European Review for Medical and Pharmacological Sciences 2019; 23: 8687-8694

Efficacy of the synergic action of myoinositol, tyrosine, selenium and chromium in women with PCOS

M. MONTANINO OLIVA[1,2], V. ZUEV[3], A. LIPPA[1], M.C. CARRA[1], F. LISI[1]

[1]Centre for Reproductive Medicine Altamedica, Rome and Milan, Italy
[2]Department of Obstetrics and Gynecology Santo Spirito Hospital, Rome, Italy
[3]Department of Obstetrics and Gynecology Sechenov First Moscow State Medical University, Moscow, Russia

Abstract. – OBJECTIVE: The aim of the study is to investigate the efficacy of a treatment with myoinositol plus L-tyrosine, selenium, and chromium in women with polycystic ovarian syndrome (PCOS).

PATIENTS AND METHODS: One hundred and eighty-six women, with diagnosis of PCOS, were divided in four groups according to their clinical features. Phenotype A: androgen excess + ovulatory dysfunction + polycystic ovarian morphology. Phenotype B: androgen excess + ovulatory dysfunction. Phenotype C: androgen excess + polycystic ovarian morphology. Phenotype D: ovulatory dysfunction + polycystic ovarian morphology. All patients were given daily for six months a compound with 2 g myo-inositol, 0.5 mg L-Tyrosine, 0.2 mg folic acid, 55 mcg selenium, 40 mcg chromium. Hormonal assessment, BMI, Ferriman-Gallway Gallway score, HOMA index, and follicular monitoring were reported before starting the therapy, three months and six months after.

RESULTS: Phenotype A showed an improvement, consistent with restored ovulation: more regular length of the menstrual cycle, detection of periovulatory follicle at ultrasound, and rising of progesterone in the luteal phase. A total of 45 patients (65.2%) ovulated after six months. In the same period glucose and HOMA index decreased. In the phenotype B, 80% of patients ovulated after six months. An improvement of the clinical and biochemical sign of hyperandrogenism was also reported. In the phenotype C, after BMI had followed the treatment for six months, it decreased in a statistically significant manner. In the phenotype D, 49 out of 82 women (59.7%) restored their regular menstrual period and ovulated.

CONCLUSIONS: Our study reported how the synergistic action of myoinositol, L-tyrosine, selenium, and chromium could restore normal menstrual cycle, ovulation, and decrease weight in these patients.

Key Words:
Polycystic ovarian syndrome, Myoinositol, Tyrosine, Selenium, Chromium.

Introduction

The polycystic ovarian syndrome (PCOS) is the most common cause of menstrual disorders, ovarian dysfunctions, and infertility in women, affecting at least 5-10% of the total reproductive population worldwide[1]. PCOS is a heterogeneous endocrine, reproductive, and metabolic disorder. PCOS encompasses a broad spectrum of biochemical/clinical signs and symptoms such as irregular menstrual cycles that include oligo/amenorrhea that very often leads to infertility[2]. Approximately 90-95% of anovulatory women who come for infertility assessment have PCOS. Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased. However, due to imbalances in factors involved in normal follicular development, follicular growth becomes blocked as follicles reach a diameter of 4-8 mm. Given that a dominant follicle does not develop, ovulation does not occur[3]. Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS. Almost 40% of women with severe acne condition are diagnosed with PCOS[4]. It was also associated with several long-term health consequences, including obesity, type 2 diabetes, cardiovascular disease, psychological distress, and mood disorders[5]. Other diagnoses, such as congenital adrenal hyperplasia, non-classic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic

Corresponding Author: Mario Montanino Oliva, MD; e-mail: m.montaninooliva@gmail.com

hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders must be excluded. The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group includes the presence of 2 out of the following 3 criteria: biochemical and/or clinical sign of hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology[6]. The polycystic ovarian morphology[7] is defined by twenty or more follicles measuring 10 mm in diameter and/or an increased ovarian volume of greater than 20 cm^3. Despite many decades of extensive research, the exact etiology of this disorder remains largely unknown. It is widely known that insulin resistance plays an important role in the pathogenesis of PCOS. Insulin stimulates ovarian theca cells to produce androgens both directly and indirectly[8]. Elevated glucose levels in turn inhibit the hepatic synthesis of sex hormone-binding globulin (SHBG), leading to increased concentration of circulating free androgens[9]. Insulin resistance is a common feature in both overweight and lean women with PCOS independent of their Body Mass Index (BMI)[10]. In the last two decades the use of metformin, in PCOS women, showed a reduction of insulin resistance and hyperandrogenism resulting in improvements of hormonal and metabolic patterns, as well as reproductive function[11,12].

The supplementation with inositols, both myo-inositol (MI) and D-chiroinositol (DCI), a natural insulin sensitizer, in women with PCOS has been evaluated over the last decade[13,14]. Inositols are incorporated into cell membranes as phosphatidyl-MI, which is a precursor of inositol triphosphate (InsP3). They act as an intracellular second messenger and regulate several hormones such as thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and insulin[15]. MI is the most abundant form of inositol in humans. An epimerase, an insulin-dependent enzyme, converts MI into DCI, depending on the specific needs of the tissue for these two molecules[16]. Myo-inositol is not only a prominent component of membrane-incorporated phosphatidylinositol, but participates with its isomers to a multitude of cellular processes, including ion channel permeability, metabolic homeostasis, mRNA export and translation, cytoskeleton remodeling, stress response[17]. The role of inositols in women with PCOS can be attributed to deficiency of inositols, which are mediators of insulin activity[18]. It is well established that different tissues have different ratios of MI/DCI and, in case of PCOS patients, the conversion is impaired due to insulin-resistance (IR)[19]. It is reported that the inositols can reduce insulin resistance, improve ovarian function, and reduce androgen levels, thus enhancing the reproductive impairments associated with PCOS[20,21]. Moreover, the administration of MI is a safe and effective method to prevent and correct metabolic disorders in teenagers affected by PCOS with cutaneous disorders[22].

L-tyrosine is a nonessential amino acid synthesized in the body from phenylalanine. L-tyrosine is found in many dietary sources, including lean proteins such as chicken, eggs, fish and whole grain oats, and dairy products including milk, cheese, and yoghurt. L-tyrosine is the precursor of thyroid hormones and many other neurotransmitters like adrenaline, nor-adrenaline, serotonin, and dopamine. It also helps in the production of melanin and in the function of organs in the body responsible for making and regulating hormones, including the adrenal, thyroid, and pituitary glands[23]. All these hormones regulate mood, therefore L-tyrosine is claimed to act as an effective antidepressant[24]. Tyrosine kinase signaling pathways are integral parts of the mammalian ovulatory process but do not involve actions on the synthesis of steroids, plasminogen activator or prostaglandins[25]. The study conducted on the old female rats has shown that when they were given L-tyrosine they would have had their regular menstrual cycle and ovulation[26]. As L-tyrosine binds to free radicals, that can potentially cause damage to the cells and tissues, it is considered to work as a mild antioxidant. Findings from a range of clinical studies using allergy vaccines containing L-tyrosine showed the lack of toxicity seen in animal studies and they have showed evidence of enhanced immunostimulatory activity. The absence of toxicological concerns in these findings supports the hypothesis that L-tyrosine is a safe adjuvant for human use[27]. In the United States L-tyrosine is Generally Recognized as Safe (GRAS). The Food and Nutrition Board of the Institute of Medicine reports that for every 1 g of protein in the diet, the body needs 47 mcg of tyrosine. Based on these recommendations, women need to intake 46 g of proteins; therefore, they need 2.2 g of tyrosine daily[28]. No exact dietary supplement recommendation for tyrosine exists. It just depends on diet, overall health, and what are the symptoms the patients are dealing with. Selenium (Se) is a trace element that is naturally presented in many foods,

like organic lean meat, fish, Brazil nuts, cheese, eggs, nutritional yeast, liver, butter, cold water fish, alliums, mushrooms, tomatoes, green vegetables[29]. Selenium, which is nutritionally essential for humans, plays a critical role in reproduction, DNA synthesis, protection from oxidative damage, and infection[30]. It is crucial for the several enzymes involved in thyroid function. What is more, it has been found that selenium diminishes thyroid autoantibody levels[31]. Selenium supplementation among PCOS women resulted in beneficial effects on reproductive outcomes[32]. The RDA for women is 55 mcg that rise in case of pregnancy to 60 mcg. Chromium Picolinate (CrPic) is a widely used nutritional supplement for optimal insulin function[33]. Apparently, it has a role in maintaining proper carbohydrate and lipid metabolism in mammals[34]. As this role probably involves potentiation of insulin signaling, chromium dietary supplementation has been postulated to potentially have effects on body composition, including reducing fat mass and increasing lean body mass, especially in women with PCOS[35].

Patients and Methods

The aim of this prospective study is to evaluate the effectiveness of a compound containing 2 g myo-inositol, 0.5 mg L-tyrosine, 0.2 mg folic acid, 55 mcg selenium, and 40 mcg chromium (Inotir®, Pharmarte, Rome, Italy) in women affected by PCOS. These data were collected from patients attending Altamedica Reproductive Medicine (Rome and Milan, Italy) from May 2017 to June 2018. The study encompassed a heterogeneous group of women ranging from 16 to 38 years with PCOS according to the Rotterdam ESHRE-ASRM criteria. Therefore, inclusion criteria were at least 2 out 3 of the following conditions: oligo- or anovulation, clinical and/or bio-chemical signs of hyperandrogenism, and polycystic ovarian morphology. Clinical hyperandrogenism was evaluated using a modified Ferriman-Gallway (FG) scoring system[36]. The result was used to evaluate hair growth at seven spots: upper lip, chin/face, chest, back, abdomen, arms, and thighs. A score of 0 (zero) was given in the absence of terminal hair growth and a score of 4 (four) was given for extensive growth with a level $\geq$ 4-6 indicating hirsutism. Ovarian morphology and monitoring of ovulation were assessed with repeated ultrasound starting at day 3, and progesterone was obtained between day 21 and 28 according to the investigator's judgment. Patients that were taking hormonal therapy such as oral contraceptive or thyroid hormones were not included in the study. We endorse the recommendation of the National Institutes of Health Office of Disease Prevention Evidence-based Methodology Workshop on Polycystic Ovary Syndrome PCOS 2012 (https://prevention.nih.gov) that specific phenotypes should be reported explicitly in all research. Therefore, one hundred and eighty-six PCOS women were enrolled in the study and divided in four groups according to their clinical features.

Phenotype A (69 women): androgen excess + ovulatory dysfunction + polycystic ovarian morphology;
Phenotype B (15 women): androgen excess + ovulatory dysfunction;
Phenotype C (21 women): androgen excess + polycystic ovarian morphology;
Phenotype D (82 women): ovulatory dysfunction + polycystic ovarian morphology.

Patients were asked to take every day, one sachet of Inotir® orally, 2 h before or after meals. FSH, LH, PRL, estradiol, TSH, free testosterone, glucose, SHBG tests were done three times: before starting the therapy and three months and six months after starting it. BMI and HOMA indexes were also calculated. Whereas monitoring of ovulation and progesterone evaluation was performed at physician's judgement in the same frame time.

Statistical Analysis

The t-test was used to evaluate a null hypothesis, which proposes that no significant difference exists in a set of given observations. A t-test assumes a normal distribution of the given sample and it is used when the population parameters (mean and standard deviation) are unknown. This test can be used to compare the means for two groups and the means from the same group at different frametime. The null-hypothesis represents, as for the *t*-test, the independence between the tested variables so, rejecting this hypothesis, we affirm that the two variables are related, and they come from the same distribution. Results are reported as means ± standard deviation (SD) and statistically significant results are considered with $p<0.05$.

Results

In the phenotype A (Table I), after three-months treatment, 19 out of 69 women (27.5%) showed an improvement in the following parameters, consistent with restored ovulation: more regular length of the menstrual cycle, detection of periovulatory follicle at ultrasound, and rising of progesterone in the luteal phase ($p<0.05$), while a total number 45 patients (65.2%) ovulated after six months (Figure 1). In the same period, glucose and HOMA indexes decreased ($p<0.05$). An improvement of the clinical and biochemical sign of hyperandrogenism was also reported ($p<0.05$). In the phenotype B (Table II), after following the treatment for three months, 30% of woman showed ultrasound and hormonal signs of ovulation, while a total number 12 patients (80%) ovulated after six months (Figure 1). In the same period, glucose and HOMA indexes decreased. An improvement of the clinical and biochemical sign of hyperandrogenism was also reported ($p<0.05$). In the phenotype C (Table III), after following the treatment for six months, BMI decreased in a statistically significant manner. Clinical evaluation of hirsutism was also improved. In the phenotype D (Table IV), after following the treatment for six months, 49 out of 82 women (59.7%) restored their regular menstrual period and ovulated (Figure 1). In oligo-anovulatory groups (phenotype A-B-D), signs of ovulation were noted, and BMI decreased ($p<0.05$) after six months (Figure 1). Regardless treatment group, BMI decreased in all phenotypes (Figure 2) after 6 months of therapy.

Discussion

Polycystic ovary syndrome is a heterogeneous endocrine disorder accompanied with an increased risk of developing type 2 diabetes mellitus and cardiovascular disease[37,38]; despite being a common condition, the pathogenesis of PCOS remains unclear. The recognition that a metabolic dysfunction, peripheral insulin resistance, might be one of the main trigger points of PCOS, has induced clinicians to compare different insulin sensitizer to rescue the ovarian response to endogenous gonadotropins[39,40]. The use of insulin sensitizer reduces hyperandrogenemia and reestablishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy[41]. Myo-inositol has been shown to be able to restore spontaneous ovarian activity, and consequently fertility, in most patients with PCOS[42].

Our study indicates, that the administration of myoinositol improves several clinical and biochemical parameters in women with PCOS.

The interesting thing is that he association with tyrosine, chromium picolinate, and selenium seems to be effective in all the four types of phenotype.

CrPic, given without change in diet or activity level, caused a 38% mean improvement in glucose disposal rate in women with PCOS[43]. This suggests that chromium may be useful as an insulin sensitizer in the treatment of polycystic ovary syndrome[44]. Based on chromium's potential to improve insulin, dopamine, and serotonin function, it has been hypothesized that chromium has a greater glucoregulatory effect in individuals

Table I. Phenotype A – Patients with PCO, hyperandrogenism and oligo/anovulation.

	T0	T3	T6
BMI	26.52 (± 3.67)	26.00 (± 2.08)	25.13 (± 3.06)
FSH (mIU/ml)	6.84 (± 2.16)	6.66 (± 1.81)	6.86 (± 2.01)
LH (mIU/ml)	8.62 (± 2.32)	8.73 (± 8.44)	8.52 (± 2.15)
PRL (ng/ml)	18.14 (± 4.43)	18.80 (± 4.22)	17.72 (± 4.81)
E2 (pg/ml)	57.46 (± 16.32)	57.49 (± 14.99)	57.65 (± 15.36)
TSH (μU/ml)	2.19 (± 0.74)	2.05 (± 0.56)	2.01 (± 0.91)*
P (ng/ml)	2.29 (± 1.41)	3.34 (± 4.38)*	9.41 (± 6.13)*
Glu (mg/dl)	89.94 (± 8.01)	85.91 (± 8.30)	85.22 (± 8.29)*
HOMA	2.87 (± 1.12)	2.86 (± 1.12)	2.82 (± 1.10)*
FreeT (ng/dl)	4.14 (± 0.94)	4.09 (± 0.93)	4.02 (± 0.90)*
SHBG (nmol/L)	31.77 (± 11.40)	32.20 (± 11.49)	41.86 (± 21.79)*
FG	8.52 (± 1.63)	8.52 (± 1.27)	8.16 (± 1.31)

Values (mean ± SD) before starting the treatment (T0) after 3 months (T3) and 6 months (T6). *$p<0.05$ compared *vs*. T0.

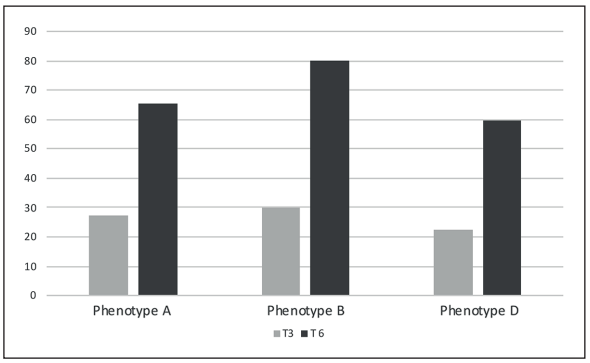

Figure 1. Patients (%) who ovulated after 3 months (T3) and 6 months (T6) of treatment. Phenotype A (69 women): androgen excess + ovulatory dysfunction + polycystic ovarian morphology; Phenotype B (15 women): androgen excess + ovulatory dysfunction; Phenotype D (82 women): ovulatory dysfunction + polycystic ovarian morphology.

who have concurrent disturbances in dopamine and serotonin function – that is, complex patients with comorbid diabetes, depression, and binge eating[45].

Evidence has also been reported that selenium may affect several reproductive complications[46]. Furthermore, current data[47,48] supports the beneficial effect of selenium supplementation on metabolic profiles and biomarkers of oxidative stress among patients with PCOS.

Our results show how all phenotypes resulted in a decrease of BMI that is the first line therapy in overweight patients with PCOS. The synergic action of chromium and tyrosine can lead to improve the physiological and neurobehavioral processes that are present in many women affected by PCOS.

The addiction of myoinositol with chromium and tyrosine, when compared to other studies,

Table II. Phenotype B – Patients with hyperandrogenism and oligo/anovulation

	T0	T3	T6
BMI	26.39 (± 5.09)	26.10 (± 2.83)	25.09 (± 2.56)
FSH (mIU/ml)	5.45 (± 1.90)	7.07 (± 1.85)*	8.05 (± 2.39)*
LH (mIU/ml)	8.25 (± 2.38)	7.15 (± 1.71)	7.51 (± 1.57)
PRL (ng/ml)	24.51 (± 5.27)	26.54 (± 5.89)	25.51 (± 4.56)
E2 (pg/ml)	63.20 (± 18.13)	54.80 (± 15.27)*	48.47 (± 14.65)*
TSH (µU/ml)	2.17 (± 0.67)	1.95 (± 0.54)	1.89 (± 0.52)*
P (ng/ml)	1.67 (± 1.08)	4.13 (± 3.50)*	10.82 (± 5.79)*
Glu (mg/dl)	90.27(± 8.95)	87 (± 8.78)*	87.20 (± 5.75)
HOMA	2.06 (± 0.44)	2.05 (± 0.41)	1.99 (± 0.33)*
FreeT (ng/dl)	3.86 (± 1.04)	3.79 (± 1.03)	3.50 (± 0.82)*
SHBG (nmol/L)	25.93 (± 7.94)	30.93 (± 10.01)*	44.47 (± 14.16)*
FG	9.93 (± 1.39)	9.73 (± 1.12)	9.00 (± 0.97)

Values (mean ± SD) before starting the treatment (T0) after 3 months (T3) and 6 months (T6); *p<0.05 compared *vs*. T0.

Table III. Phenotype C – Patients with PCO and hyperandrogenism.

	T0	T3	T6
BMI	25.84 (± 3.13)	24.91 (± 3.23)	23.90 (± 3.32)*
FSH (mIU/ml)	5.99 (± 1.88)	7.22 (± 2.37)	7.60 (± 1.65)*
LH (mIU/ml)	5.84 (± 2.16)	6.99 (± 1.96)	6.37 (± 1.60)
PRL (ng/ml)	24.09 (± 5.91)	22.91 (± 8.40)	24.04 (± 5.62)
E2 (pg/ml)	52.33 (± 17.13)	54.33 (± 19.66)	50.57 (± 17.22)
TSH (µU/ml)	2.35 (± 0.69)	2.30 (± 0.67)	2.20 (± 0.59)
P (ng/ml)	7.1 (± 2.1)	8.3 (± 1.7)	8.1 (± 3.1)
Glu (mg/dl)	86.61 (± 8.16)	86.62 (± 8.69)	85.43 (± 7.49)
HOMA	1.37 (± 0.37)	1.94 (± 0.38)	1.92 (± 0.37)
FreeT (ng/dl)	3.31 (± 0.85)	3.10 (± 0.83)	3.01 (± 0.82)
SHBG (nmol/L)	22.57 (± 11.12)	22.33 (± 10.58)	28.10 (± 1.06)
FG	8.62 (± 1.17)	7.85 (± 1.08)	6.62 (± 1.09)

Values (mean ± SD) before starting the treatment (T0) after 3 months (T3) and 6 months (T6); *p<0.05 compared *vs*. T0

Table IV. Phenotype D – Patients with PCO and oligo/anovulation.

	T0	T3	T6
BMI	26.52 (± 2.98)	26.12 (± 3.07)	25.01 (± 3.05)*
FSH (mIU/ml)	6.84 (± 2.16)	7.22 (± 2.16)*	7.29 (± 2.13)*
LH (mIU/ml)	8.71 (± 2.45)	8.47 (± 2.30)	7.05 (± 2.15)*
PRL (ng/ml)	19.44 (± 5.97)	19.43 (± 5.98)	19.37 (± 5.37)
E2 (pg/ml)	61.39 (± 15.95)	60.62 (± 15.97)	60.21 (± 23.45)*
TSH (μU/ml)	2.07 (± 0.89)	2.05 (± 0.87)	1.93 (± 0.77)*
P (ng/ml)	2.13 (± 1.33)	3.53 (± 4.58)	9.10 (± 6.10)*
Glu (mg/dl)	86.21 (± 8.52)	85.57 (± 8.21)*	84.73 (± 7.81)*
HOMA	2.55 (± 0.69)	2.68 (± 0.69)	2.91 (± 0.76)
FreeT (ng/dl)	1.56 (± 0.33)	1.53 (± 0.44)	1.51 (± 0.44)*
SHBG (nmol/L)	55.65 (± 25.28)	60.21 (± 23.45)	60.21 (± 23.45)
FG	1.82 (± 1.07)	1.82 (± 1.07)	1.80 (± 1.09)

Values (mean ± SD) before starting the treatment (T0) after 3 months (T3) and 6 months (T6); *$p<0.05$ compared *vs*. T0.

seems particularly efficient to use a lower dosage of myoinositol when compared to the vast majority of the studies[49].

Treatment duration seems crucial, as far as the androgen profile is concerned. This agrees with the previous observation on acne, whose improvement with MI required at least 6 months supplementation[50]. Indeed, insulin affects the androgenic state not only directly by interfering with metabolism of ovarian androgens, but also indirectly by decreasing circulating SHBG levels. SHBG is a protein that binds to testosterone, making it unavailable to target tissues. Higher levels of SHBG lead to lower bioavailability of testosterone, thus minimizing the hyperandrogenic features[51]. Furthermore, SHBG appears to be a potentially valuable marker of IR in PCOS.

In addition, there is also increasing evidence to suggest that PCOS links to the increased prevalence of thyroid diseases such as nodular goiter and autoimmune thyroiditis[52]. Some studies[53,54] report how the association of MI and selenium could help to keep a euthyroid state in patients with Hashimoto disease and reduce the risk of developing overt hypothyroidism in women with autoimmune disease.

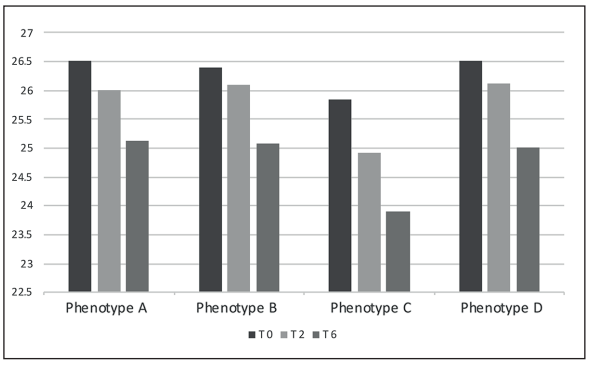

Figure 2. BMI Changing since starting therapy (T0) after 3 (T3) and 6 (T6) months.

Conclusions

According to randomized controlled trials involving inositol supplementation in women with PCOS, inositol provides improvement in almost all pathologic conditions in PCOS such as recovery of reproductive abnormalities, decreased androgen levels, and improved insulin levels. Chromium has been widely studied in the treatment of hyperglycemia, because chromium deficiency leads to disorders in glucose homeostasis and IR. Biochemical studies have shown that women with PCOS have lower tyrosine and selenium level compared with controls. In our study the association of these elements seems to induce a faster improvement in all four phenotypes when compared to the previously reported studies that used myoinositol.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget 2017; 8: 96351-96358.

2) Bozdag G, Sezcan M, Zengin D, Karabulut E, Yildiz Bulent O. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2016; 31: 2841-2855.

3) Astapova O, Minor BMN, Hammes SR. Physiological and pathological androgen actions in the ovary. Endocrinology 2019; 160: 1166-1174.

4) Franik G, Bizoń A, Włoch S, Kowalczyk K, Biernacka-Bartnik A, Madej P. Hormonal and metabolic aspects of acne vulgaris in women with polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 2018; 14: 4411-4418.

5) Gilbert EW, Tay CT, Hiam DS, Teede HJ, Moran LJ. Comorbidities and complications of polycystic ovary syndrome: an overview of systematic reviews. Clin Endocrinol (Oxf) 2018; 89: 683-699.

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

7) Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018; 33: 1602-1618.

8) Nelson VL, Qin KN, Rosenfield RL, Wood JR, Penning TM, Legro RS, Strauss JF 3rd, McAllister JM. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2001; 86: 5925-5933.

9) Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012; 33: 981-1030

10) Tan S, Scherag A, Eilard Janssen O, Hahn S, Lahner H, Dietz T, Scherag S, Grallert H, Ganz Vogel CI, Kimmig R, Illig T, Mann K, Hebebrand J, Hinney A. Large effects on body mass index and insulin resistance of fat mass and obesity associated gene (FTO) variants in patients with polycystic ovary syndrome (PCOS). BMC Med Genet 2010; 11: 12.

11) Neil PJ. Metformin use in women with polycystic ovary syndrome. Ann Transl Med 2014; 2: 56.

12) Siebert TI, Viola MI, Steyn DW, Kruger, TF. Is metformin indicated as primary ovulation induction agent in women with PCOS? A systematic review and meta-analysis. Gynecol Obstet Invest 2012; 73: 304-313.

13) Bizzarri M, Carlomagno G. Inositol: history of an effective therapy for polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 2014; 18: 1896-1903.

14) Milewska EM, Czyzyk A, Meczekalski B, Genazzani AD Inositol and human reproduction. From cellular metabolism to clinical use. Gynecol Endocrinol 2016; 32: 690-695.

15) Thomas RM, Nechamen CA, Mazurkiewicz JE, Ulloa-Aguirre A, Dias JA. The adapter protein APPL1 links FSH receptor to inositol 1,4,5-trisphosphate production and is implicated in intracellular Ca(2+) mobilization. Endocrinology 2011; 152: 1691-1701.

16) Heimark D, McAllister J, Larner J. Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls. Endocr J 2014; 61: 111-117.

17) Bizzarri M. Fuso A. Dinicola S. Cucina A. Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opin Drug Metab Toxicol 2016; 12: 1181-1196.

18) Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiroinositol in the polycystic ovary syndrome. N Engl J Med 1999; 340: 1314-1320.

19) Unfer V, Carlomagno G, Papaleo E, Vailati S, Candiani M, Baillargeon JP. Hyperinsulinemia alters myoinositol to d-chiroinositol ratio in the follicular fluid of patients with PCOS. Reprod Sci 2014; 21: 854-858.

20) Facchinetti F, Bizzarri M, Benvenga S, D'Anna R, Lanzone A, Soulage C, Di Renzo GC, Hod M, Cavalli P, Chiu TT, Kamenov ZA, Bevilacoua A, Carlomagno G, Gerli S, Oliva MM, Devroey P. Results from the international consensus conference on myo-inositol and d-chiro-inositol in obstetrics and gynecology: the link between metabolic syndrome and PCOS. Eur J Obstet Gynecol Reprod Biol 2015; 95: 72-76.

21) Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, Marelli G, Cino I, Redaelli A, Ferrari A. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol 2007; 23: 700-703.

22) Pkhaladze L, Barbakadze L, Kvashilava N. Myo-Inositol in the treatment of teenagers affected by PCOS. Int J Endocrinol 2016; 2016: 1473612.

23) Venegas-Meneses B, Padilla JF, Juárez CE, Morán JL, Morán C, Rosas-Murrieta NH, Handal A, Domínguez R. Effects of ovarian dopaminergic receptors on ovulation. Endocrine 2015; 50: 783-796.

24) Jongkees BJ, Hommel B, Kühn S, Colzato LS. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands--A review. J Psychiatr Res 2015; 70: 50-57.

25) Matousek M, Mikuni M, Mitsube K, Yoshida M, Brännström M. Inhibition of ovulation by tyrosine kinase inhibitors in the in vitro perfused rat ovary. J Reprod Fertil 1999; 117: 379-385.

26) Cooper RL, Linnoila M. Effects of centrally and systemically administered L-tyrosine and L-leucine on ovarian function in the old rat. Gerontology 1980; 26: 270-275.

27) Baldrick P, Richardson D, Wheeler AW. Review of L-tyrosine confirming its safe human use as an adjuvant. J Appl Toxicol 2002; 22: 333-344.

28) van de Rest O, Bloemendaal M, de Heus R, Aarts E. Dose-dependent effects of oral tyrosine adminis-

tration on plasma tyrosine levels and cognition in aging. Nutrients 2017; 9. pii: E1279.

29) Kieliszek M, Błażejak S. Current knowledge on the importance of selenium in food for living organisms: a review. Molecules 2016; 21. pii: E609.

30) Negro R. Selenium and thyroid autoimmunity. Biologics 2008; 2: 265-273.

31) Razavi M, Jamilian M, Kashan ZF, Heidar Z, Mohseni M, Ghandi Y, Bagherian T, Asemi Z. Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. Horm Metab Res 2016; 48: 185-190.

32) Kowalczyk K, Franik G, Kowalczyk D, Pluta D, Blukacz Ł, Madej P. Thyroid disorders in polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 2017; 21: 346-360.

33) Vincent JB. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. Sports Med 2003; 33: 213-230.

34) Broadhurst CL, Domenico P. Clinical studies on chromium picolinate supplementation in diabetes mellitus-a review. Diabetes Technol Ther 2006; 8: 677-687.

35) Fazelian S, Rouhani MH, Bank SS, Amani R. Chromium supplementation and polycystic ovary syndrome: a systematic review and meta-analysis. J Trace Elem Med Biol 2017; 42: 92-96.

36) Wild RA, Vesely S, Beebe L, Whitsett T, Owen W. Ferriman-Gallwey self-scoring: performance assessment in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90: 4112-4114.

37) Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. 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 2010: 95; 2038-2049.

38) Bil E, Dilbaz B, Cirik DA, Ozelci R, Ozkaya E, Dilbaz SJ. Metabolic syndrome and metabolic risk profile according to polycystic ovary syndrome phenotype. Obstet Gynaecol Res 2016; 42: 837-843.

39) Nas K, Tűű L. A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women. Eur Rev Med Pharmacol Sci 2017; 21: 77-82.

40) Cappelli V, Musacchio MC, Bulfoni A, Morgante G, De Leo V. Natural molecules for the therapy of hyperandrogenism and metabolic disorders in PCOS. Eur Rev Med Pharmacol Sci 2017: 21 (2 Suppl): 15-29.

41) Matsuzaki T, Tungalagsuvd A, Iwasa T, Munkhzaya M, Yano K, Mayila Y, Tokui T, Yanagihara R, Matsui S, Kato T, Kuwahara A, Irahara M. Clinical outcome of various metformin treatments for women with polycystic ovary syndrome. Reprod Med Biol 2017; 16: 179-187.

42) Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocr Connect 2017; 8: 647-658.

43) Lucidi RS, Thyer AC, Easton CA, Holden AE, Schenken RS, Brzyski RG. Effect of chromium supplementation on insulin resistance and ovarian and menstrual cyclicity in women with polycystic ovary syndrome. Fertil Steril 2005; 84: 1755-1757.

44) Lydic ML, McNurlan M, Bembo S, Mitchell L, Komaroff E, Gelato M. Chromium picolinate improves insulin sensitivity in obese subjects with polycystic ovary syndrome. Fertil Steril 2006; 86: 243-246.

45) Brownley KA, Boettiger CA, Young L, Cefalu WT. Dietary chromium supplementation for targeted treatment of diabetes patients with comorbid depression and binge eating. Med Hypotheses 2015; 85: 45-48.

46) Mistry HD, Broughton Pipkin F, Redman CW, Poston L. Selenium in reproductive health. Am J Obstet Gynecol 2012; 206: 21-30.

47) Zagrodzki P, Krzyczkowska-Sendrakowska M, Nicol F, Wietecha-Posłuszny R, Milewicz T, Kryczyk-Kozioł J, Chaykivska Z, Jach R. Selenium status parameters in patients with polycystic ovary syndrome. J Trace Elem Med Biol 2017; 44: 241-246.

48) Kose SA, Naziroglu M. Selenium reduces oxidative stress and calcium entry through TRPV1 channels in the neutrophils of patients with polycystic ovary syndrome. Biol Trace Elem Res 2014; 158: 136-142.

49) Gateva A, Unfer V, Kamenov Z. The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review. Gynecol Endocrinol 2018; 34: 545-550.

50) Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol 2009; 25: 508-513.

51) Calzada M, López N, Noguera JA, Mendiola J, Hernández AI, Corbalán S, Sanchez M, Torres AM. AMH in combination with SHBG for the diagnosis of polycystic ovary syndrome. J Obstet Gynaecol 2019; 17: 1-7.

52) Ding X, Yang L, Wang J, Tang R, Chen O, Pan J, Yang H, Chen X, Chen Z, Mu L. Subclinical hypothyroidism in polycystic ovary syndrome: a systematic review and meta-analysis. Front Endocrinol 2018; 9: 700.

53) Nordio M, Basciani S. Myo-inositol plus selenium supplementation restores euthyroid state in Hashimoto's patients with subclinical hypothyroidism. Eur Rev Med Pharmacol Sci 2017; 21 (2 Suppl): 51-59.

54) Ferrari SM, Fallahi P, Di Bari F, Vita R, Benvenga S, Antonelli A. Myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with autoimmune thyroiditis. Eur Rev Med Pharmacol Sci 2017; 21 (2 Suppl): 36-42.