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Original Article

Serum Caspase-1 levels in women with polycystic ovary syndrome

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ABSTRACT

Objective: Caspase-1 is implicated in several important inflammatory diseases and controls adipocyte differentiation and insulin sensitivity. Interleukin-10 (IL-10) is an anti-inflammatory cytokine and plays an important role in chronic inflammatory conditions. This study was planned to determine if there is any relationship between Caspase-1 and IL-10 levels in women with PCOS.
Materials and methods: Forty-two women with PCOS and thirty-seven healthy controls were evaluated in this controlled clinical study. Caspase-1 and IL-10 levels, serum lipid sub-fractions, fasting glucose, fasting insulin and other hormones (gonadotropins, androgens), malondialdehyde (MDA) and glutathione (GSH) levels were measured. Homeostasis model assessment (HOMA-IR) was used to estimate insulin resistance.
Results: Free androgen index (FAI), HOMA-IR, MDA and Caspase-1 levels were significantly higher in subjects with PCOS. However, the women with PCOS had considerably lower GSH concentration levels than healthy subjects. Serum IL-10 levels were higher in study subjects than in controls, though it was statistically insignificant. Caspase-1 was positively associated with IL-10.
Conclusion: These outcomes propose that Caspase-1 may have a role in triggering the processes leading to chronic low-grade inflammation in women with PCOS, independent of insulin resistance, androgen excess and oxidative stress. Nevertheless, the precise role of Caspase-1 in the pathogenesis of the disease remains to be elucidated.
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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder, affecting about 7% of women of childbearing age [1], and is characterized by chronic anovulation, hyperandrogenism, and disordered gonadotropin secretion [2]. Its clinical and biochemical manifestations may include oligo-amenorrhea, visceral obesity, enlarged cystic ovaries, elevated luteinizing hormone (LH), signs of androgen overproduction and subfertility.

Independent of obesity, insulin resistance plays pivotal roles in the pathogenesis of PCOS, though the mechanisms underlying PCOS are not entirely understood [3]. Hyperinsulinemia accelerates the ovarian hyperandrogenism [4]. It may also contribute to the development of diabetes and dyslipidemia in women with PCOS [2].

Oxidative stress is an imbalance between the productions of free radicals and antioxidant status [5]. It is considered that increased chemical reactivity may cause molecular damage [5,6]. Oxidative stress is also known to be increased in the pathogenesis of several diseases such as diabetes and PCOS [6,7].

Caspases (cysteine-aspartic proteases) are a family of cysteine proteases, which play essential roles in apoptosis [8]. Caspase-1 is also a protease that activates some proinflammatory cytokines like proIL-1β [9]. Caspase-1 is implicated in several important inflammatory diseases. Caspase-1 activation controls adipocyte differentiation and insulin sensitivity [10]. Studies show that PCOS may also be related to a low-grade chronic inflammation, most probably through the development of insulin resistance [11].

Interleukin-10 (IL-10) is an anti-inflammatory cytokine [12]. IL-10 plays important role in chronic inflammatory conditions [13]. It

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limits inflammatory responses and thus prevents damage to the host. In addition, it was shown in some animal studies that IL-10 might increase insulin sensitivity [14].

All of the aforementioned data can address the question as to whether there is an association between serum Caspase-1 and IL-10 levels in women with PCOS.

This study was designed to determine serum Caspase-1 and IL-10 levels and establish whether serum Caspase-1 and IL-10 levels are related with insulin resistance, oxidative stress, ovarian hyperandrogenism, and dyslipidemia in women with PCOS. Oxidative stress and antioxidant statuses were evaluated by the levels of malondialdehyde (MDA) and glutathione (GSH), respectively. To the best of our knowledge, we present the first study concerning serum Caspase-1 levels in PCOS.

Materials and Methods

Subjects

Forty-two patients with PCOS (study group) aged between 16 and 39 years and thirty-seven healthy women (control group) aged between 18 and 37 years were included in the study. Health status of subjects was determined by medical history, physical and pelvic examinations, and blood chemistry. This investigation was approved by local medical ethics committee and all participants gave informed consent before the onset of study.

The diagnosis of PCOS was based on the recommendations of Rotterdam consensus conference on PCOS by at least two of the following three features: i) oligo- or anovulation, ii) clinical and/or biochemical signs of hyperandrogenism, and iii) polycystic ovaries [15]. Common findings of the PCOS group were; 12 or more subcapsular follicles by transvaginal ultrasonography, clinical hyperandrogenism with the presence of acne and hirsutism (Ferriman-Gallwey score of $\geq$8), [16] and oligomenorrhea (fewer than six menstrual periods in the preceding year). Exclusion criteria comprised endocrinopathies including Diabetes Mellitus, Cushing's syndrome, androgen secreting tumors, late-onset 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia, infectious diseases, hypertension, family history of cardiovascular disease, use of medications known to alter insulin secretion or action and lipoprotein metabolism, contraceptive pill or any type of medication for the treatment of PCOS and consuming alcohol and/or smoking.

The subjects in healthy group had regular menstrual cycles (cyclic uterine bleedings with duration of 4–5 days and a frequency of 25–34 days) and none of them met any exclusion criteria mentioned above.

Biochemical analysis

Venous blood samples were drawn in the morning after at least 10 h of fasting on the study day (on cycle days 3–5 after spontaneous or progesterone-induced menses in the healthy and PCOS groups). Samples were collected in serum separator tubes, allowed to clot for 30 min, centrifuged for 15 min at 2000×*g* at room temperature, and aliquoted into polypropylene tubes. All biochemical measurements were performed on same day except Caspase-1 and IL-10. Measurement of serum Caspase-1and IL-10 level was not included in our routine, and commercial kits for Caspase-1 were limited quantities; thus for serum Caspase-1and IL-10 measurements, blood samples were centrifuged to obtain plasma samples and were kept at −80 °C until they were analyzed. Biochemical measurements were done by using commercial kits. The sera were assayed for fasting glucose (F.Glc), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), insulin, sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, MDA, GSH. Serum glucose, total cholesterol and triglyceride concentrations were measured using standard enzymatic methods (Roche Diagnostics, IN, US) with a fully automated analyzer (Roche Modular PE, Roche Diagnostics, IN, US). HDL concentrations were measured without precipitation by using liquid selective detergent homogeneous technique (Roche HDL plus 2nd generation, Roche Diagnostics, IN, US). Low-density lipoprotein cholesterol (LDL) levels were calculated by Friedewald's formula. SHBG measurements were performed using a solid phase competitive chemiluminescence immunoassay (IMMULITE 2000, DPC Biosystems, CA, USA). FSH, LH, total testosterone and Fasting insulin concentrations were measured using electrochemiluminescence's immunoassay (Roche Diagnostics, IN, US) with a fully automated analyzer (Roche Modular PE, Roche Diagnostics, IN, US).

Insulin resistance was calculated by using homeostasis model assessment (HOMA-IR) score that employs the formula: fasting insulin concentration (mIU/l) × glucose (mmol/l)/22.5 [17]. Individuals with HOMA-IR > 2.7 were accepted as insulin resistant [18]. Free androgen index (FAI) was defined here as 100 times the molar ratio of total testosterone to SHBG [FAI = 100 × total testosterone (nmol/l)/SHBG (nmol/l)].

The serum MDA levels were determined by the procedure of Ohkawa et al. [19] 0.5 ml of serum was mixed with 1.5 ml thiobarbituric acid (0.8%), 1.5 ml acetic acid (pH 3.5, 20%), 0.2 ml sodium dodecyl sulfate (8.1%) and 0.5 ml distilled water. After mixing, all samples and standards were heated at 100 °C for 1 h. The absorbance was recorded at 532 nm and compared with those of MDA standards.

GSH estimation was achieved by our modified procedure described previously [20]. After hemolysis and filtration with deproteinization solution (sodium chloride, metaphosphoric acid, EDTA and distilled water), 0.4 ml filtrate is mixed with 1.6 ml Na_2HPO_4 (0.3 M) solution and 0.2 ml Ellman reactive (DTNB; dithiodinitrodibenzoic acid, sodium citrate, distilled water). The absorbance was recorded at 412 nm.

ELISA was used to determine the plasma levels of Caspase-1 (USCN Life Science Inc.) and performed according to the manufacturer's instructions. Briefly, standard control samples for Caspase-1 were diluted serially between 20 and 0 ng/ml. The standard samples (100μl/well) and plasma samples (100μl/well) were added to the primer antibody coated microplate and incubated for 24 h at 37 °C. Then, the secondary antibody solution (100μl/well) was added to the wells and incubated at 37 °C for 30 min. The washing steps were applied after both primary and secondary antibody incubations. Following TMB substrate incubation, the color reaction was stopped and the optical density of each sample was measured at 450 nm wavelength. All samples were tested in triplicate.

Plasma IL-10 concentration was determined by ELISA using Human IL-10 ELISA kit (Boster Immunoleader). In brief, the standard control samples were prepared from stock solution in concentrations ranging from zero to 500 pg/ml. The standards and plasma samples (100μl/well) were transferred into the wells of the primer antibody coated microplate. Following a 90 min incubation at 37 °C, the freshly prepared anti-antibody solution (100μl/well) was added to the wells and the plate was incubated for 1 h at 37 °C followed by three washing step. Then, TMB substrate solution was transferred into the wells. In order to obtain readable O.D. values at 450 nm wavelength, the reaction was stopped by adding stopping solution. All analyses were performed in triplicate.

Anthropometric measurements

All anthropometric measurements were done by the same physician on the day blood specimen were taken. Height, weight,

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and waist circumferences of the subjects were obtained in light clothing without shoes. Height was measured as the distance from the top of the head to the bottom of the feet (no shoes) using a fixed stadiometer. Waist circumference (cm) was taken with a tape measure as the point midway between the costal margin and iliac crest in the mid-axillary line with the subject standing and breathing normally. Body mass index (BMI) (Body weight (kg)/ height m^2) was computed.

Statistical analysis

At the beginning of the study, all study participants were matched for age and BMI. The healthy controls were defined as age- and BMI-matched with subjects when the number of year's ± age of subjects and the BMI of subjects were less than to 2 years and less than to 1 kg/m^2, respectively. Data were analyzed with the SPSS (Statistical Package for the Social Science, version 17.0). Since many variables had a Gaussian distribution with no significant skewness, statistical analysis was performed with a parametric test: Student's t-test. Correlations between variables were calculated with Pearson's correlation coefficient. The data are expressed as means ± SE. All P values presented are two-tailed; $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences in the waist measurements, serum LH, total testosterone, fasting glucose, and HDL levels between the groups *($p > 0.05$)*. The women with PCOS had considerably higher LH/FSH ratio, FAI, HOMA-IR, serum fasting insulin, total cholesterol, triglyceride, LDL, MDA and Caspase-1 levels than healthy women *($p < 0.05$)*. However, serum FSH, SHBG, and GSH concentrations were significantly lower in patients with PCOS compared with healthy women *($p < 0.05$)*. Serum IL-10 levels were higher in study subjects than in controls, although it was statistically insignificant (Tables 1 and 2).

Caspase-1 was positively associated with IL-10 ($r = 0.37$, $p = 0.001$). GSH was negatively correlated with triglyceride levels ($r = -0.29$, $p = 0.01$). LH/FSH ratio was inversely related with BMI ($r = -0.24$, $p = 0.036$). Insulin was negatively correlated with SHBG ($r = -0.26$, $p = 0.021$), but positively with FAI ($r = 0.23$, $p = 0.042$). As expected HDL was inversely associated with LDL ($r = -0.22$, $p = 0.049$).

Table 1
Clinical features and steroid levels for both the women with PCOS and the healthy controls.

Variable	Women with PCOS (n = 42)	Healthy Controls (n = 37)	*p*
Age (years)	24.4 ± 0.6	25.6 ± 0.7	0.18
BMI (kg/m^2)	23.4 ± 0.7	23.1 ± 0.5	0.71
Waist (cm)	79.8 ± 2.0	81.8 ± 2.3	0.53
FSH (mIU/ml)	5.6 ± 0.2	6.5 ± 0.3	0.008[a]
LH (mIU/ml)	10.2 ± 0.6	8.3 ± 0.8	0.08
LH/FSH ratio	1.9 ± 0.1	1.3 ± 0.1	0.001[a]
Total testosterone (ng/ml)	0.34 ± 0.03	0.32 ± 0.02	0.44
SHBG (nmol/l)	21.9 ± 1.7	36.8 ± 7.7	0.0001[a]
FAI	7.6 ± 1.1	4.1 ± 0.6	0.008[a]

[a]$p < 0.05$ statistically significant. BMI: Body Mass Index, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, SHBG: Sex Hormone-Binding Globulin, FAI: Free Androgen Index.

Table 2
Metabolic characteristics, oxidants, antioxidants, IL-10 and Caspase-1 levels for both the women with PCOS and the healthy controls.

Variable	Women with PCOS (n = 42)	Healthy Controls (n = 37)	*p*
Fasting glucose (mg/dl)	91.5 ± 2.6	90.6 ± 1.8	0.77
Fasting Insulin (μIU/ml)	13.3 ± 1.2	8.7 ± 1.1	0.006[a]
HOMA-IR	3.1 ± 0.3	2.0 ± 0.3	0.021[a]
Total cholesterol (mg/dl)	172.7 ± 3.9	152.2 ± 3.8	0.0001[a]
Triglyceride (mg/dl)	102.0 ± 8.2	62.0 ± 4.3	0.0001[a]
HDL (mg/dl)	56.9 ± 2.2	60.2 ± 2.2	0.29
LDL (mg/dl)	95.4 ± 3.9	79.6 ± 3.1	0.003[a]
MDA (nmol/ml)	12.2 ± 3.0	2.3 ± 0.06	0.002[a]
GSH (μmol/gHb)	3.01 ± 0.2	4.10 ± 0.3	0.001[a]
IL-10 (pg/ml)	64.7 ± 23.6	34.6 ± 13.3	0.28
Caspase-1(pg/ml)	7.3 ± 2.6	1.7 ± 0.1	0.039[a]

[a]$p < 0.05$ statistically significant. HOMA-IR: homeostasis model assessment HDL: high-density lipoprotein-cholesterol, LDL: low-density lipoprotein-cholesterol, MDA: Malondialdehyde, GSH: Glutathione, IL-10: Interleukin 10.

Discussion

A chronic low-grade subclinical inflammation has been observed in PCOS [21]. In fact, the serum IL-18 levels are elevated in patients with PCOS, and polymorphisms of the IL-1a, IL-1b, and IL-6 genes have been related with PCOS [22]. On the other hand, caspase-1 induces innate inflammatory response by activating the maturation and extracellular secretion of some proinflammatory cytokines such as IL-1β and IL-18 [23]. Caspase-1 activation occurs in special inflammasome complexes. Furthermore, Caspase-1 is involved in necrotic inflammatory host cell death [24]. In our investigation, a significant increase in serum Caspase-1 levels was determined in women with PCOS. There were no relationship between Caspase-1 and other parameters except serum IL-10 concentrations. It can be assumed that Caspase-1 might have a role in triggering the processes leading to chronic low-grade subclinical inflammation in PCOS independent of insulin resistance, androgen excess and oxidative stress.

IL-10 is a regulatory cytokine of chronic inflammatory circumstances [12]. It has a suppressive effect on the production of interferon gamma (IFNγ) in T cells and IL-1α, IL-1β, IL-6, IL-8, IL-12 and tumor necrosis factor-alpha (TNF-α) in macrophages [25]. IL-10 levels in study subjects were increased but this was not statistically significant. Interestingly, IL-10 levels were positively related with Caspase-1 levels. This increase in serum IL-10 levels may be compensatory against the chronic inflammatory process. These outcomes propose that an impaired balance between anti-inflammatory and proinflammatory cytokines may contribute to inflammatory responses in the pathogenesis of PCOS.

It was suggested that high IL-10 levels might ameliorate insulin resistance by regulating inflammatory responses of TNF-α and IL-6 [26]. However, the outcomes of current study were not consistent with the observation mentioned above. The explanation may be that the association between IL-10 and insulin resistance and androgen excess may not be as strong as we thought in women with PCOS.

Oxidative stress is one of the major reasons of several pathological disorders, especially in terms of molecular damage to cellular structures [27]. We previously showed that there was increased oxidative stress and decreased antioxidant capacity in women with PCOS [7]. MDA is a biomarker using to determine oxidative damage to biomolecules [28]. In this study, considerably higher serum MDA levels were observed in study group. Thus, it is clear that there is an increased oxidative stress in PCOS. On the other hand, serum MDA levels were not correlated with other parameters. The few numbers of the subjects in this study may be a reason.

Antioxidant status has a multicompartmental protective effect on cellular and tissue structures. The reduction in antioxidant capacity contributes to the molecular damage of oxidative stress. Antioxidant capacity is a consequence of the interactions between

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individual antioxidants. Therefore, the cumulative index of plasma antioxidant levels are described as total antioxidant status. GSH is one of the several biomarkers to determine antioxidant status. Significantly lower erythrocyte reduced GSH levels in women with PCOS were found in our study. These outcomes were in agreement with some previous studies [6,7]. It will be logical to assume that decreased antioxidant capacity may further contribute to the harmful effects of increased oxidative stress in patients with PCOS.

The most frequent forms of dyslipidemia contain reduced HDL, and elevated LDL, total cholesterol, triglyceride levels. Dyslipidemia is related with oxidative stress and insulin resistance [29]. In current study, we did not observe any association between serum Caspase-1 levels and lipid fractions. Nevertheless, considerably increased total cholesterol, triglyceride and LDL levels in women with PCOS were found in this study. HDL level was slightly lower in study group; but the difference was statistically insignificant. We could not found any relationship between lipid fractions and insulin resistance and oxidative stress parameters. Only, serum GSH level was negatively correlated with triglyceride level. The selection of the subjects, who had normal BMI, might be a reason. Further studies including both obese and lean PCOS patients and controls are needed for better assessment of the issue.

There is a positive relationship between hyperinsulinemia and the ovarian hyperandrogenism [4]. This observation was also confirmed by the outcomes of the current study. In fact, insulin levels were positively correlated with FAI, and increased clinical and biochemical signs of hyperandrogenism were observed in women with PCOS in our study.

In conclusion, the results of this study suggest that Caspase-1 may have a role in triggering the processes leading to chronic low-grade inflammation in the pathogenesis of PCOS, although increased circulating Caspase-1 level was not associated with insulin resistance, ovarian hyperandrogenism, and oxidative stress in women with PCOS. Nevertheless, the precise role of Caspase-1 in the pathogenesis of the disease remains to be elucidated. In terms of Caspase-1 activity, further studies are needed in PCOS, especially in molecular basis.

Declaration of Competing Interest

Authors declare that there is no funding for the study.

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