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Does Alpha-lipoic acid improve effects on polycystic ovary syndrome?

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Abstract. – Alpha-lipoic acid (ALA) plays a key role in many physiological processes, exerting anti-inflammatory, immunomodulatory, antioxidant, detoxifying, and insulin sensitizing activities. Since ALA improves insulin resistance (IR), it has been suggested that ALA could be beneficial it in the treatment of PCOS. The natural polyol *myo*-Inositol (*myo*-Ins) and its isomers (D-Chiro-Inositol, D-*Chiro*-Ins) has proven to improve PCOS features and clinical outcome, according to a compelling body of available studies. Few studies have proposed to strengthen the inositol effect by associating ALA. ALA does not seem to influence significantly reproductive hormones, while its beneficial effects are presumably restricted to the metabolic features of insulin resistant PCOS women. Therefore, ALA usefulness in improving inositol activity still awaits convincingly confirmation. Experimental studies as well as proper randomized, clinical trials should be specifically tailored to assess this hypothesis. In absence of reliable evidence, ALA should not be recommended in the routinary clinical management of PCOS, even if associated to *myo*-Ins.

Key Words:
Alpha-lipoic acid, Myo-Inositol, Steroidogenesis, Insulin resistance, Polycystic ovary syndrome.

Alpha-Lipoic Acid: A Molecule of Interest

Alpha-lipoic acid (ALA) was first isolated in 1937 from potatoes[1]. ALA is synthesized in plants and animals, while humans produce ALA in very low amounts. Potatoes, broccoli, spinach, tomatoes, Brussels sprouts, peas, brown rice contain great quantities of ALA; however, the most relevant source of ALA in human nutrition is provided by red meat (especially liver, heart, and kidney). Noticeably, humans absorb ALA in biologically active form only in few quantities. Moreover, ALA is rapidly metabolized, and then it does not accumulate appreciably in human tissues. In living organisms, ALA is found either in its oxidized (alpha lipoic acid, ALA) or in the reduced form (dhydrolipoic acid, DHLA)[2]. Data gathered up to now, showed that ALA plays a key role in many physiological processes, exerting anti-inflammatory, immunomodulatory, antioxidant, detoxifying, and insulin sensitizing activities[2]. Overall, this evidence prompted to speculate that ALA could be a promising nutraceutical/pharmaceutical support in the management of several conditions, including inflammation, immune system modulation, oxidation, tissue damage[3].

Namely, ALA demonstrated to exert beneficial effects in several gynecological settings, especially in pregnancy-related critical conditions. Oral and vaginal ALA supplementation has shown to be safe[4] and effective, as it promotes faster resorption of sub-chorionic hematoma in women with abortion threats[5]. Additionally, ALA reduces the incidence of uterine contractions during pregnancy, the preterm birth admissions rate[6], preventing the cervical shortening in women at risk of preterm birth[7], and mitigating the associated symptoms.

ALA and Insulin Resistance

It is worth of interest that recent investigations have established an intriguing link between ALA, diabetes, and insulin resistance (IR)[8]. Namely, it has been demonstrated that ALA can efficiently antagonize IR in different experimental and clinical settings[9].

Since IR has been surmised to participate in the pathogenesis of Polycystic Ovary Syndrome

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(PCOS), it has been hypothesized that ALA supplementation could be beneficial for harnessing some PCOS symptoms[10].

PCOS is a syndrome with a complex and still poorly understood etiology, characterized mainly by chronic ovulation dysfunction and hyperandrogenism[11]. Noticeably, in a fraction of PCOS women, deregulation of glucose pathway and insulin resistance are involved in the pathogenesis of that syndrome[12]. Consequently, several antidiabetic drugs, like metformin[13], have been tested to evidence if some befit – if any – could be triggered in such a cohort of patients. Promising preliminary results have fostered research into new directions to identify new molecules able in counteracting IR. Among those substances, the natural polyol *myo*-Inositol (*myo*-Ins) and its isomer (D-Chiro-Inositol, D-*Chiro*-Ins), seems to play a pivotal role in exerting several pleiotropic actions[14], including the modulation of insulin transduction and glucose metabolism in a wide array of animal and human tissues[15]. Furthermore, inositol-based treatments improve PCOS features and clinical outcome, according to a compelling body of published studies.

Namely, a recent meta-analysis carried out on nine randomized clinical trials (RCTs) – comprising 247 cases and 249 controls – evaluated the efficacy of Inositol-based therapy in PCOS[16]. In those studies, changes in fasting insulin (primary parameter), HOMA-IR index, testosterone, androstenedione, and sex hormone binding globulin (SHBG) plasma levels (secondary parameters) were assessed throughout the survey. Significant decreases in fasting insulin and homeostasis model assessment (HOMA) index have been observed after *myo*-Ins supplementation. A slight trend toward a reduction of testosterone concentration by *myo*-Ins with respect to controls was also found, whereas androstenedione levels remained unaffected. The subgroup's meta-analysis demonstrated that a meaningful increase in serum SHBG could be recorded only when *myo*-Ins was administered for at least 24 weeks. These results showed that *myo*-Ins were instrumental in effectively reducing IR, while antagonizing the associated hyperandrogenism (reduction in free testosterone levels).

Unfortunately, a fraction of inositol-treated patients demonstrated inositol resistance and was refractory to the treatment[17]. At least in part, this can be ascribed to poor bioavailability of *myo*-Ins after oral assumption[18], besides that the concomitant participation of other factors cannot be discarded.

Therefore, a few studies have proposed to strengthen the inositol effect by associating ALA.

ALA Supplementation in PCOS Treatment

In a very preliminary report, Masharani et al[19] administrated ALA (600 mg twice a day for 16 weeks) in a group of six lean women affected by PCOS. Despite the absence of severe insulin resistance in this group, ALA treatment lowered triglyceride levels, improved insulin sensitivity and menstrual frequency. However, this study is seriously flawed by inconsistency in the number of patients.

Few years later, it was observed that a daily combination of 400 mg of ALA plus inositol (1 g *myo*-Ins) for at least 3 months reduced IR and glucose-load induced hyperinsulinemia in a group of thirty-four PCOS patients, also improving gonadotropin secretion[20]. Limitations of the study are related to the lack of control groups (ALA- or *myo*-Ins-only treated patients), and the excessively small number of patients.

A further article[21] has assessed the effectiveness of the combined administration of *myo*-Ins and ALA in PCOS patients that previously undergone intracytoplasmatic sperm injection (ICSI). Thirty-seven normal-weight patients affected by PCOS, previously treated with *myo*-Ins without achieving pregnancy, were re-enrolled and further given a combined treatment of *myo*-Ins (2 g/day) plus ALA (800 mg/day). After ALA supplementation, a significant reduction of insulin levels was observed when data were compared with the previous *myo*-Ins treatment. Unexpectedly, BMI was also reduced, suggesting that ALA supplementation exerted some metabolic effects, albeit no significant changes in the ratio of LH/FSH were observed after ALA. Noticeably, about 52% of patients achieved pregnancy under ICSI. Given that those patients showed normal BMI index, and no compelling evidence of insulin resistance was provided by the study, these results can hardly be ascribed to the mild reduction observed in insulin levels. Therefore, other unknown factors should have been investigated to explain the recorded outcome.

A pilot cohort study[22] was performed to investigate the effects of a combined treatment with ALA (800 mg/day) and *myo*-Ins (2 g/day) for six months (Table I). Forty overweight/obese (BMI > 25) women with PCOS were enrolled and clinical, hormonal, and metabolic parameters were assessed before and after treatment. The authors observed an increase in the number of menstrual

Table I. Schematic brief of clinical results on treatment with ALA and/or myo-Ins.

References	Patient and Clinical manifestation	Treatment	Results
Masharani et al[19] (2010)	· 6 women PCOS · 23-34 yrs · BMI = 22 ± 1.4 · Any other medical problems	· ALA 600 mg · Twice a day for 16 weeks	· Lowering of triglyceride levels · Improvement in insulin sensitivity · Improvement menstrual frequency
Genazzani et al[20] (2014)	· 34 women PCOS · 26.4 ± 0.8 yrs · BMI > 25 · (n=28) hyperinsulinemic · (n=6) normoinsulinemic	· ALA 400 mg with inositol (1 g myo-Ins) · For at least 3 months.	· Both groups demonstrated the reduction of LH and LF/FSH ratio · Only hyperinsulinemic PCOS showed the significant decrease of HOMA index · Hyrinsulinemic PCOS showed the significant decrease of HOMA index · Normoinsulinemic patients showed a perfectly normal HOMA index both before and after the treatment interval · Reduced IR and glucose-load induced hyperinsulinemia · Improving gonadotropin secretion
Rago et al[21] (2015)	· 37 women PCOS · normal-weight	· Previously treated with myo-Ins without achieving pregnancy · Combined treatment of myo-Ins (2 g/day) plus ALA (800 mg/day)	· After ALA supplementation a significant reduction of insulin levels · BMI was also reduced · No significant changes in the ratio LH/FSH were observed after ALA
De Cicco et al[22] (2017)	· 40 women PCOS · BMI > 25	· ALA 800 mg/day and myo-Ins 2 g/day · For six months	· Increase in the number of menstrual cycles · Improvement of the hormonal milieu · Decrease of BMI after 6 months of treatment
Genazzani et al[23]	· 32 women PCOS: · 24.5 ± 1.3 yrs · BMI > 25	· ALA 400 mg/day · 3 months	· No statistically significant changes in the hormonal parameters were recorded · Metabolic markers – namely insulin, glucose levels and BMI/ HOMA index – were appreciably improved upon ALA treatment
Genazzani et al[24] (2019)	· 76 PCOS women · 25.6 ± 1.3 yrs · BMI ≥ 25.1 and ≤ 31.3 · (n=18) amenorrhoeic condition: · (n=45) oligomenorrhea (menstrual cyclicity above 45 days or more), · (n=13) eumenorrhea	· Group A (n=24): myo-Ins 1 g/day · Group B (n=24): ALA 400 mg/day · Group C (n=28): myo-Ins 1 g/day and ALA 400 mg/day	· Only myo-Ins induces relevant endocrine modifications · ALA improves metabolic parameters and insulin levels · The combined formula (ALA + myo-Ins) triggers both metabolic and endocrine effects, showing a remarkable additive outcome
Fruzzetti et al[27] (2020)	· 44 women PCOS · BMI = 27.05 ± 4.17 · 25% of the women were insulin resistant (HOMA-IR > 2.5)	· myo-Ins 2000 mg/day, and ALA 800 mg/day	· Shortening of the cycle length, obtained in 86% of patients after 6 months of treatment. · After an initial decrease during the first 6 months, BMI returned to the starting values
Fruzzetti et al[28] (2020)	· 71 women PCOS · 21.56 ± 4.77 · 26.97 ± 5.15	· Group A: (n=43) myo-Ins, 2000 mg/day and ALA 800 mg/day · 6 months of treatment · Group B: (n=28) myo-Ins, 1000 mg/day and ALA 800 mg/day · 6 months of treatment	· Group A showed a significant change of BMI and E2 and AUC-insulin · Group B showed a significant change of FSH and LH and E2 but no changes in the metabolic parameters · Cycle length was improved in 85.7% of patients in group A and in 50% of those in group B

cycles, an improvement of the hormonal milieu, and a decrease of BMI after 6 months of treatment. However, those results seem to be independent from insulin modulation, as parameters belonging to insulin and glucose metabolism apparently did not change in a significant manner. Moreover, the independent effects exerted either by myo-Ins or ALA were not assessed and the clinical results cannot be ascribed to the addition of ALA as myo-Ins has already been demonstrated to improve the hormonal and metabolic profile of such patients when given as single drug. Consequently, the causative role of ALA in improving PCOS features in those patients – in which insulin-related pathways do not seem to be modulated – should be seriously questioned.

A further study[23] carried out to evaluate the efficacy of ALA on PCOS patients, investigated the hormonal and metabolic parameters of 32 obese PCOS women. Patients were treated for 3 months with ALA, 400 mg/day. No statistically significant changes in the hormonal parameters (LH, FSH, estradiol, androstenedione, and testosterone) were recorded. On the contrary, metabolic markers – namely insulin, glucose levels and BMI/ HOMA index – were appreciably improved upon ALA treatment. This study clearly pointed out how ALA could be instrumental in triggering significant metabolic improvements, while the overall endocrine picture was left unchanged. These results should be emphasized, given that they demonstrate that amelioration of the metabolic profile cannot be enough in correcting the hormonal imbalance.

Curiously, these results were at odds with those reported in a previous study[21] from the same authors, albeit this discrepancy was unnoticed, and no clear-cut explanation for this conundrum has been offered.

Moreover, the same group has authored in 2019 a retrospective study to evaluate the effects of *myo*-Ins, ALA, and the combination of the two molecules in overweight/obese women with PCOS[24]. The study involved 76 PCOS women, with BMI $\geq$ 25.1. Patients were partitioned into three groups according to the treatment, as follows: Group A (n=24): *myo*-Ins 1 g/day; Group B (n=24): ALA 400 mg/day; Group C (n=28): *myo*-Ins 1 g/day plus ALA 400 mg/day. After three months, data were recorded showing that ALA improves metabolic parameters and insulin levels, significantly better when compared to those obtained in the group treated with *myo*-Ins alone. However, as previously noticed, ALA was unable to modulate endocrine parameters, including LH, while only *myo*-Ins induces relevant endocrine modifications. On the contrary, the combined formula (ALA + *myo*-Ins) triggers both metabolic and endocrine effects, showing a remarkable additive outcome.

In detail, this study shows that *myo*-Ins administration improves several hormonal and metabolic parameters according to published literature[25]. When ALA is associated to myo-Ins, several metabolic parameters and insulin response were further ameliorated. Namely, ALA administration decreases IR. Yet, no modulation of reproductive hormones, such as LH and FSH was noticed. These results suggest that ALA significantly improves the glucose pathway but does not entail modulation of main endocrine parameters involved in PCOS pathogenesis, like LH and FSH. A significant modulation of LH and FSH can be obtained only when *myo*-Ins is associated to ALA, as evidenced by previously reports[21,26].

Recently, a retrospective study to evaluate the effects of a long-term treatment with ALA combined with *myo*-Ins on clinical and metabolic features of women with PCOS has been published[27]. Forty-four women with PCOS and BMI averaging 27.05 ± 4.17, were considered eligible for the study and were treated with *myo*-Ins (2000 mg/day), and ALA (800 mg/day). Only 25% of the women were insulin resistant (HOMA-IR > 2.5). Information about cycle length and BMI after 6, 12, and 24 months was also recorded. Thirty healthy subjects with normal cycles and no symptoms of hyperandrogenism were included as a control. The most relevant result consisted in the shortening of the cycle length, obtained in 86% of patients after 6 months of treatment. Unexpectedly, after an initial decrease during the first 6 months, BMI returned to the starting values. This study is seriously biased by the lack of a proper control group, clinical heterogeneity of PCOS patients, and by the inadequate size dimension of the pooled sample.

Another retrospective study was published by the same group[28] to evaluate the effects of ALA associated with two different doses of *myo*-Ins on the clinical and metabolic features of women with PCOS. Seventy-one women with PCOS were considered eligible for the study and were partitioned into two groups: 43 patients received *myo*-Ins, 2000 mg/day plus ALA, 800 mg/day; 28 received *myo*-Ins, 1000 mg/day plus ALA, 800 mg/day. Thirty healthy subjects with normal cycles and no symptoms of hyperandrogenism

were included as controls for baseline characteristics. Hormonal and metabolic parameters were evaluated before and after 6 months of treatment. The results show an improvement of menstrual cycles in women with PCOS, as well as of many endocrine and metabolic parameters. Yet, the most impressive results were obtained only with higher doses of *myo*-Ins (85.7% *vs.* 50% obtained with low doses). These findings clearly evidence that myo-Ins plays a prominent role in ameliorating mostly of the PCOS features, while ALA contribution is debatable.

Perspectives

ALA seems to be a promising agent in the management of a wide array of clinical conditions, characterized by chronic inflammation, oxidative processes, and deregulated immunological reactions. Indeed, several studies provided a reliable amount of data related to therapeutic use of ALA in different disorders such as cancer, neurodegenerative diseases and neuropathy, tissue regeneration, ischemia-reperfusion injury, diabetes, and insulin resistance[29,30]. Since ALA improves insulin resistance, it has been suggested that ALA could be beneficial it in the treatment of PCOS. However, only a fraction of PCOS women shows signs of IR, and, to date, insulin resistance is still not included among the distinctive diagnostic features of PCOS31. Moreover, the beneficial effects exerted by *myo*-inositol on PCOS can be explained only partially by the modulation exerted by *myo*-Ins upon glucose metabolism. Indeed, *myo*-Ins treatment is highly effective in women that do not show either insulin resistance or features of metabolic syndrome[32,33]. On the contrary, compelling evidence suggests that *myo*-Ins can modify the hormonal pattern of PCOS by acting through other pathways - including hormonal responsiveness and cytoskeleton rearrangement[34] – that are independent from the metabolomic fingerprint. According to clinical data, ALA does not seem to influence significantly the reproductive hormone pattern, while its beneficial effects are presumably restricted to the metabolic features of insulin-resistant PCOS women. Therefore, ALA usefulness in improving inositol activity still awaits convincingly confirmation. Experimental studies as well as proper randomized, clinical trials should be specifically tailored to assess this hypothesis. Currently, no investigations have been so far carried out *in vitro* to ascertain if ALA could modify the endocrine pattern of response of both normal and PCOS ovary cells (theca and granulosa). Based on the available clinical findings, we can surmise that ALA is probably ineffective in influencing LH/FSH dependent pathways, its regulation of insulin levels notwithstanding. Moreover, in the reported clinical trials, the combination of Inositol plus ALA has not demonstrated any superiority when compared to treatments with *myo*-Ins alone. Furthermore, unexpected long-term effects of ALA upon glucose metabolism should still be carefully assessed[35].

Conclusions

According to the observed effect exerted by ALA on glucose metabolism, some studies suggested that ALA could be beneficial in reliving symptoms and biochemical features of PCOS when given in association with myo-Ins. However, evidence is scarce, and ALA does not seem to influence significantly reproductive hormones, while its beneficial effects are presumably restricted to the metabolic features of insulin resistant PCOS women. Therefore, further investigations are warranted to substantiate the clinical utility of ALA supplementation in PCOS subjects. Specifically, randomized clinical trials should be tailored to assess this hypothesis. In the meantime, ALA should not be recommended in the routine clinical management of PCOS, even if associated to myo-Ins.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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