Le Donne et al. 2019).

On these premises, we can derive that even if women with PCOS and hyperinsulinemia may experience an initial benefit from supplementation with D-chiro-inositol, ovarian alterations may occur in the case of long-term treatment with doses $\geq$1200 mg/die (Bevilacqua et al. 2021; Gambioli, Forte, et al. 2021). This results in irregular or impaired menstrual cycle and in harmful increase of androgens that may exacerbate PCOS symptoms. The only potential clinical application of D-chiro-inositol in PCOS with insulin resistance may reside in the ovulation induction. Indeed, Nestler at al. demonstrated that 6–8 weeks of oral supplementation successfully restored ovulatory function in over 85% of insulin-resistant patients (Nestler et al. 1999). Longer periods of supplementation seem to have no beneficial effect on ovarian functionality, as Nordio et al. demonstrated by treating women with PCOS for 3 months (Nordio et al. 2019). However, one should wonder, which is the clinical advantage when drugs such as clomiphene citrate induce ovulation within days with greater efficacy?

I shall conclude by rephrasing the initial statement in the article by Cianci and Vitale. This is an ever-evolving picture rather than a never-ending story, as researchers keep providing additional evidence on the physiological role of D-chiro-inositol that allows to better understand its potential fields of therapeutic application.

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