Effects of a Combination of Alpha Lipoic Acid and Myo-Inositol on Insulin Dynamics in Overweight/Obese Patients with PCOS

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Abstract

Myo-inositol increases insulin sensitivity in insulin resistant patients with PCOS since it improves the insulin post-receptor pathways. Since previous reports suggested that also alpha lipoic acid has specific positive effects on glucose control, we aimed to evaluate the specific effects of a combination of alpha lipoic acid and myo-inositol on insulin resistance in obese patients with PCOS.

We studied a group of obese PCOS patients (n=34, BMI= 30.1 ± 0.9) according to the revised 2003 Rotterdam consensus diagnostic criteria. Among the PCOS patients, 16 out of 34 had diabetic type II relatives (parents and/or grandparents). Patients were administered a combination of alpha lipoic acid (400 mg) and myo-inositol (1 gr.) (Sinopol, Laborest, Italy) every day for at least 12 weeks. Patients underwent to baseline hormone determination and to an oral glucose tolerance test (OGTT) before and at the 12th week of treatment.

After the treatment interval, HOMA index decreased significantly as well as the glucose-induced insulin response with no changes of BMI. Interestingly the treatment did not change insulin dynamics in normo-insulinemic PCOS while significant insulin decrease was observed in hyperinsulinemic PCOS patients. 87.5% (14 out of 16) of the PCOS patients with diabetic relatives resulted to be among the hyperinsulinemic patients. Hyperinsulinemic PCOS patients showed the significant decrease of the insulin plasma levels (from 14 ± 2.1 to 9.5 ± 0.8 µU/ml, p<0.05), of HOMA index (from 3.3 ± 0.4 to 2.1 ± 0.1, p<0.05) and showed the significant decrease of insulin response to glucose load.

In conclusion, the combination of alpha lipoic acid plus MYO was effective in improving insulin sensitivity in obese PCOS patients that resulted to be hyperinsulinemic under OGTT. Moreover the more peculiar and relevant positive changes were observed in obese PCOS with diabetic first grade relatives.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common diseases affecting women during their reproductive life since it affects 5-21% of them [1]. The Consensus Meeting in Rotterdam [2,3] defined that PCOS requires two or more of the following requirements: chronic anovulation disorder (oligo- to anovulation or amenorrhea), presence of hyperandrogenism (clinical and/or in laboratory tests) and ultrasound evidence of polycystic ovaries. Recently, an additional feature seems to be relevant for the syndrome: insulin resistance. Indeed, several studies reported that insulin resistance is common in PCOS patients, regardless of the body mass index (BMI). In fact, compensatory hyperinsulinemia due to insulin resistance occurs in approximately 80% of women with PCOS and central obesity as well as in 15–30% of lean women diagnosed with PCOS [3,4].

The cause of the insulin resistance observed in PCOS women is not yet clear, especially in lean patients, but a post-receptor defect that could affect glucose transport has been proposed [5-7]. Obesity exacerbates insulin resistance and it is a fundamental causal factor in the pathogenesis of anovulation and hyperandrogenism.

Beyond the reproductive consequences of PCOS, these patients are at high risk to develop metabolic abnormalities, mainly type II diabetes, starting from the hyperinsulinemia they might develop. Indeed, conversion from normal glucose tolerance to hyperinsulinemia due to impaired glucose tolerance and later to type II diabetes is accelerated in PCOS patients [8-13]. For this reason, many organizations recommend screening women with PCOS for glucose intolerance [14-16] at least with a 2-hour oral glucose tolerance test (OGTT). Based on such indications, early detection and lifestyle changes or pharmacological interventions have been reported to delay or block the development of type II diabetes [5,17].

Among the many possible intervention in PCOS, other than pharmacological treatments such as the use of metformin (5), various integrative compounds have been proposed such as the two isoforms of inositol, that is myo-inositol (MYO) and d-chiro-inositol (DCI), and alpha lipoic acid (ALA). Both inositols and ALA were reported to be effective in reducing the insulin resistance in PCOS patients [17-19]. While inositols are involved in the structure of the post receptor transduction of the signal induced by the linkage of insulin on its receptor [20], ALA has been demonstrated in the animal model to increase glucose utilization trough the increase of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscles.
[21] thus increasing glucose-transporter-4 (GLUT-4) [22,23]. It is interesting to observe that also metformin treatment seems to activate AMPK [24]. On such basis and evidences, we aimed to evaluate the effects of a combination of inositol (MYO) and ALA on insulin sensitivity and hormonal parameters in a group of overweight/obese PCOS patients.

Materials and Methods

Subjects

Among the many PCOS patients attending our outpatient Clinic between June 2012 and December 2013, a group of 44 PCOS overweight/obese patients, requiring treatment for their condition, were recruited for this study after informed consent. These patients were selected among those attending the Gynecological Endocrinology Center at the University of Modena and Reggio Emilia, Italy, according to the revised 2003 Rotterdam consensus diagnostic criteria for 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 35 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, g) body mass index (BMI) above 25.

Among the 44 patients, 8 preferred not to participate and/or requested a contraceptive method and were excluded from the study. Among the remaining 36 PCOS patients, 2 became pregnant within 6-8 weeks after starting the study. The patients finally considered for treatment were required from the patients. All patients were studied the first time on day 3-6 of the menstrual cycle. Control was performed at least at the 12th week of treatment or few intervals longer than 35 days, b) clinical (acne, hirsutism) or other endocrine disease, including diabetes, f) normal PRL levels, g) no hormonal treatment for at least 6 months after the study, h) body mass index (BMI) above 25.

Table 1: Biochemical parameters of PCOS patients (n=34) before and under treatment. Data are shown as mean (SEM).

| PCOS (n=34) | LH mU/ml | FSH IU/ml | LH/FSH | E2 pg/ml | P ng/ml | A ng/100 ml | Insulin μU/ml | PRL μU/ml | HOMA index | BMI |
|------------|----------|-----------|--------|----------|---------|-------------|---------------|-----------|------------|-----|
| Baseline   | 11.2 (0.6) | 6.4 (0.1) | 1.8 (0.1) | 45.3 (2.5) | 0.4 (0.02) | 194.4 (18.6) | 13.4 (1.8) | 2.9 (0.4) | 30.1 (0.9) |
| Under treatment | 8.3 (0.5)** | 6.6 (0.3) | 1.3 (0.07)** | 39.4 (3.2) | 0.4 (0.04) | 205 (10.5) | 9.5 (0.7)* | 2.0 (0.1)* | 29.6 (0.6) |

Table 1: Biochemical parameters of PCOS patients (n=34) before and under treatment. Data are shown as mean (SEM).

LH: luteinizing hormone; FSH: follicle stimulating hormone; E2: estradiol; P: progesterone; 17OHP: 17 hydroxyprogesterone; A: androstenedione; BMI: body mass index.

***p<0.001; **p<0.02; *p<0.05 vs baseline

The study protocol was approved as observational study by the Human Investigation Committee of the University of Modena and Reggio Emilia, Italy (registration n. 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) [27]. 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 [28]. Within- and between assay coefficients of variation were 4.1% and 9.5%. Plasma insulin was determined using an immunoradiometric assay (Biosource Europa S.A., Nivelles, Belgium). Within- and between-assay coefficients of variation were 4.5% and 11.7%.

Statistical analysis

As in previous studies [29], overweight and obese PCOS patients were considered all together. 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), HOMA index was computed to estimate the sensitivity to insulin [25] 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 [25]. The cutoff value we used is 2.71 as previously stated [25,26] while it is 2.5 for children and adolescents [30].

Results

All hormonal parameters of patients under study are summarized in Table 1. Insulin plasma levels and HOMA index resulted significantly reduced after the treatment interval. BMI decreased but did not reach significance. In addition, LH plasma levels, LH/FSH ratio (Table 1) and insulin response to the oral glucose tolerance test (OGTT) (Figure 1) were significantly decreased.
When we subdivided the PCOS patients in hyperinsulinemic (n=28) and normoinsulinemic (n=6) patients according to the insulin response to the OGTT (Table 2) both groups demonstrated the reduction of LH and LF/FSH ratio but only hyperinsulinemic PCOS showed the significant decrease of HOMA index. Normoinsulinemic patients showed a perfectly normal HOMA index both before and after the treatment interval. Interestingly, when considering the insulin response to glucose load only the hyperinsulinemic PCOS patients showed a reduced insulin release (Figure 2) while no change was observed for the normoinsulinemic subjects.

Considering that some patients reported diabetic first-grade relatives, we reconsidered the hormonal profiles (Table 3) and the insulin response (Figure 3) subdividing our PCOS patients into two groups: those with diabetic relatives (n=16) and those with no diabetic relatives (n=18). Patients with diabetic relatives showed significant reduction of LH, LH/FSH ratio, insulin and HOMA index while patients who had no diabetic relatives had only the reduction of LH and LH/FSH ratio (Table 3). It is to note that 14 out of 16 (87.5%) of the PCOS patients with diabetic relatives were hyperinsulinemic under OGTT and they represented 57.1% of all the hyperinsulinemic PCOS we studied. Both groups showed the significant reduction of the insulin response under glucose load (Figure 3) but only the PCOS with diabetic relatives showed a significantly reduced insulin levels at time 0, similarly to hyperinsulinemic PCOS (Figure 2).

![Figure 1: Insulin response to glucose load decreased after the treatment interval both before and after the glucose load. (*p< 0.05, **p<0.01, ***p<0.001 vs before treatment).](image-url)

Table 2: Biochemical parameters of PCOS patients subdivided according to the insulin response to OGTT, data are shown as mean (SEM).

| PCOS Hyperinsulinism (n=28) | LH mIU/ml | FSH mIU/ml | LH/FSH | E2 pg/ml | P ng/ml | A ng/100 ml | Insulin µU/ml | HOMA index | BMI |
|----------------------------|-----------|------------|---------|-----------|---------|-------------|---------------|-------------|-----|
| Baseline                   | 12.4 (0.6)| 6.1 (0.1)  | 2.0 (0.1)| 53.5 (5.1)| 0.5 (0.03)| 254.0 (21)  | 14.0 (2.1)    | 3.3 (0.4)   | 29.8 (1.5) |
| Under treatment            | 9.0 (0.6) | 6.6 (0.4)  | 1.4 (0.06)| 42.4 (4.1)| 0.5 (0.05)| 247.0 (11)  | 9.5 (0.8)    | 2.1 (0.1)** | 29.0 (2.5) |
| PCOS No insulinism (n=6)   |           |            |         |           |         |             |               |             |     |
| Baseline                   | 8.6 (1.1) | 7.2 (0.6)  | 1.2 (0.1)| 46.0 (7.7)| 0.3 (0.06)| 143.3 (20.4)| 6.0 (0.5)    | 1.3 (0.2)   | 30.3 (1.4) |
| Under treatment            | 6.3 (1.2) | 6.4 (1.2)  | 0.9 (1.0)| 33.3 (1.3)| 0.3 (0.06)| 160.0 (25)  | 6.8 (1.5)    | 1.5 (0.3)   | 29.4 (1.7) |

Table 2: Biochemical parameters of PCOS patients subdivided according to the insulin response to OGTT, data are shown as mean (SEM).

* LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; P: progesterone; 17OHP: 17 hydroxyprogesterone; A: androstenedione; BMI: body mass index.

**p<0.001; ***p<0.01; *p<0.05 vs baseline
Table 3: Biochemical parameters of PCOS patients subdivided according to the presence (upper panel) or absence (lower panel) of diabetic relatives (mean ± SEM).

|          | Under treatment |          |          |          |          |          |
|----------|----------------|----------|----------|----------|----------|----------|
| LH       | 7.6 (0.8)**    | 6.8 (1.1)| 1.2 (0.1)** | 30.8 (2.3)* | 0.35 (0.06) | 223.0 (12) |
| FSH      | 10.3 (1.2)     |          |          |          |          |          |
| E2       | 2.2 (0.2)      |          |          |          |          |          |
| P        | 28.2 (0.9)     |          |          |          |          |          |
| 17OHP    |                |          |          |          |          |          |
| A        |                |          |          |          |          |          |
| BMI      |                |          |          |          |          |          |

Note: LH: luteinizing hormone; FSH: follicle stimulating hormone; E2: estradiol; P: progesterone; 17OHP: 17 hydroxyprogesterone; A: androstenedione; BMI: body mass index. **p<0.01; *p<0.05 vs baseline

Figure 2: When subdividing the PCOS patients according to insulin response to glucose load (OGTT), only hyperinsulinemic PCOS showed improvement after the treatment interval since insulin decreased at time 0 and after time 90 of OGTT. No changes for normoinsulinemic PCOS patients. (*p<0.05, ***p<0.001 vs before treatment).

Figure 3: After the treatment interval PCOS with diabetic relatives had the significant decrease of insulin plasma levels at time 0 as well as after 90 minutes of the OGTT. PCOS with no diabetic relatives showed only the reduction of insulin response to glucose load after 90 minutes. (*p<0.05, **p<0.01 vs before treatment).
Discussion

This manuscript reports the ability of a combination of alpha lipoic acid (ALA) and myo-inositol (MYO) to modulate and reduce insulin resistance and glucose-load induced insulin hypersecretion in a group of PCOS patients, improving also gonadotropin secretion.

Recently we reported the efficacy of MYO [26,31,32] as well as of DCI [18] to modulate insulin sensitivity and hormonal profiles in PCOS patients and we demonstrated that when there is the presence of first grade diabetic relatives the putative DCI administration seems to be more effective than MYO in the control of insulin sensitivity [18]. Such hypothesis was enforced by the fact that growing evidences suggest that a deficiency of d-chiro-inositol (DCI) containing IPG might be at the basis of insulin resistance, so frequent in PCOS patients. Moreover, recently it has been reported that PCOS patients have abnormally high urinary clearance of DCI [6] and that metformin administration in obese PCOS patients improves the release of DCI-IPG mediator [33]. Such observations have clearly suggested that an impairment of IPG mediator(s) might be one of the putative causal factors of the insulin resistance and of the compensatory hyperinsulinemia that most PCOS patients show. It is relevant to remember that DCI is synthesized by an epimerase that converts MYO into DCI and that, depending on the specific needs of the two molecules, each tissue has a typical conversion rate [34,35]. Such MYO-to-DCI conversion seems to be insulin dependent since ratios of MYO to DCI is increased to about 10- to 20-fold in type I diabetic patients, in first-degree relatives of type II diabetic patients, and in type II diabetic subjects [34].

On such basis, it seemed logical to test the efficacy of a combination of alpha lipoic acid (ALA) and MYO to evaluate what improvement might be induced by this combination.

Our data demonstrated that only PCOS patients with an abnormal HOMA index showed a significant improvement undergoing to the treatment of ALA+MYO. In fact, though being a very limited amount of patients, normoinsulinemic PCOS, though obese, did not show any modification of HOMA index and of insulin response to glucose load, similarly to what recently reported [26]. Moreover, it is interesting to observe that among the hyperinsulinemic PCOS there was the highest rate (87.5%) of patients with diabetic first grade relatives. As additional fact, under ALA+MYO administration, only PCOS patients with diabetic relatives showed the significant modification of insulin plasma levels in fasting conditions. This is interesting since it suggests that insulin and/or the intracellular IPG-mediator modulate a specific and positive role, which is different from the other PCOS patients with no diabetic relatives. Such data fit perfectly with what previously demonstrated for ALA [19,36,37]. In fact, ALA administration has been reported to be effective on reducing insulin resistance in PCOS patients [19], with also specific effects on triglycerides plasma levels. In animal models and in humans 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 mammalian liver [36,37]. Reduced ALA synthesis results in a decrease in mitochondrial lipoic acid that induces a lower glucose uptake in skeletal muscle cells that is at the basis of insulin resistance [37]. In fact, ALA modulates glucose utilization through the increase of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscles [21] thus increasing glucose-transporter-4 (GLUT-4) [23,24] in the animal model. It is interesting to observe that also metformin treatment seems to activate AMPK [24].

Unfortunately, the study protocol was approved with no ALA- or MYO-only treated group. This would have given a more detailed insight on the efficacy of these integrators. Nevertheless, considering other reports on MYO or ALA administration, our data support the hypothesis that not only MYO is effective in overweight PCOS, as previously reported [26,31] but the addition of ALA improved glycemic control. In fact as previously reported [37] a consistent part of the insulin sensitivity is related to the LASY expression and activity. In animal models as well as in diabetes patients the abnormal LASY function decreases ALA synthesis affecting insulin sensitivity [37].

Our data let us infer that these mechanism(s) are at the basis of the efficacy of the ALA+MYO combination on all overweight/obese PCOS patients. In addition, the fact that those patients who had diabetic relatives showed more relevant and significant changes of plasma insulin levels and HOMA index sustain the hypothesis that the LASY abnormal expression might be a relevant causal co-factor of the insulin resistance and of the compensatory hyperinsulinemia. Indeed a higher improvement on insulin sensitivity is given by ALA administration, as demonstrated previously [19,37] and by the greater availability of MYO, due to the treatment, modulated insulin response, similarly to what previously reported in normal weight [32] and in obese PCOS patients [26,31]. According to our data the concomitant presence of these two compounds modulate insulin-induced pathways. In these analogous settings, the combination of ALA+MYO improved the insulin response to glucose load and those who had diabetic relatives such effect showed up early, that is in fasting conditions. These observations let us infer that the presence of ALA together with MYO is highly effective mainly in obese hyperinsulinemic PCOS who had diabetic relatives since probably restores the reduced ALA endogenous concentrations, improving ALA modulatory effects on insulin sensitivity.

Finally yet importantly, it is relevant to point out the significant changes of the mean LH plasma levels, independently from the subdivision adopted on the patients. Such data give clear relevance to the fact that insulin and/or the intracellular IPG-mediator modulate the pituitary function in terms of LH secretion and sustain the hypothesis that metabolic pathways and its hormonal modulators play a primary role on endocrine glands activity. These data are in agreement with previous studies [26,31,32] and disclose the fact that LH changes occur also in normoinsulinemic PCOS patients and/or without first grade diabetic relatives. Though we did not assay testosterone plasma levels, the androgenic milieu did not change since androstenedione plasma levels did not change. This observation is not in agreement with previous data on MYO administration in overweight PCOS patients [26,31] but the population of patients we studied was different and had not a so elevated androstenedione plasma levels as the above mentioned studies. This observation confirms that PCOS may show some variability of one or more of the many hormones that have been demonstrated to be part of the syndrome.

In conclusion, though the number of the patients studied represents a limiting factor, our data support the hypothesis that integrative administration of ALA+MYO combination improved insulin sensitivity in overweight/obese PCOS. In addition, our data suggest that ALA might be a relevant helper for the insulin resistance and metabolic impairment that characterize a high percentage of PCOS patients, especially if they have diabetic relatives. Though lifestyle modification should be the first significant change to adopt [17] to avoid the evolution of PCOS towards the more dangerous and risky metabolic syndrome [38], the use of appropriate feeding integration(s)
might help a lot. More studies should be addressed to better disclose the role of ALA on the biochemical control of the metabolic pathways in PCOS patients.

References

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, et al. (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 89: 2745-2749.

2. The Rotterdam ESHE/ASRM-Sponsored PCOS Consensus Workshop Group (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004; 81: 19-25.

3. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, et al. (2012) Women on sexual health aspects of polycystic ovarian syndrome (PCOS): the Amsterdam ESHE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 97: 28-38.

4. Ciampelli M, Fulghesu AM, Cecinelli F, Pavone V, Ronsisvalle E, et al. (1999) Impact of insulin and body mass index on metabolic and endocrine variables in polycystic ovary syndrome. Metabolism 48: 167-172.

5. Genazzani AD, Richirieri F, Lanzoni C (2010) Use of metformin in the treatment of polycystic ovary syndrome. Womens Health (Lond Engl) 6: 577-593.

6. Baillargeon JP, Diamanti-Kandarakis E, Ostlund RE Jr, Apriodnti Z, Luorno MJ, et al. (2006) Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabetes Care 29: 300-305.

7. Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18: 774-800.

8. Norman RJ, Masters L, Miller CR, Wang JX, Davies MJ (2001) Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 16: 1995-1998.

9. Legro RS, Gnaat CL, Kunselman AR, Dunaif A (2005) Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab 90: 3236-3242.

10. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J (1999) Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 22: 141-146.

11. Pesant MH, Baillargeon JP (2011) Clinically useful predictors of conversion to abnormal glucose tolerance in women with polycystic ovary syndrome. Fertil Steril 95: 210-215.

12. Hudecova M, Holte J, Olovsson M, Larsson A, Berne C, et al. (2011) Diabetes and impaired glucose tolerance in patients with polycystic ovary syndrome—a long term follow-up. Hum Reprod 26: 1462-1468.

13. Celik C, Tasdemir N2, Abali R2, Bastu EU, Yilmaz M4 (2014) Progression to impaired glucose tolerance or type 2 diabetes mellitus in polycystic ovary syndrome: a controlled follow-up study. Fertil Steril 101: 1123-1128.

14. American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee (2005) American Association of Clinical Endocrinologists Position Statement on Metabolic and Cardiovascular Consequences of Polycystic Ovary Syndrome. Endocr Pract 11: 126-134.

15. ACCOG Committee on Practice Bulletins—Gynecology (2009) ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. Obstet Gynecol 114: 936-949.

16. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, et al. (2010) Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 95: 2038-2049.

17. Genazzani AD, Prati A, Despini G, Marinì G, Richirieri F (2014). PCOS: from Lifestyle to the Use of Inositol and Insulin Sensitizers. In A.R. Genazzani and M. Brancat (eds.), Frontiers in Gynecological Endocrinology, ISGE Series 1, pp 59-67.

18. Genazzani AD, Santagiti S, Rattighieri E, Chierchia E, Despini G, et al. (2014) Modulatory role of D-chiro-inositol (DCI) on LH and insulin secretion in obese PCOS patients. Gynecol Endocrinol, DOI: 10.3109/09513590.2014.897321.

19. Masharani U, Gjerde C, Evans JL, Youngren JF, Goldfine ID (2010) Effects of controlled-release alpha-lipoic acid in lean, non-diabetic patients with polycystic ovary syndrome. J Diabetes Sci Technol 4: 359-364.

20. Minunyawa R, Montagnani M, Koh KK, Quon MJ (2007) Cardiovascular actions of insulin. Endocr Rev 28: 463-491.

21. Wang Y, Xiaoioe L, Guo Y, Chan L, Guan X (2010) A-lipoic acid increases energy expenditure by enhancing adenosine monophosphate-activated protein kinase–peroxisome proliferator-activated receptor-β coactivator-1α signaling in the skeletal muscle of aged mice. Met Clin and Experimental 39: 967-976.

22. Lee WJ, Song KH, Koh EH, Won IC, Kim HS, et al. (2003) Alpha-lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle. Biochem Biophys Res Commun 332: 885-891.

23. Shen QW, Zhu MJ, Tong J, Ren J, Du M (2007) Ca2+/calmodulin-dependent protein kinase is involved in AMP-activated protein kinase activation by alpha-lipoic acid in C2C12 myotubes. Am J Physiol Cell Physiol 293: C1395-1403.

24. Musi N, Hirshman MF, Nygren J, Svanfeldt M, Bavenholm P, et al. (2002) Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. Diabetes 51: 2074-2081.

25. Madeira IR, Carvalho CN, Gazolla FM, de Matos HJ, Borges MA, et al. (2008) Cut-off point for Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index established from Receiver Operating Characteristic (ROC) curve in the detection of metabolic syndrome in overweight prepubertal children. Arq Bras Endocrinol Metabol 52:1466-1473.

26. Genazzani AD, Prati A, Santagiti S, Richirieri F, Chierchia E, et al. (2012) Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. Gynecol Endocrinol 28: 969-973.

27. Genazzani AD, Petraglia F, Benatti R, Montanini V, Algeri I, et al. (1991) Luteinizing hormone (LH) secretory burst duration is independent from LH, prolactin, or gonadal steroid plasma levels in amenorrheic women. J Clin Endocrinol Metab 72: 1220-1225.

28. Genazzani AD, Chierchia E, Rattighieri E, Santagiti S, Casarosa E, et al. (2010) Metformin administration restores allopregnanolone response to adrenocorticotropic hormone (ACTH) stimulation in overweight hyperinsulinemic patients with PCOS. Gynecol Endocrinol 26: 684-689.

29. Cengiz H, Ekin M2, Dagdeviren H2, Yildiz S2, Kaya C2, et al. (2014) Comparison of serum anti-Müllerian hormone levels in normal weight and overweight-obese adolescent patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 180: 46-50.

30. Geloneze B, Vasques AC, Stabe CF, Pareja JC, Rosado LE, et al. (2009) HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). Arq Bras Endocrinol Metabol 53: 281-287.

31. Genazzani AD, Lanzoni C, Richirieri F, Jassoni VM (2008) Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 24: 139-144.

32. Genazzani AD, Santagiti S, Richirieri F, Campedelli A, Rattighieri E, et al. (2014) Myo-inositol modulates insulin and luteinizing hormone secretion in normal weight patients with polycystic ovary syndrome. J Obstet Gynaecol Res 40: 1353-1360.

33. Baillargeon JP, Nesterle JF (2006) Commentary: polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab 91: 22-24.

34. Larner J (2002) D-chiro-inositol--its functional role in insulin action and its deficit in insulin resistance. Int J Exp Diabetes Res 3: 47-60.

35. Sun TH, Heimark DB, Nguyen T, Nadler JL, Larner J (2002) Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-
inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. Biochem Biophys Res Commun 293: 1092-1098.

36. Morikawa T, Yasuno R, Wada H (2001) Do mammalian cells synthesize lipoic acid? Identification of a mouse cDNA encoding a lipoic acid synthase located in mitochondria. FEBS Lett 498: 16-21.

37. Padmalayam I, Hasham S, Saxena U, Pillarisetti S (2009) Lipoic acid synthase (LASY): a novel role in inflammation, mitochondrial function, and insulin resistance. Diabetes 58: 600-608.

38. Caserta D, Adducchio G, Picchia S, Ralli E, Matteucci E, et al. (2014) Metabolic syndrome and polycystic ovary syndrome: an intriguing overlapping. Gynecol Endocrinol 30: 397-402.