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Serum Preptin and Amylin Levels with Respect to Body Mass Index in Polycystic Ovary Syndrome Patients

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Background: Preptin and amylin are pancreatic hormones which participate in glucose homeostasis. This study aimed to evaluate how serum preptin and amylin levels are altered in polycystic ovary syndrome (PCOS) patients and healthy women based on BMI groups (<25 kg/m² and ≥25 kg/m²).





Material/Methods: This was a prospective randomized control study of 40 PCOS patients and 40 healthy women who were matched with respect to BMI (<25 kg/m² and ≥25 kg/m²).

Results: When compared to the healthy women, PCOS patients had significantly higher ovarian volumes, Ferriman-Gallwey scores, and free and total testosterone levels, but significantly lower amylin concentrations (p=0.001, p=0.001, p=0.049, p=0.021, and p<0.001, respectively). Both the normal-weight and overweight PCOS patients had significantly lower amylin levels than the normal-weight and overweight controls (p<0.001, p=0.009, p=0.001, and p=0.001, respectively). Amylin levels were negatively and significantly correlated with the Ferriman-Gallwey scores (r=-0.272, p=0.001) and ovarian volume (r=-0.206, p=0.007). Serum preptin levels were not elevated in either group.

Conclusions: Serum preptin levels are statistically similar in PCOS patients and BMI-matched healthy controls. Serum amylin levels are significantly higher in healthy controls than PCOS patients whether they are slim or overweight. These findings suggest the presence of mechanisms that can prevent the elevation in serum amylin concentrations that can occur in response to the impaired glucose metabolism in PCOS patients.

MeSH Keywords: **Body Mass Index • Islet Amyloid Polypeptide • Polycystic Ovary Syndrome**

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Background

Polycystic ovary syndrome (PCOS) is characterized by chronic oligo-anovulation, clinical or biochemical hyperandrogenism, hirsutism, acne, and male-type alopecia. PCOS is the most common endocrinopathy in females of reproductive age, with a prevalence ranging from 6% to 25%, depending on diagnostic criteria [1,2]. In addition, PCOS is closely associated with obesity, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, hypertension, and cardiovascular diseases [3,4].

Preptin is a peptide containing 34 amino acids and is secreted from pancreatic beta cells together with insulin, amylin, and pancreostatin in response to glucose. The preptin molecule is thought to be a physiological stimulant of insulin secretion. This peptide is derived from the area E of proinsulin-IGF-II, a precursor of mitogenic insulin-like growth factor II (IGF-II) which participates in regulating cell growth, differentiation, and metabolism. A relationship has been observed between preptin levels and insulin resistance in pancreatic beta cells. Although it has been shown that serum preptin levels increase in hyperinsulinemic conditions, the role of preptin in the pathogenesis of PCOS still remains unclear [5–7].

Amylin is also a pancreatic hormone with a neuropeptide structure. Amylin plays a role in glucose homeostasis by acting centrally to suppress glucagon secretion, which in turn inhibits hepatic glucose secretion. Amylin also reduces food intake and slows gastric emptying. Amylin is elevated in obesity and lowered in patients with diabetes. The use of pramlintide, a synthetic amylin analog, can reduce food intake in obese patients, leading to significant weight losses [8–11]. However, studies assessing serum amylin levels in PCOS patients have yielded inconsistent results [12–14].

The present study evaluated how serum preptin and amylin levels are altered in PCOS patients and healthy women based on body mass index (BMI) groups.

Material and Methods

This prospective randomized controlled study was conducted at the Gynecology and Obstetrics Clinic of the Recep Tayyip Erdoğan University Research and Training Hospital with the permission of the Non-Invasive Clinical Research Ethics Board at Recep Tayyip Erdoğan University (Grant number: 114/2017), between June and October 2017.

As the study was undertaken at the study center between June 2017 and November 2017, written informed consent was obtained from each participant.

Study design

This was a prospective randomized controlled study of 40 PCOS patients and 40 healthy women who were consecutively admitted to the Gynecology Department of the study center. Special care was taken to match PCOS patients and healthy women with respect to BMI.

The diagnosis of PCOS was made according to the criteria set by the PCOS Consensus Workshop Group, supported by the European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) [4]. A patient was diagnosed with PCOS if at least 2 of the following 3 criteria were fulfilled: (i) The presence of oligo-anovulation, oligomenorrhea, or amenorrhea, (ii) The presence of hirsutism, acne, and androgenic alopecia or biochemical hyperandrogenism (serum testosterone >60 ng/dl), and (iii) ultrasound imaging of increased volume (>10 ml) in at least 1 ovary and/or sonographic visualization of 12 or more follicles with diameters of 2 to 9 mm.

We assured that the healthy controls in this study did not have irregular menstrual cycles, increased androgen levels, hirsutism, or polycystic ovaries on ultrasonography.

Patients with Cushing's syndrome, 21-hydroxylase deficiency, congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, and diabetes were excluded from the study. The patients with chronic cardiovascular, hepatic, renal, and hematologic diseases and malignancies were also excluded. Moreover, patients using oral contraceptives, anti-androgens, glucocorticoids, anti-hypertensives, anti-diabetics, calcium supplements, and anti-obesity drugs and those who smoked tobacco or consumed alcohol were not included.

Transvaginal and/or transabdominal ultrasonography was performed in all patients so that the uterus size, endometrial thicknesses, and ovarian size were measured and follicle numbers were counted.

BMI values were computed as follows:
 $BMI = \text{body weight (kg)} / \text{height}^2 (\text{m}^2)$.

The individuals with $BMI < 25 \text{ kg/m}^2$ were defined as normal weight, and the individuals with $BMI \geq 25 \text{ kg/m}^2$ were defined as overweight according to the World Health Organization criteria [15]. The Ferriman-Gallwey scoring system was used to evaluate hirsutism. The absence of terminal hair growth was scored as 0 and the maximal growth was scored as 4+ and a total sum of ≥ 6 in 11 body parts was defined as hirsutism [16].

Laboratory studies

Venous blood samples were obtained in the early morning (9–10 am) on the 3rd to 5th days of the menstrual cycle, which was spontaneous or induced by progesterone. Fasting plasma glucose levels were measured by photometric analysis (Abbott Architect C16000 AutoAnalyzer, Abbott Diagnostics, USA). Fasting serum insulin, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, dehydroepiandrosterone sulfate (DHEAS), total testosterone, and thyroid stimulating hormone (TSH) levels were measured by chemiluminescent microparticle enzyme immunoassay (Abbott Architect i2000, Abbott Diagnostics, USA). Serum 17 hydroxyprogesterone (17-OHP) and free testosterone levels were specified by radioimmunoassay and high-sensitive C-reactive protein (hs-CRP) concentrations were measured by immunoturbidimetry (Abbott Architect C16000 AutoAnalyzer, Abbott Diagnostics, USA). The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index was calculated as follows: $HOMA-IR = \text{Fasting plasma glucose (mmol/l)} \times \text{Fasting serum insulin (mIU/ml)} / 22.5$

Measurement of preptin and amylin

Serum preptin levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available matched antibodies (SunRed, Shanghai, China). Serum amylin levels were specified by enzyme-linked immunosorbent analysis (ELISA) using commercially available matched antibodies (RayBiotech, Norcross GA 30092, USA). The assumption and intermediary coefficients of variation were 10.0% and 15%, respectively. Absorbance was measured at 450 nm wave length using an ELISA reader and the sensitivity was calculated to be 620 pg/ml. Preptin and amylin levels are given in pg/ml.

Statistical analysis

Collected data were analyzed using the Statistical Package for Social Sciences version 24.0 (SPSS, SPSS IBM, Armonk, NY, USA). Data distribution and variance homogeneity were tested by Shapiro-Wilk test and Levene test, respectively. Continuous variables are expressed as mean \pm standard deviation (range: minimum-maximum). The independent-samples *t* test was used with the bootstrap results and the Mann-Whitney U test was used with Monte Carlo simulation technique for continuous variables of 2 independent groups. One-way analysis of variance was used to compare the categorical variables of independent multiple groups when Fisher's least significant difference and Games-Howell tests were used for the post hoc analyses. The Kruskal-Wallis H test was used with the Monte Carlo simulation method when Dunn's test was used for the post hoc analyses. Kendall's tau-b test was used to assess the correlations among variables. The variables were analyzed at 95% confidence level, and *p* values lower than 0.05 were regarded as significant.

Results

Demographic and clinical characteristics of the PCOS patients and healthy controls are shown in Table 1. The PCOS patients were significantly younger than the healthy women ($p=0.008$). When compared to the healthy women, PCOS patients had significantly higher ovarian volumes, Ferriman-Gallwey scores, and free and total testosterone levels, but significantly lower amylin concentrations ($p=0.001$, $p=0.001$, $p=0.049$, $p=0.021$, and $p<0.001$, respectively).

Table 2 compares the demographic and clinical characteristics of the overweight PCOS patients, normal-weight PCOS patients, overweight controls, and normal-weight controls. The normal-weight PCOS patients were significantly younger than the normal-weight controls ($p=0.001$) and overweight controls ($p=0.032$). The overweight PCOS patients had significantly higher HOMA-IR than the normal-weight PCOS patients ($p=0.003$), the overweight controls had significantly higher HOMA-IR than the normal-weight controls ($p=0.001$), and the overweight controls had significantly higher HOMA-IR than the normal-weight PCOS patients ($p=0.001$).

The normal-weight PCOS patients had significantly higher Ferriman-Gallwey scores and ovarian volumes but significantly lower serum amylin levels than the normal-weight and overweight healthy controls ($p=0.001$, $p=0.001$, $p=0.012$, $p=0.003$, $p<0.001$, and $p=0.009$, respectively). The overweight PCOS patients had significantly higher Ferriman-Gallwey scores and ovarian volumes but significantly lower serum amylin levels than the normal-weight and overweight controls ($p<0.001$ for all).

Table 3 demonstrates the correlations of amylin and preptin values. Preptin levels were negatively and significantly ($r=-0.209$; $p=0.008$) correlated with age. Amylin levels were negatively and significantly ($r=-0.206$, $p=0.007$) correlated with the Ferriman-Gallwey scores ($r=-0.272$, $p=0.001$) and ovarian volume.

Discussion

It is well known that the risk of cardiovascular diseases is elevated in patients with PCOS due to increased insulin resistance and impaired glucose tolerance [8,17]. Previously reported findings about insulin metabolism and resistance provide new clues in the treatment of PCOS and related complications. However, controversial results have been obtained regarding the physiological role of preptin in PCOS. Preptin is a peptide which is co-secreted with insulin from pancreatic beta cells. Successful clinical results have been achieved in the treatment of diabetes and obesity with the use of an amylin analog, pramlintide [10,18].

Table 1. Demographic and clinical characteristics of healthy controls and PCOS patients.

	Healthy controls		PCOS patients		P
	(n=40)		(n=40)		
	n	(%)	n	(%)	
Normal (BMI <25kg/m ²)	20	(50)	21	(52.5)	1
Overweight (BMI >25kg/m ²)	20	(50)	19	(47.5)	
	Median (Min–Max)		Median (Min–Max)		
Body mass index (kg/m ²)	24.6	(17.7–34.9)	24.3	(19.1–52.8)	0.793
Age (years)	24	(17–35)	20.5	(17–35)	0.008*
Amylin (pg/ml)	801.2	(267.5–2532.2)	383.4	(100.7–2600.9)	<0.001*
Preptin (pg/ml)	1136.6	(448.1–5562.2)	1675.7	(128.4–8518.8)	0.729
HOMA-IR	2.1	(0.5–7.5)	1.9	(0.7–4.8)	0.849
LH (IU/L)	4.9	(1.4–23.5)	5.8	(0.5–19.6)	0.902
Estradiol (pg/ml)	44	(15–101)	44.5	(12–117)	0.985
TSH (µU/ml)	1.7	(0.4–8.7)	1.6	(0.5–4.7)	0.982
Prolactin (ng/ml)	16.1	(5.3–53.3)	17.1	(3.3–38.1)	0.723
hs-CRP (mg/ml)	0.2	(0–2.2)	0.2	(0–2.4)	0.896
Waist circumference (cm)	82	(60–113)	78	(13–129)	0.372
FSH (IU/l)	4.8	(2.5–10.4)	4.6	(3–7.9)	0.178
Uterus volume (cm ³)	44.45	(15.4–115.2)	42.99	(16.8–138.9)	0.715
	Mean ±SD		Mean ±SD		
Ovarian volume (cm ³)	4.83±1.94		9.616.2±4.131.18		0.001*
Ferriman-Gallwey score	3.9±1.9		11.9±3.94		0.001*
Total testosterone (ng/dl)	43.4±16.3		52.5±17.31		0.021*
Free testosterone (ng/dl)	2.4±1.2		3.0±1.44		0.049*
DHEAS (µg/dl)	263.9±112.5		278.4±108.82		0.533

HOMA-IR – homeostatic model assessment – insulin resistance; TSH – thyroid stimulating hormone; hs-CRP – high-sensitive C-reactive protein, DHEAS – dehydroepiandrosterone sulfate. * p<0.05 was accepted to be statistically significant.

In 2011, Celik et al. found that serum preptin levels were significantly higher in patients with PCOS than in healthy controls. In addition, preptin concentrations were shown to be positively correlate with HOMA-IR, Ferriman-Gallwey score, and fasting insulin levels [7]. A year later, Bu et al. showed that serum preptin levels of PCOS patients and healthy controls were statistically similar, but the women with impaired glucose tolerance had significantly higher preptin levels than those with normal glucose tolerance, and preptin levels were positively correlated with HOMA-IR values [8]. Thus, it was concluded that preptin levels were rather associated with insulin resistance and impaired glucose tolerance in PCOS patients [7,8].

In the present study, PCOS patients and healthy controls had statistically similar prepreptin levels, and prepreptin levels did not differ significantly with respect to BMI groups in both PCOS patients and healthy controls. This discrepancy may be attributed to the relatively small cohort size and statistically similar HOMA-IR values of the PCOS patients and healthy controls in this study. Another explanation might be the relatively younger age of PCOS patients; sufficient time might not have passed for metabolic disorders such as impaired glucose intolerance and diabetes to occur in PCOS patients.

Amylin is another peptide which is co-secreted with insulin [9]. It has been reported that amylin acts in glucose metabolism [13]. In the pathogenesis of type 2 diabetes, amylin deposition begins

Table 2. Demographic and clinical characteristics of PCOS patients and healthy controls with respect to body mass index.

	Overweight PCOS	Normal weight PCOS	Overweight controls	Normal weight controls	p	
	(A, n=20)	(B, n=20)	(C, n=20)	(D, n=20)		
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)		
Age (years)	21.5 (17–35)	19 (17–29)	24 (17–35)	24.5 (19–35)	0.005*	
Amylin (pg/ml)	363.8 (100.7–723.9)	392.9 (202.9–2600.9)	949.7 (312.3–2341.7)	775.8 (267.5–2532.2)	<0.001*	
Preptin (pg/ml)	1995.9 (128.4–8518.8)	1545.0 (240.7–6454.9)	755.8 (448.1–5562.2)	1320.8 (478.5–4538.8)	0.933	
HOMA-IR	2.6 (1.5–4.8)	1.7 (0.7–3.8)	3.2 (1.1–7.5)	1.5 (0.5–6.4)	<0.001*	
TSH (µU/ml)	1.6 (0.5–3.8)	1.7 (0.7–4.7)	2.7 (0.8–8.7)	1.3 (0.4–2.7)	0.015*	
hs-CRP (mg/ml)	0.2 (0.1–2.4)	0.1 (0–0.7)	0.4 (0.1–2.2)	0.1 (0–1.3)	0.006*	
FG score	14 (2–20)	10 (3–17)	5 (2–6)	3.5 (0–9)	<0.001*	
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD		
Ovarian volume (cm ³)	8.71±4.30	10.52±3.85	5.09±2.62	4.58±1.57	<0.001*	
Waist circumference (cm)	88.0±22.4	71.4±8.0	91.2±9.5	74.1±7.7	<0.001*	
FSH (IU/l)	4.3±0.8	5.0±1.2	4.5±1.0	6.0±2.0	0.001*	
Total testosterone (ng/dl)	49.0±16.2	56.1±18.1	45.5±18.2	41.3±14.3	0.048*	
Free testosterone (ng/dl)	3.2±1.6	2.8±1.2	2.7±1.2	2.2±1.0	0.085	
DHEAS (µg/dl)	282.9±121.0	273.9±98.1	298.7±114.2	229.1±101.8	0.223	
	Multiple comparisons					
	A–B	A–C	A–D	B–C	B–D	C–D
Age (years)	0.051	0.848	0.132	0.032*	0.001*	0.189
Amylin (pg/ml)	0.324	<0.001*	<0.001*	<0.001*	0.009*	0.180
Preptin (pg/ml)	ns.	ns.	ns.	ns.	ns.	ns.
HOMA-IR	0.003*	0.825	<0.001*	0.001*	0.617	<0.001*
TSH (µU/ml)	0.772	0.086	0.144	0.154	0.080	0.002*
hs-CRP (mg/ml)	0.003*	0.723	0.017*	0.010*	0.581	0.042*
FG score	0.332	<0.001*	<0.001*	<0.001*	<0.001*	0.260
Ovarian volume (cm ³)	0.506	0.012*	0.003*	<0.001*	<0.001*	0.845
Waist circumference (cm)	0.022*	0.937	0.065	<0.001*	0.696	<0.001*
FSH (IU/l)	0.128	0.889	0.009*	0.456	0.248	0.028*
Total testosterone (ng/dl)	0.187	0.511	0.153	0.049*	0.007*	0.435
Free testosterone (ng/dl)	ns.	ns.	ns.	ns.	ns.	ns.
DHEAS (µg/dl)	ns.	ns.	ns.	ns.	ns.	ns.

ns – non-significant; BMI – body mass index, HOMA-IR – homeostatic model assessment – insulin resistance; TSH – thyroid stimulating hormone; hs-CRP – high-sensitive C-reactive protein; FG – Ferriman-Gallwey score; DHEAS – dehydroepiandrosterone sulfate. * p<0.05 was accepted to be statistically significant.

Table 3. Correlations of amylin and preptin.

	Amylin (pg/ml)		Preptin (pg/ml)	
	r	p	r	p
Age (years)	-0.032	0.680	-0.209	0.008*
Body mass index(kg/m ²)	0.014	0.858	0.026	0.736
HOMA-IR	-0.029	0.705	-0.007	0.924
TSH (μU/ml)	0.026	0.733	-0.022	0.778
hs-CRP (mg/ml)	0.081	0.289	0.094	0.217
Ferriman-Gallwey score	-0.272	0.001*	0.095	0.228
Ovarian volume (cm ³)	-0.206	0.007*	-0.092	0.225
Waist circumference (cm)	-0.035	0.644	-0.076	0.320
Total testosterone (ng/dl)	-0.101	0.186	0.060	0.430
Free testosterone (ng/dl)	-0.108	0.164	-0.032	0.683
DHEAS (μg/dl)	-0.072	0.343	0.005	0.947

r – correlation coefficient; BMI – body mass index; HOMA-IR – homeostatic model assessment – insulin resistance; TSH – thyroid stimulating hormone; hs-CRP – high-sensitive C-reactive protein; FG – Ferriman-Gallwey score; DHEAS – dehydroepiandrosterone sulfate; * p<0.05 was accepted to be statistically significant.

in the pancreatic islets even before the onset of fasting hyperglycemia, and diffuse amylin depositions are observed in pancreatic tissues of the patients with type 2 diabetes [19]. Therefore, serum amylin levels are expected to increase in patients with insulin resistance, and it has been hypothesized that an elevation in amylin levels might be an important marker in the development of type 2 diabetes.

James et al. performed a case-control study on 20 women with PCOS and 10 ovulatory women who were matched with respect to BMI. The patients with PCOS were found to have significantly higher serum amylin levels than the control group and there was a significant positive correlation between fasting insulin and amylin levels in PCOS patients and healthy controls. After glucose ingestion, amylin response was correlated with the glucose response in women with PCOS, and metformin treatment reduced serum amylin levels [12].

However, in the present study we found that patients with PCOS had lower serum amylin levels than healthy controls. When a subgroup analysis based on BMI was made, normal-weight PCOS patients were found to have significantly lower amylin levels than the normal-weight and overweight controls, and the overweight PCOS patients also had significantly lower amylin levels than the normal-weight and overweight controls. Amylin levels were also found to correlate negatively with Ferriman-Gallwey scores and ovarian volumes.

These contradictory results might be due to the lack of obese and morbidly obese groups, the differences in the laboratory skills, and the variations in the techniques used for the measurement of serum amylin concentrations. Another reason might be the existence of mechanisms that prevent the elevation in serum amylin concentrations that would occur in relation with the glucose intolerance in PCOS patients.

Conclusions

In conclusion, serum amylin concentrations were decreased and serum preptin levels remained unchanged in PCOS patients when compared to BMI-matched healthy controls. Subgroup analysis based on BMI groups indicated that serum amylin levels are significantly higher in healthy women than in PCOS patients, regardless of whether these patients are slim (BMI <25 kg/m²) or overweight (BMI ≥25 kg/m²). These findings suggest the presence of mechanisms that block the elevation in serum amylin concentrations that would occur in response to the impaired glucose metabolism in PCOS patients. Further research is warranted to clarify how serum preptin and amylin levels are altered with respect to BMI in ovulatory women and PCOS patients.

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