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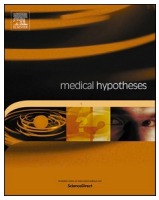

Adjuvant treatment with D-chiro-inositol: A possible therapeutic strategy for insulin resistant and obese women with endometrial hyperplasia?

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ABSTRACT

Endometrial hyperplasia is a common gynecologic disease which typically occurs when progesterone levels fail to balance the effects of estrogens. This clinical picture is further complicated by insulin resistance and hyperinsulinemia, which stimulate the cellular proliferation of the hyperplastic tissues. Up to date, standard therapeutical approaches with progestogens and aromatase inhibitors aim to restore the hormonal balance, without affecting the altered metabolic pattern of these patients. Promising but yet inconclusive results emerged by combining the progestogen-based treatments with insulin sensitizers, which proved to shorten fertility-sparing treatments for endometrial hyperplasia (EH) in case of insulin resistant obese women.

On these premises and considering that D-chiro-inositol (DCI) acts both as insulin sensitizer and aromatase down-modulator, we put forward the hypothesis to consider its supplementation as a valid adjuvant approach for EH patients, especially when insulin resistance and obesity are present. In particular, we suggest associating DCI with progestogens to shorten the treatments with these medications. This could allow patients to benefit from a natural and well tolerated molecule which can contrast insulin resistance and rebalance the unopposed estrogens at the same time.

Introduction

Eutrophic endometrium benefits from a proper balance between estrogens and progestogens. Indeed, progestogens are essential to maintain a eutrophic endometrium, preparing it for implantation, overcoming the proliferative effect of estrogens and inducing the differentiation of endometrial glands, stroma, and vessels [1].

When levels of progestogens are insufficient, unopposed estrogens take over, stimulating an abnormal proliferation of endometrial glands and leading to endometrial hyperplasia (EH) [2].

Basically, EH is a benign precancerous lesion, diagnosed in women with uterine bleeding abnormalities during their menstrual cycle or after menopause. Although EH does not represent a serious health risk for women, care should be taken because it may evolve to atypical hyperplasia, which represents a precursor for endometrial cancer [1].

Medical treatments for EH aim to manage symptoms and limit the abnormal vaginal bleeding, in order to improve patients' quality of life and avoid progression to cancer.

In the absence of atypia, EH is essentially treated with hormonal therapies, while hysterectomy is the recommended approach when atypia occurs, unless the patient wishes to seek pregnancy.

In such case, hormonal therapy can also be taken into account after appropriated evaluations.

Progestogens represent the first-line pharmacological treatment for EH, considering their efficacy and tolerability, despite the vascular effects, as the higher resting vascular resistance and increased pressor responsiveness [3,4]. However, the major concern is mainly related to the risk of recurrence after a complete resolution, which ranges between 14 and 30% [5].

Also, the optimal duration of progestogen-based treatments is highly debated to avoid unnecessarily long-lasting therapies, especially for women in the reproductive age who desire to preserve their fertility.

To shorten the treatments for EH, some clinical trials combined standard progestogen-based therapies with insulin sensitizers, especially

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metformin [5,6]. Furthermore, the sole metformin was investigated as potential treatment for EH [5].

The rationale behind this therapeutical choice is that insulin resistance and hyperinsulinemia are among the main risk factors for developing EH, highlighting the positive correlation between glucose dysmetabolism and gynecological diseases [7].

Indeed, compensatory hyperinsulinemia, consequent to insulin resistance, is thought to exhibit mitogenic effects, triggering cell division and endometrial proliferation [8,9]. Moreover, insulin resistance supports the progression of endometrial hyperplasia to cancer through different mechanisms, including the increase of local estrogen levels or estrogen sensitivity in endometrium through inflammation-induced pathways [10–12].

The combined use of metformin and progestogens was particularly successful in case of insulin resistant obese women with EH, allowing these patients to achieve a complete response in a shorter time with respect to those receiving only the hormonal therapy [13].

Despite these interesting reports, literature evidence on the uses of metformin in women with EH is quite conflicting. As a matter of fact, Clement and Yang independently stated that these findings are not strong enough to support its use either alone or in association with progestogens as a clinical routine [5,14].

The hyperplastic endometrial tissue expresses high levels of aromatase, the enzyme that converts androgens into estrogens [15]. Therefore, clinicians evaluated the use of aromatase inhibitors (AIs), like anastrozole and letrozole, as potential treatments for EH, especially for obese women, being aromatase mainly expressed in the adipose tissue [15–17].

Particular attention, however, must be paid to the potential adverse effects of AIs, which may lead to cardiovascular alterations [18].

Therefore, the evaluation of chemical species that reduce insulin resistance and modulate aromatase at the same time is extremely interesting to avoid the limitations of the current therapeutical approaches.

The hypothesis: D-chiro-inositol supplementation as alternative integrative therapy for EH

We hypothesize that D-chiro-inositol (DCI) may constitute an adjuvant therapy to treat EH patients, especially those with insulin resistance and obesity.

DCI is a natural polyol present in all mammals. In the human body, it is synthesized from myo-inositol by an insulin-dependent epimerase and its physiological function is principally to mediate the intracellular signal of insulin, storing glucose in the form of glycogen. DCI supplementation proved beneficial in restoring normal insulin signal in case of insulin resistance [19].

While the activity of DCI as insulin second messenger has largely been studied, more recent findings suggested its role as endocrine modulator [20–22]. The first evidence of DCI involvement in steroidogenesis dates back at the end of the ’90 s, when Nestler observed that both insulin and DCI directly stimulate testosterone production from cultured theca cells of PCOS women. Antibodies against DCI blocked in both cases the biosynthesis of testosterone, demonstrating the function of DCI as insulin second messenger [23].

More recently, Sacchi and coworkers reported that DCI downregulates the gene expression of aromatase enzyme in human granulosa cells [24], thus increasing endogenous testosterone.

Bevilacqua et al. confirmed these findings on a murine model, underlining the negative effects on the ovaries due to increased androgen production when mice receive elevated doses of DCI [25].

Importantly, in a recent paper, Monastra et al. deeply debated on the possibility that DCI might function as anti-aromatase agent [26], thus paving the way for its proper and tailored use in gynecological clinical practice.

Indeed, because of both metabolic and endocrine activities, DCI seems a promising candidate for the management of hyperestrogenic female disorders, especially if complicated by insulin resistance and obesity.

Based on the studies with metformin, DCI supplementation can be combined with the gold standard progestogen-based therapies for managing EH [13], to reduce the symptoms and the duration of the therapy. Moreover, DCI is safe when used in low/medium dosages [21] and may substitute the effects of both metformin and AIs without the risk of important side effects. As such, DCI can be used also as supportive care during the long-term follow up to reduce the risk of recurrence after suspending the therapy with progestogens.

Testing the hypothesis

To assess the strength of our hypothesis, we are planning clinical trials to compare the effectiveness of DCI plus standard progestogen-based therapies *versus* progestogens alone in women with EH (without atypia) and with different baseline features, in terms of insulin sensitivity and BMI. Our purpose is to demonstrate that DCI, once supplemented together with progestogens, especially to insulin resistant and overweight/obese women with EH, can reduce the duration of the hormonal treatments and concomitantly improve the metabolic status of these patients. This is a very critical point, considering that very often insulin resistant and obese patients with EH approach fertility-sparing procedures to seek pregnancy in the near future. For these patients the length of the hormonal therapies is a remarkable factor to take into account.

While recent scientific literature features publications on the comparison between progestogen therapies with and without associated metformin, analogous studies with DCI have yet been published.

We do expect that DCI shortens the therapeutic duration of progestogen-based protocols to achieve a complete response from EH, in the same way of or better than metformin, with minimal risk of side effects.

Replying to possible objections against the hypothesis

One might argue that, by triggering testosterone production in the theca cells and down-modulating aromatase in granulosa cells, DCI supplementation may cause a hyperandrogenic status. This is particularly relevant in the case of hyperandrogenic patients, like those with insulin resistance.

However, we should keep in mind that the effect of DCI on the hormonal balance depends on the dosage [22].

Indeed, as reported by Gambioli et al., while high doses of DCI may heavily affect steroidogenesis, increasing testosterone levels and worsening patients’ clinical picture [27], low/medium dosages [21] of DCI in insulin-resistant patients improve insulin sensitivity and contributes to reduce testosterone levels. Hence, DCI has different clinical effects depending on the dosage and the patients’ characteristics. On these premises, low/medium dosages of DCI may represent an effective and safe therapeutic strategy for insulin resistant and obese women with EH.

Authors’ roles

The authors equally contributed to write and revise the present manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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