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ORIGINAL ARTICLE

Modulatory effects of alpha-lipoic acid (ALA) administration on insulin sensitivity in obese PCOS patients

A. D. Genazzani[1] · K. Shefer[1] · D. Della Casa[1] · A. Prati[1] · A. Napolitano[1] · A. Manzo[1] · G. Despini[1] · T. Simoncini[2]

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Abstract
Purpose To evaluate the efficacy of alpha-lipoic acid (ALA) administration on hormonal and metabolic parameters of obese PCOS patients.
Methods A group of 32 obese PCOS patients were selected after informed consent. 20 patients referred to have first grade relatives with diabetes type I or II. Hormonal and metabolic parameters as well as OGTT were evaluated before and after 12 weeks of ALA integrative administration (400 mg per os every day).
Results ALA administration significantly decreased insulin, glucose, BMI and HOMA index. Hyperinsulinemia and insulin response to OGTT decreased both as maximal response (Δmax) and as AUC. PCOS with diabetes relatives showed the decrease also of triglyceride and GOT. Interestingly in all PCOS no changes occurred on all hormonal parameters involved in reproduction such as LH, FSH, and androstenedione.
Conclusions ALA integrative administration at a low dosage as 400 mg daily improved the metabolic impairment of all PCOS patients especially in those PCOS with familiar diabetes who have a higher grade of risk of NAFLD and predisposition to diabetes.

Keywords PCOS · Hyperinsulinemia · Familiar diabetes · Alpha-lipoic-acid · Insulin resistance

✉ A. D. Genazzani
algen@unimo.it

[1] Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Via del Pozzo 71, 41100 Modena, Italy

[2] Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy

Introduction

Although polycystic ovary syndrome (PCOS) has been widely studied, its etiology and diagnosis are controversial. The Consensus Meeting in Rotterdam [1] defined that the presence of PCOS needs to be present at least two of the following criteria: (1) chronic anovulation disorder (oligo- or anovulation up to amenorrhea); (2) clinical (acne, hirsutism) or biochemical signs of hyperandrogenism; and (3) presence of micro polycystic ovaries at ultrasound or presence of 12 or more follicles with a diameter of 2–9 mm in each ovary, and/or increased ovarian volume (> 10 ml) [2]. However, in this last decade, a new clinical aspect has been recognized as relevant for the syndrome: the dismetabolic feature of insulin resistance. Although insulin resistance is a specific biological adaptation that induces a compensatory hyperinsulinemia in approximately 70–80% of women with PCOS and overweight or central obesity, it occurs as well in 15–30% of lean women diagnosed with PCOS [1, 3] thus sustaining the hypothesis of a built-in predisposition to a metabolic impairment [4]. As a possible solution insulin sensitizers have been proposed to counteract such compensatory hyperinsulinemia together with a change in life-style [3, 5], and the best drug actually used is metformin, at variable dosages, depending on the severity of the glucose metabolic impairment [3, 6, 7]. However, even though metformin has been demonstrated as a safe drug, it induces various gastrointestinal side effects such as diarrhea, vomiting, nausea thus reducing the compliance [8].

Recently a new integrative approach to PCOS insulin resistance has been proposed using inositols in the two clinically active isoforms, i.e., myo-inositol (MYO) and D-chiro-inositol (DCI) [4]. Such approach stands on the fact that inositols are deeply involved in the post-receptorial signal transmission of several peptide hormones such as insulin,

TSH and FSH [4]. Moreover, hyperinsulinemic PCOS patients often show a reduced function/expression of the specific enzyme, i.e., epimerase, which converts MYO to DCI permitting the post receptor transduction [4, 9]. These facts explain, at least in part, the hyperinsulinemia that can be observed in lean PCOS patients [4]. The integration with MYO [10] or DCI [11] or with a combination of both these inositols [12] significantly improve the metabolic impairment of PCOS patients [4], especially those that have familiar predisposition to diabetes and take DCI [4].

In very recent times, another compound has been considered relevant to treat insulin resistance, that is alpha lipoic acid (ALA). In the animal model ALA has been demonstrated to modulate and increase glucose utilization trough the increase of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscles thus increasing glucose-transporter-4 (GLUT-4) [13, 14]. Recently ALA has been proposed as pleiotropic compound with potential therapeutic use in diabetes and other endocrine diseases [15, 16] such as PCOS [17] to improve dismetabolic-induced impairment. On such basis and evidences, we aimed to evaluate the effects of an integrative treatment with ALA on insulin sensitivity and hormonal parameters in a group of obese PCOS patients.

Materials and methods

Subjects

Among the many patients attending the outpatients Clinic of the Gynecological Endocrinology Centre at the University of Modena and Reggio Emilia, Italy, between June 2013 and December 2015, a group of overweight/obese PCOS patients [24.5 ± 1.3 years, mean ± standard error of the mean (SEM)] requiring treatment for their condition ($n = 32$), were enrolled for this study. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were those according to the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology consensus meeting to diagnose the presence of PCOS. The diagnosis of PCOS was based on the association of at least two of the following criteria: (a) oligomenorrhea with inter-menstrual intervals longer than 45 days, (b) clinical (acne, hirsutism) or biochemical signs of hyperandrogenism, (c) presence of micro polycystic ovaries at ultrasound. In addition, patients had to fulfill the following criteria (e) absence of enzymatic adrenal deficiency and/or other endocrine disease, including diabetes, (f) normal PRL levels (range 5–25 ng/ml), (g) no hormonal treatment for at least 6 months before the study, (h) body mass index (BMI) above 25.

Table 1 Hormonal characteristics of all PCOS patients under study

PCOS patients ($n = 32$)	LH (mIU/ml)	FSH (mIU/ml)	Estradiol (pg/ml)	*A* (ng/ml)	*T* (ng/ml)	Insulin (μU/ml)	Glucose (mg/dl)	Trygliceride (mg/dl)	GOT (U/l)	GPT (U/l)	BMI	HOMA index
Baseline	10.1 ± 1.3	5.50.4	52.8 ± 9.5	325.7 ± 47.1	0.4 ± 0.04	14.9 ± 2.1	92.1 ± 1.9	94.0 ± 10.0	21.6 ± 1.6	24.5 ± 2.8	32.5 ± 1.9	3.4 ± 0.5
Under ALA	10.7 ± 2.0	5.4 ± 0.4	78.7 ± 20.0	320.0 ± 51.8	0.3 ± 0.04	9.8 ± 1.2	87.2 ± 2.2	79.5 ± 5.9	19.0 ± 1.4	20.5 ± 3.8	30.5 ± 1.9	2.1 ± 0.3
p vs baseline						***	*		*		***	***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.0007$ vs baseline

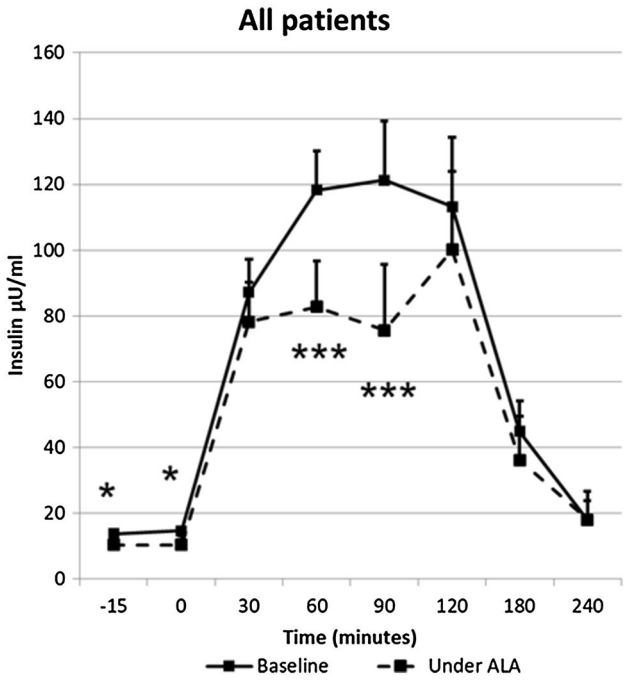

Fig. 1 Insulin response to oral glucose tolerance test (OGTT) in all patients. *$p < 0.05$; ***$p < 0.00001$

None of the subjects recruited was taking medications (e.g., steroids, oral contraceptives, metformin) within 3 months of the evaluation. All the patients were interviewed in regards to the presence of one or more diabetic relatives (parents and/or grandparents). From the anamnestic investigation 20 patients out of 32 reported first grade diabetic relatives.

All patients were administered alpha-lipoic acid (ALA) (400 mg) once a day (Laborest, Nerviano, Milan, Italy), every morning around 10 a.m., for at least 3 months (12 weeks). No changes of life style or diet were required from the patients. All patients were studied the first time on day 3–6 of the menstrual cycle, if present. The post treatment endocrine control was performed at least at the 12th week of treatment or few days later, so that to be on day 3–6 of the first menstrual cycle occurring after the treatment interval.

All patients were evaluated for LH, FSH, estradiol (E2), progesterone (P), androstenedione (A), insulin, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT); HOMA index was computed to estimate the sensitivity to insulin [18]. Oral glucose tolerance test (OGTT), for insulin and glucose determinations, was performed sampling before and 30, 60, 90, 120, 180 and 240 min after the oral assumption of 75 g of glucose, before and after the 12 weeks of integrative treatment.

Hyperinsulinemic response is recognized when insulin plasma levels are above 50 µU/ml within 90 min from glucose load [19]. The mean treatment interval was 94.5 ± 3 days [mean ± standard error of the mean (SEM)], being the range of 89–110 days. The study protocol was approved as observational study by the Human Investigation Committee of the University of Modena and Reggio Emilia, Italy (Registration No. 181/12).

Assay

All samples were assayed in duplicate in the same assay. Plasma LH and FSH concentrations were determined using a previously described immunofluorimetric assay (IFMA) [20]. Intra-assay and inter-assay coefficients of variation were 5.1 and 7.3%, respectively. Plasma E2, P, A were determined by radioimmunoassay (Radim, Pomezia, Rome, Italy) as previously described [6]. Within- and between-assay coefficients of variation were 4 and 9.1%. Plasma insulin was

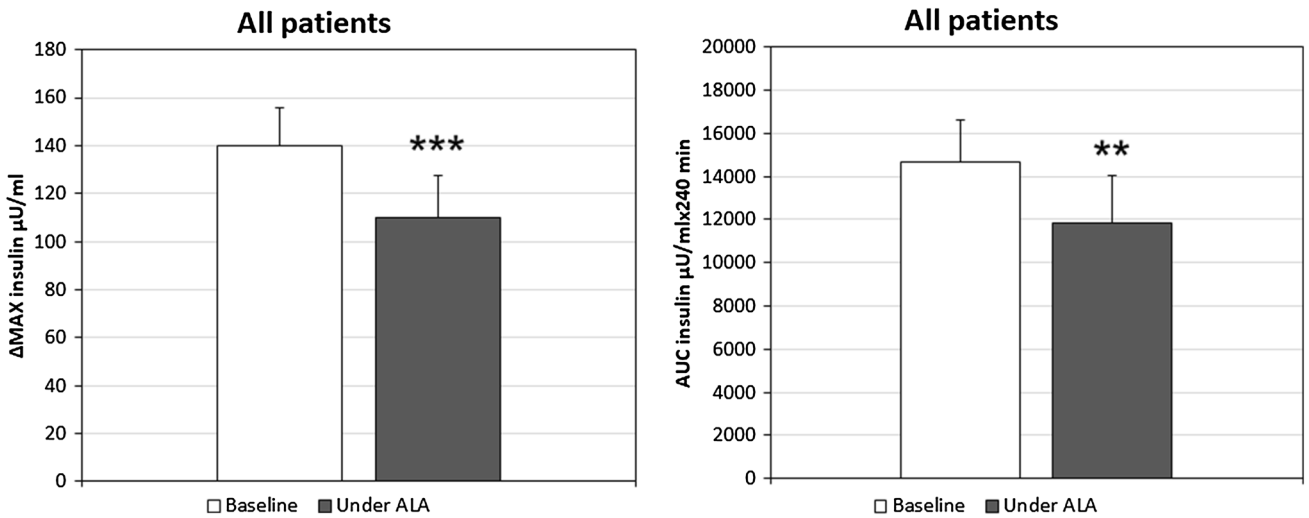

Fig. 2 Maximal insulin response (Δmax) of insulin to OGTT (left) and AUC of insulin (right). **$p < 0.008$; ***$p < 0.001$

Table 2 Hormonal characteristics of PCOS patients according to the presence or absence of diabetic relative(s)

PCOS patients	LH (mIU/ml)	FSH (mIU/ml)	Estradiol (pg/ml)	*A* (ng/ml)	*T* (ng/ml)	Insulin (μU/ml)	Glucose (mg/dl)	Trygliceride (mg/dl)	GOT (U/l)	GPT (U/l)	BMI	HOMA index
Diabetic relatives ($n = 20$)												
Baseline	9.2 ± 1.1	5.7 ± 0.5	51.1 ± 19.0	281.6 ± 58.1	0.33 ± 0.06	15.5 ± 2.9	92.6 ± 3.3	91.5 ± 17.5	23.4 ± 2.2	27.5 ± 4.1	35.5 ± 1.5	3.2 ± 0.6
Under ALA	8.9 ± 1.5	5.5 ± 0.4	65.1 ± 15.0	277 ± 37.2	0.3 ± 0.03	10.3 ± 1.6	88.9 ± 2.2	75.7 ± 7.6	18.8 ± 1.2	22.9 ± 4.9	32.5 ± 2.2	2.2 ± 0.3
p vs Baseline						$p < 0.01$		$p < 0.01$	$p < 0.02$		$p < 0.002$	$p < 0.03$
No diabetic relatives ($n = 12$)												
Baseline	8.7 ± 1.6	4.9 ± 0.4	49.8 ± 15.3	428 ± 113	0.4 ± 0.06	14 ± 3.3	95 ± 3.8	89.3 ± 18.6	19 ± 1.4	19.5 ± 2.4	30.1 ± 3	3.3 ± 0.7
Under ALA	13.6 ± 4	5 ± 0.5	80 ± 35.2	391.6 ± 106	0.4 ± 0.08	8.8 ± 1.1	82.8 ± 3.2	85.8 ± 5.4	18.8 ± 2.6	16.6 ± 3	27.3 ± 1.9	1.8 ± 0.2
p vs baseline						$p < 0.5$	$p < 0.009$				$p < 0.05$	$p < 0.04$

determined using an immunoradiometric assay (Biosource Europa S.A., Nivelles, Belgium). Within- and between-assay coefficients of variation were 4.2 and 10.9%.

Statistical analysis

Data are expressed as mean (SEM). We tested data for significant differences between groups, after analysis of variance (one-way ANOVA), using Student's *t* test for paired data (baseline vs. under treatment).

The area under the curve (AUC) of OGTT (AUC, subtracted from the baseline value) was computed using the trapezoid formula so that to evaluate the insulin response to oral glucose load. The maximal response (Δmax) to the stimulation test was computed as the difference between the maximal hormonal response and the hormonal concentration before the stimulation (time 0).

HOMA index was computed to estimate the sensitivity to insulin [18] since it is considered the main index of the metabolic syndrome and a common link between the coexisting abnormalities; it can be calculated by homeostasis model assessment of insulin resistance (HOMA-IR) as (fasting insulin mU/l) × (fasting glucose mmol/l)/22.5 [18]. The cutoff value we used is 2.71 as previously stated [18, 19] while it is 2.5 for children and adolescents [21].

Results

Table 1 summarizes the hormonal characteristics of all PCOS under study. As it can be seen, ALA administration significantly improved various parameters such as insulin, glucose, GOT, BMI and HOMA index. ALA treatment was able to positively modulate the response of insulin to the glucose load (OGTT) (Fig. 1). In particular insulin response decreased both in terms of maximal response (Δmax) and of AUC (Fig. 2).

When PCOS patients were reconsidered subdividing them in 2 groups according to the presence or absence of diabetic relative(s), interesting results were observed.

As it can be seen in Table 2, both groups showed significant changes for insulin plasma levels, BMI and HOMA index, but only PCOS with diabetes relatives showed the decrease also of triglyceride and GOT, while PCOS with no diabetic relatives showed the decrease of glycaemia.

Interestingly no changes were observed in both groups of PCOS for all hormonal parameters involved in reproduction such as LH, FSH or in the hyperandrogenic condition such as androstenedione (Table 2).

When considering the response to OGTT we observed the significant improvement of insulin sensitivity in both groups

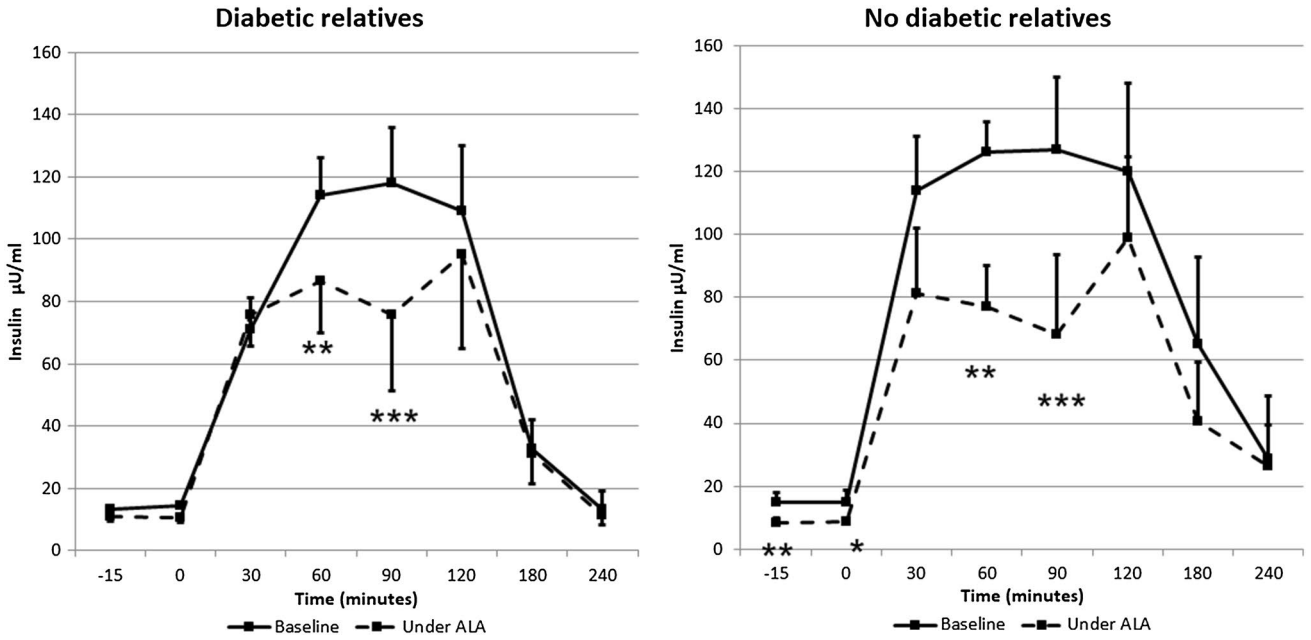

Fig. 3 Insulin response to oral glucose tolerance test (OGTT) in patients with (left) or without (right) diabetic relatives. $^{**}p < 0.004$; $^{***}p < 0.0008$

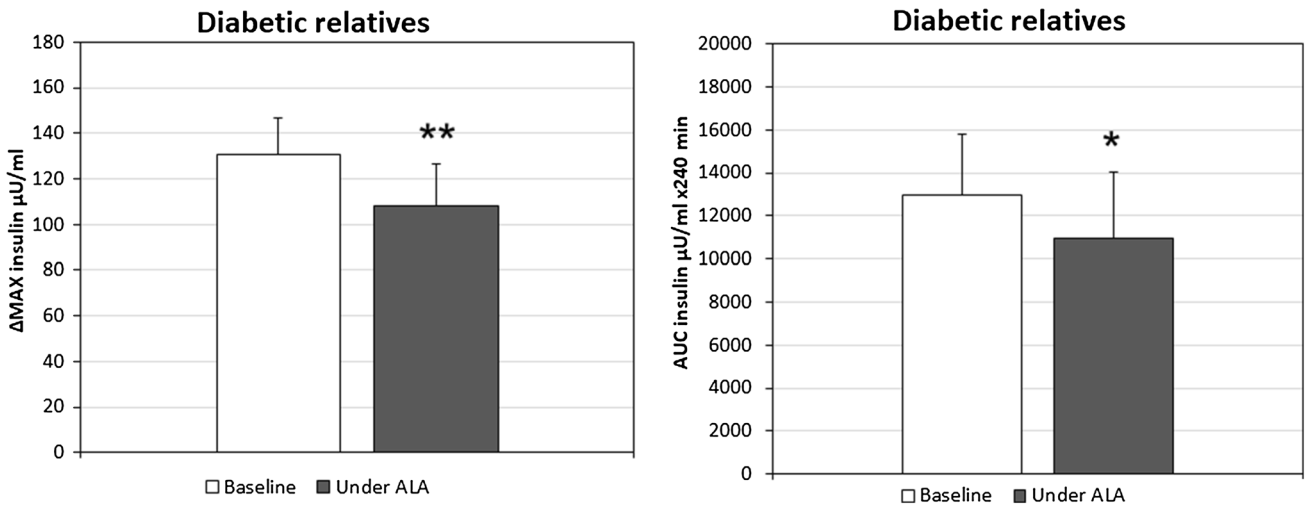

Fig. 4 Maximal insulin response (Δmax) of insulin to OGTT (left) and AUC of insulin (right) in patients with diabetic relatives. $^{*}p < 0.05$; $^{**}p < 0.006$

since the insulin response to glucose load decreased (Fig. 3a, b) as well as both Δmax and AUC of insulin (Figs. 4, 5).

Discussion

The present study demonstrated that the integrative administration of ALA at a low dosage as 400 mg die was able to improve insulin sensitivity in obese PCOS patients, independently from the presence or not of the familiar predisposition to diabetes.

Previous report by Masharani et al. [17] demonstrated that ALA administration at the high daily dosage of 1200 mg was effective in reducing triglyceride plasma levels and improving insulin sensitivity in a group of PCOS patients. Our data are in perfect agreement with these observation using a lower dosage and gave more insights on the metabolic impairments of obese PCOS.

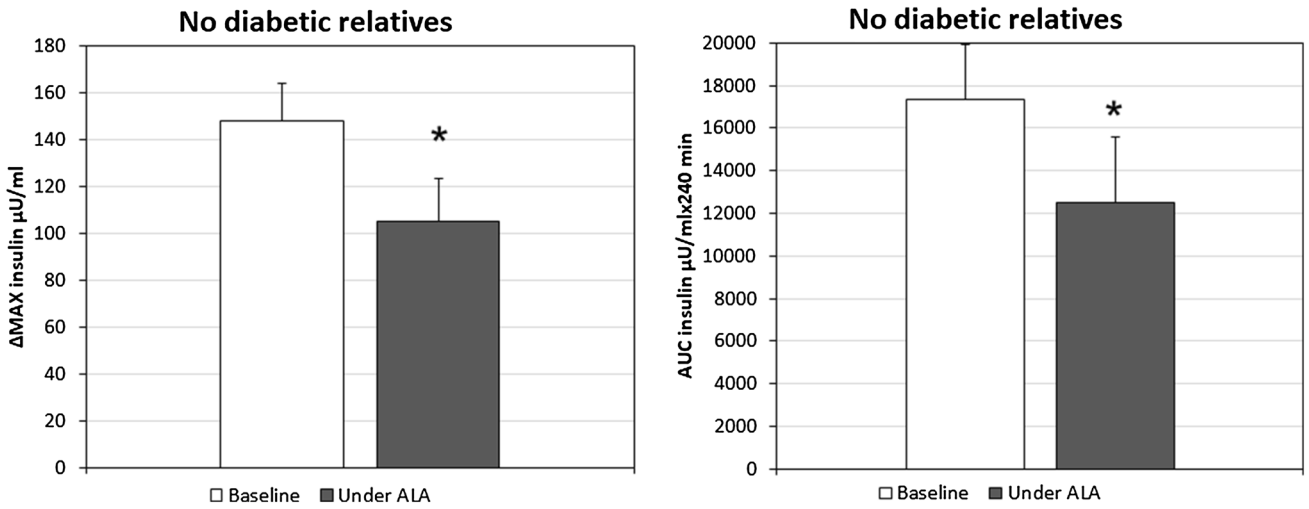

Fig. 5 Maximal insulin response (Δmax) of insulin to OGTT (left) and AUC of insulin (right) in patients without diabetic relatives. *$p < 0.05$

Similarly to previous studies on the efficacy of inositols [4, 10, 11], for the first time, our study on the use of ALA considered obese PCOS patients according also to the presence or absence of familiar diabetes. In previous studies on obese PCOS this aspect has been considered as extremely relevant when dealing on the choice of the integrative treatment of the metabolic impairments of the syndrome [4, 11, 22]. In our study ALA improved insulin sensitivity, as demonstrated by the reduced AUC and Δmax of insulin under glucose load, and by the reduced HOMA index, on the whole group of PCOS patients independently from to the presence or absence of familiar diabetes. Such positive effect of ALA on PCOS patients with diabetic relatives is of extreme interest since support what previously reported in animal models and in humans. These studies demonstrated that the presence of diabetes type II downregulates the expression of lipoic acid synthase (LASY) which is responsible of the synthesis of ALA inside the mitochondria of mammalians [23, 24]. In fact reduced endogenous ALA synthesis induces a decrease in mitochondrial lipoic acid that induces a lower glucose uptake in skeletal muscle cells that is at the basis of insulin resistance [24]. Endogenous ALA modulates glucose utilization through the increase of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscles [4] thus increasing glucose-transporter-4 (GLUT-4) [14, 25]. Our data consistently demonstrated that ALA integrative administration (mimicking endogenous ALA) eliminated most of the metabolic impairment of all PCOS subjects under study. Practically ALA administration improved insulin sensitivity especially in those patients with diabetic relatives (i.e., those with a lower LASY function) and in these patients ALA administration overcome the impairment due to defect in function and/or mitochondrial LASY synthesis, in agreement with previous studies [23, 24].

It is interesting to note that even though both groups of PCOS patients showed the reduction of insulin plasma levels, only PCOS patients with a familiar diabetes showed, as additional fact, the significant decrease of triglyceride and GOT plasma levels (GPT did not make to reach the significance in our study) thus supporting the hypothesis that ALA administration has a specific efficacy also on liver. Though we did not perform an ultrasound of liver to our patients to assess the presence of a liver steatosis as index of non-alcoholic fat liver disease (NAFLD), a recent review states that NAFLD is a finding in a high percentage of PCOS patients [26] and the combination of PCOS with obesity and insulin resistance (IR) is a dangerous cocktail that triggers not only NALFD but also, at a high grade, the occurrence of diabetes type 2 [26, 27]. The fact that ALA administration decreases the GOT levels which are close to the high level of normality in the group of obese PCOS patients with familiar diabetes clearly suggests that ALA greatly improved and/or protected liver function in these patients, reducing the risk to develop a liver impairment such as a NAFLD and, later, type II diabetes.

Our study let us make another interesting observation. As everyone knows, inositols have been demonstrated to be greatly helpful in PCOS metabolic impairment [4] and their utilization is of great relevance to improve not only the metabolic aspects [4, 10, 11, 22] but also the fertility problems [28, 29]. Indeed, recently, various studies have demonstrated that also the combination of ALA with MYO and/or DCI are effective in resolving the metabolic, endocrine and reproductive disease of PCOS patients both with or without familiar diabetes [2, 30]. According to our data, after ALA administration, no changes of both gonadotropins were observed, as well as of androgens (i.e., androstenedione and/or testosterone). Our present data let

us infer that when administering ALA, though insulin plasma levels and insulin response to OGTT are greatly improved, only the metabolic imbalance is resolved with no effect on the hormonal profiles of reproduction. Though our data seem to be in contrast with previous studies where ALA was used in combination with inositols [2] but it has to be mentioned that inositols have been demonstrated to be intracellular second messenger not only of insulin signal but also of TSH and FSH [4, 31]. In fact, on the contrary to ALA administration alone, the combination of ALA + inositols not only modulate insulin plasma levels but also, thanks to inositols, improved the reproductive pathways. Any improvement on FSH signal transduction might be relevant in the restoration of a correct ovarian stimulation and reproductive function. These facts explain why the combination of ALA plus MYO [2] or plus DCI [30] have been demonstrated effective in improving at the same time both metabolic and reproductive impairments, also in PCOS with familiar diabetes [2].

In conclusion our study demonstrated the efficacy of ALA integrative administration at a low dosage as 400 mg die on insulin resistance in all PCOS patients. In addition to metabolic impairment ALA integration improved also liver function in those PCOS patients with familiar diabetes who have a higher risk of NAFLD and diabetes. Our data sustain the relevant role of the ALA on PCOS metabolic disease.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent Informed consent was obtained from all patients participating in the study.

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