Plasma apelin levels in patients with polycystic ovary syndrome

Polikistik over sendromlu hastalarda plazma apelin düzeyleri

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Abstract

Objective: The aim of the study was to evaluate plasma apelin levels in patients with polycystic ovary syndrome (PCOS) and healthy controls.

Material and Methods: Plasma apelin levels, serum lipid levels, serum hormone levels, and homeostasis model assessment-insulin resistance (HOMA-IR) values of 32 patients with PCOS and 31 healthy women forming the control group were checked.

Results: Plasma apelin levels of the PCOS group (0.350±0.083 ng/ml) were significantly higher than those of the control group (0.246±0.045 ng/ml) ($p<0.001$). No significant correlation was detected between apelin levels and biochemical or clinical data in PCOS group.

Conclusion: Plasma apelin levels were significantly higher in PCOS patients. (J Turkish-German Gynecol Assoc 2012; 13: 27-31)

Key words: Apelin, polycystic ovary syndrome, Homeostatic Model Assessment insulin resistance (HOMA-IR), Ferriman Gallwey score (FGS), waist to hip ratio

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Özet

Amaç: Bu çalışmanın amacı, polikistik over sendromu (PKOS) hastaları ve sağlıklı kontrol grubundaki hastalarda, plazma apelin düzeylerini değerlendirmektir.

Gereç ve Yöntemler: Plazma apelin düzeyleri, serum lipid düzeyleri, serum hormon düzeyleri ve homeostasis model assessment-insulin rezistans (HOMA-IR) değerleri 32 PCOS'lu hasta ve sağlıklı kadın kontrol grubunu oluşturan 31 hastada ölçüldü.

Bulgular: Plazma apelin düzeyleri PKOS grubunda (0.350±0.083 ng/ml), kontrol grubuna göre (0.246±0.045 ng/ml) ($p<0.001$) anlamlı olarak daha yüksek bulundu. PKOS grubundaki apelin düzeyleri ile biyokimyasal veya klinik veriler arasında anlamlı bir ilişki tespit edilmedi.

Sonuç: Plazma apelin düzeyleri PCOS'lu hastalarda anlamlı olarak daha yüksektir.(J Turkish-German Gynecol Assoc 2012; 13: 27-31)

Anahtar kelimeler: Apelin, polikistik over sendromu, Homeostatic Model Assessment insülin rezistansı (HOMA-IR), Ferriman Gallwey skoru (FGS), bel kalça oranı

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Introduction

Polycystic ovary syndrome (PCOS) is the most frequent reproductive endocrinopathy in fertility age women and, although varying among different diagnostic criteria, its frequency is about 6-8% in the reproductive period (1). PCOS is a syndrome characterized by menstrual dysfunction, infertility, hyperandrogenism and insulin resistance (2). Patients with PCOS have long term risks such as cardiovascular diseases, type 2 diabetes mellitus (DM), dyslipidemia and endometrial cancer (3). In addition, more than 50% of patients have android type obesity and increased waist to hip ratio (WHR), which are related with cardiovascular disease and increased diabetes mellitus risk (4).

After the discovery of adipokines, which are adipose tissue derived peptides, authors have recently become interested in the relationship of PCOS with adipokines. Adipokines are biologically active peptides secreted from adipose tissue (5), and it has been shown that tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), C reactive protein (CRP), insulin like growth factor 1 (IGF-1), sex steroids, resistin, visfatin, adiponectin and apelin had connection with insulin resistance (6). Apelin is a recently discovered peptide that was designated as an endogenous receptor ligand and is found in several organs like heart, brain, kidneys and lungs (7, 8). In recent studies, various levels of apelin and apelin receptor (APJ) expression have been observed in different stages of cattle ovarian follicles (9, 10).

Apelin was found to be related with obesity and insulin resistance (11, 12). It has been shown that this adipokine had effects on water intake and hypothalamo-hypophyseal axis (13). Apelin has also been found to effect cardiovascular system in

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terms of hypotension (14), positive inotrophy and angiogenesis (15, 16). It has also been reported that apelin and apelinergic system were effective on mammalian ovarian development, follicular atresia and thecal tissue angiogenesis (9, 10).
The aim of our study was to compare plasma apelin levels in patients with PCOS and healthy control subjects and to determine the correlations between apelin and hormonal and biochemical data.

Materials and Methods

We enrolled 32 women with PCOS and 31 healthy controls, between ages 18 to 35 years. All subjects were given informed consent prior to the study. Local ethical committee approval was obtained before the study was undertaken.
The inclusion criteria for both groups were being between ages 18-35 years not having systemic diseases like atherosclerosis, diabetes mellitus and hypertension, not using oral contraceptives during or 6 months before the research period and not having undiagnosed uterine bleeding or a diagnosis of neoplasia before being included into the study. Diagnosis of PCOS was made according to the diagnostic criteria of European Society for Human Reproduction and Embryology and The American Society for Reproductive Medicine (ESHRE/ASRM) guidelines (17). According to these guidelines, it was possible to reach a diagnosis of PCOS when at least 2 of these 3 elements are present: hyperandrogenism, chronic anovulation and polycystic ovaries.

Biochemical evaluation and Ultrasonography
Age, weight and height of all subjects included in the study were noted and body mass indices were calculated as kg/m^2. Hirsutism was evaluated with Ferriman Gallwey score (FGS) (17) and the waist to hip ratio (WHR) values was obtained by taking waist measurement (narrowest point between the ribs and iliac crest) and hip measurement (at the point of the greatest protrusion of the buttocks) and finding the ratio of the two measurements (18). Luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, free testosterone, total testosterone, androstenedione, sex hormone binding globulin (SHBG), dehydroepiandrostenedione sulphate (DHEA-S), 17-0H progesterone, prolactin, free T3 (fT3), free T4 (fT4), thyroid stimulating hormone (TSH), aspartate amino transferase (AST), alanine amino transferase (ALT), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, total cholesterol, fasting glucose and insulin levels were measured from the blood specimen taken between 08:00-10:00 am. on the 3rd day of the menstrual cycle, after 10 hours of fasting.
Serum glucose was measured with commercial kits (Roche Hitachi, Roche Diagnostics, Mannheim, Germany). Insulin resistance is defined as reduced glucose response to a given amount of insulin. The estimate of insulin resistance by the homeostasis model assessment-insulin resistance (HOMA-IR) was calculated in all patients with the following formula: HOMA-IR= Fasting insulin (mU/L) x fasting glucose (mmol/L)/ 22.5 (19). Of the hormonal parameters, LH, FSH, estradiol, total testosterone, DHEA-S, insulin, prolactin, fT3, fT4 and TSH were analyzed by immune chemiluminesance method (Roche-Hitachi Modular Analytics E-170, Indianapolis/USA), androstenedione, SHBG, 17-0H progesterone and free testosterone by micro ELISA method (Bio-tek instruments inc. Miroquant Cal/USA) and the biochemical parameters were studied by enzymatic colometric methods (Olympus AU 600 Tokyo/Japan).
Four cc blood specimen was centrifuged at 3500 revolution per minute (rpm) for 7 minutes in lavender tubes with EDTA, and the obtained plasma specimen were saved in -70°C to be further analyzed for plasma apelin levels. Plasma apelin levels were analyzed by enzyme immunoassay (EIA) method by using Phoenix Pharmaceuticals Apelin-36 (Human) EIA Cal./USA. kit, and Bio-tek instruments inc. Miroquant Cal/USA, Bio-tek instruments inc. ELX 50 auto strip washer Cal./USA and IKA schutter MTS-2 shaker Staufen/Germany devices were used.
Pelvic (Siemens Acuson CH6-2 5.71 MHz. abdominal probe, USA) or transvaginal (Siemens Acuson EC9-4 6.15 MHz. transvaginal probe, USA) ultrasonography was performed to all women (Siemens Acuson Antares™, USA). The ultrasonographic finding of 10-15 follicles with a diameter of 2-8 mm, forming the appearance of a pearl necklace and an increase in stroma and ovarian volume was considered as polycystic ovary appearance (1).

Statistical analysis
Data obtained from the study was analyzed by using 'Statistical Package for the Social Science' (Version 15.0; Inc, Chicago, IL, USA). The results were expressed as means±SD. The distribution of each variable was assessed by the Kolmogorov-Smirnov one sample test. When the data was in accordance with the normal distribution, Student's t-test was used, otherwise Mann Whitney U test was used to compare the groups. The relationship between continuous variables were evaluated by Pearson correlation coefficients. $p<0.05$ was considered statistically significant. Power analysis was performed by Power and Sample Size Calculator V.3.0 for apelin.

Results

There was no significant difference between the ages of women with PCOS and the control group ($p>0.05$). Apelin levels ($p<0.001$), waist to hip ratios ($p=0.002$), Ferriman Gallwey scores, free testosterone levels ($p=0.034$), triglyceride levels ($p=0.021$), 17-OH progesterone levels ($p=0.048$) and LH/FSH ratio ($p=0.011$) of the PCOS group were significantly higher than the control group and HDL and SHBG levels of the PCOS group were lower than the control group ($p=0.005$ and $p=0.01$ respectively). No significant difference was found between the other parameters. The comparison of clinical and biochemical parameters were shown in Tables 1 and 2.
No significant correlation was detected between apelin levels and biochemical or clinical data in patients with PCOS and the control group except for the negative correlation between apelin and SHBG levels in the control group ($r=-0.492$, $p=0.004$). Besides, significant positive correlations were detected between BMI and waist to hip ratio and BMI and HOMA-IR

values in the PCOS group (r=0.459, p=0.008 and r=0.365, p=0.040 respectively).

Discussion

In our study, apelin levels were found to be higher in patients with PCOS compared to the controls. No correlation was found between apelin and the other parameters in either groups except for the negative correlation between apelin and SHBG in the control group. We have also found positive correlations between BMI and waist to hip ratio and BMI and HOMA-IR values in patients with PCOS. Both groups consisted of subjects with normal weights and there was no significant difference between the groups in terms of BMI. Obesity is observed about 50-70% in patients with PCOS and mostly in the form of android obesity where waist to hip ratio increases. Android type obesity and increase in intraabdominal adiposity were also shown in non-obese PCOS patients (18). In this study, waist to hip ratios were found to be significantly higher in the PCOS group and this complies with the literature verifying an increase in waist to hip ratios in normal weighted PCOS patients. In recent studies it has been found that BMI and apelin levels were positively correlated (11, 12). In the present study although apelin levels and WHR were higher in the PCOS group, there was no correlation between WHR and apelin levels. In this context, higher levels of apelin in patients with PCOS may be associated with the other mechanisms besides android obesity.

Android type obesity seen in polycystic ovary syndrome is related with hyperinsulinemia, glucose tolerance impairment, diabetes and increase in androgen production (20). In our study, no statistically significant correlation was established between apelin and HOMA-IR levels. However, previous studies demostrated the relationship between apelin and insulin resistance in humans and rats (6, 11). In our study, mean HOMA-IR

Table 1. Demographic characteristics of the PCOS and the control groups

	PCOS Mean±SD	CONTROL Mean±SD	p
Age (Years)	23.81±4.38	23.55±4.13	0.807
BMI (kg/m^2)	22.51±3.20	21.94±1.63	0.376
WHR	0.75±0.06	0.71±0.03	0.002
FGS	14.31±3.89	4.32±1.68	<0.001

BMI: body mass index, WHR: waist to hip ratio, FGS: Ferriman Gallwey score

Table 2. The comparison of PCOS and the control groups in respect of biochemical and hormonal parameters

	PCOS Mean±SD	CONTROL Mean±SD	p
Apelin (ng/ml)	0.350±0.083	0.246±0.045	<0.001
LH/FSH	1.91±0.85	1.38±0.74	0.011
E2 (pg/ml)	54.24±27.65	52.97±23.58	0.846
Prolactin (ng/ml)	15.87±4.52	13.96±6.22	0.166
TSH (μU/ml)	1.94±1.02	1.98±0.83	0.857
FT3 (pg/ml)	3.32±0.43	4.24±5.53	0.351
FT4 (pg/ml)	16.59±2.11	16.76±1.82	0.734
DHEA-S (μg/dl)	285.36±119.22	256.01±122.33	0.339
Androstenedione (ng/ml)	3.02±1.43	2.85±1.19	0.597
Free testosterone (pg/ml)	2.40±1.67	1.59±1.29	0.034
Total testosterone (ng/ml)	0.639±0.356	0.605±0.488	0.752
SHBG (nmol/L)	47.26±28.83	68.48±34.45	0.010
17-OHP (ng/ml)	1.40±1.10	1.00±0.50	0.048
Insulin (μU/ml)	11.52±6.91	10.02±5.02	0.331
Glucose (mg/dl)	89.56±8.85	87.74±9.64	0.438
HOMA-IR	2.58±1.65	2.17±1.05	0.245
TG (mg/dl)	86.97±35.01	69.48±22.93	0.021
HDL (mg/dl)	54.29±10.74	63.16±13.31	0.005
LDL (mg/dl)	80.67±24.37	81.54±21.70	0.881
Total cholesterol (mg/dl)	154.13±26.96	158.16±25.22	0.542

LH: luteinizing hormone, FSH: follicle stimulating hormone, E2: estradiol, SHBG: sex hormone binding globulin, DHEA-S: dehydroepiandrostenedione sulphate, 17-OHP: 17-0H progesterone, FT3: free T3, FT4: free T4, TSH: thyroid stimulating hormone, TG: triglyceride LDL: low density lipoprotein, HDL: high density lipoprotein, HOMA-IR: homeostatic model assessment insülin resistance

values in the PCOS group were higher than that of the controls, although the difference was not statistically significant. In the literature, many studies demostrating insulin resistance in non-obese PCOS patients exist (21-23), as well as the other studies stating that insulin resistance was not different than the normal population as in our study (24, 25).

Although it is difficult to evaluate, apelin levels in patients with PCOS due to lack of sufficient studies, other studies assessing different adipokines may be illuminating. For example, TNF-α levels were found to be higher in patients with PCOS than healthy women in some studies (26), and similar in others (27). Also, TNF-α was shown to contribute to insulin resistance in non-obese PCOS patients (28). It was shown that TNF-α increased apelin levels in human adipose tissue (29). There are also studies emphasizing visfatin, which is an adipokine that has similar properties like apelin, increased in patients with PCOS (30). Adiponectin levels were found to be lower in PCOS patients than healthy women (31). We have observed higher levels of apelin in patients with PCOS but the mechanisms underlying were not investigated in this study. In cause-effect relationship, higher levels of plasma apelin in PCOS might be related to androgenic obesity, increased waist to hip ratio, increased adiposity, impairment in LH/FSH interaction, hypothalamo-hypophyseal axis effects and local paracrine and endocrinological attitudes deriving from the nature of the polycystic ovaries and also the compensatory mechanisms due to the metabolic changes in PCOS.

Recent studies have shown that apelin had potential therapeutic effects. Centrally (ICV) injected apelin-13, decreased food intake in both fed and hungry mice; this effect was not seen in peripheral usage of apelin and this shows that apelin induces anorectic effects (32). Apelin increased core body temperature independent of food intake, increased locomotor activity and contributed to negative energy balance (33). Also apelin inhibited glucose induced insulin secretion (34). In a recent study, it has been shown that 14 days of apelin application to lean and obese mice, decreased body fattening independent of food intake, decreased insulin, leptin and triglyceride levels and increased the expression of non-binding proteins and adiponectin levels (35). Although apelin is a potential treatment agent for cardiovascular diseases, insulin resistance, obesity and diabetes mellitus co-occur with PCOS, this subject is still disputable and broad comprehensive studies are required.

In our study, TG levels were found to be significantly higher and HDL levels were significantly lower in patients with PCOS than the control group, consistent with the literature (36). As in other studies, we have found that 17-OH progesterone and free testosterone levels were significantly higher and SHBG levels significantly lower in patients with PCOS (37). Also LH/FSH levels were significantly higher in the PCOS group, which is consistent with the literature (38).

In conclusion, we have found that the plasma apelin levels were higher in patients with PCOS compared to health controls. This high levels might be independent of serum androjen levels and BMI or IR. Further studies are required for clearly enlightening the mechanisms and physiopathology.

Conflict of interest

No conflict of interest was declared by the authors.

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