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The relationship between prolactin and adipose tissue and metabolic parameters in patients with polycystic ovary syndrome

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ABSTRACT

Objectives: Polycystic ovary syndrome is a reproductive endocrinopathy, predominantly accompanied by insulin resistance, obesity, and metabolic disorder. In this study, we aimed to investigate the possible relationship between prolactin and adipose tissue and metabolic parameters in patients with polycystic ovary syndrome (PCOS).

Methods: A total of 58 patients with PCOS and 34 body mass index (BMI)-matched healthy controls between September 2018 and March 2019 were included in the study. Visceral and subcutaneous adipose tissues were measured using ultrasonography. Serum prolactin, fasting blood glucose, insulin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, total cholesterol, luteinizing hormone (LH), total testosterone, dehydroepiandrosterone sulfate (DHEA-S), and 17-hydroxyprogesterone (17-OHP) levels were measured.

Results: The median BMI ($p = 0.001$), waist circumference ($p = 0.002$), hip circumference ($p = 0.003$), waist-to-hip ratio ($p = 0.013$), LH ($p = 0.012$), total testosterone ($p = 0.004$), DHEA-S ($p = 0.049$), 17-OHP ($p = 0.001$), insulin ($p = 0.001$), minimum preperitoneal fat thickness (p = 0.001), maximum preperitoneal fat thickness ($p = 0.048$), and intraperitoneal fat thickness ($p = 0.018$) were significantly higher in the PCOS group compared to the control group. However, there was no significant correlation between prolactin levels and adipose tissue parameters and insulin levels in the patients with PCOS.

Conclusions: Although there was an increase in the preperitoneal and intraperitoneal fat thickness in the PCOS group compared to the control group, no significant correlation was observed between prolactin and visceral and subcutaneous adipose tissues and metabolic parameters.

Keywords: Prolactin, polycystic ovary syndrome, adipose tissue

Prolactin (PRL) is a versatile hormone which plays a central role in metabolic functions and tumorogenesis, as well as reproductive and immune system [1]. It is mainly produced in the pituitary gland and in extrapituitary tissues such as human endometrium, decidua, brain, breast, and adipose tissue [2]. Previous studies have shown a complex relationship between PRL and adipose tissue and PRL is implicated in the regulation of adipogenesis and function of adipocytes [2] .

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Polycystic ovary syndrome (PCOS) is a common hormonal disorder in women of reproductive age characterized by irregular menstruation, chronic anovulation, and clinic and/or biochemical hyperandrogenism with morphologically characteristic feature of polycystic ovaries [3]. Metabolic disorders are more common in these patients, compared to healthy individuals, due to insulin resistance and abdominal obesity [4].

Although the regulation of PRL release is altered in PCOS patients, the relationship between PRL and adiposity is still unclear [5]. Therefore, the relationship between PRL and increased adipose tissue and metabolic disorders still remains to be elucidated in this patient population.

In the present study, we aimed to investigate the possible relationship between PRL and adipose tissue and metabolic parameters in patients with PCOS compared to healthy controls.

METHODS

Study population

This cross-sectional study was carried out at Department of Obstetrics and Gynecology of Bursa Yüksek İhtisas Training and Research Hospital between September 2018 and March 2019. A total of 58 patients with PCOS and 34 body mass index (BMI)-matched healthy controls were included. In the patient group, the diagnosis of PCOS was made according to the Rotterdam criteria including at least two of the following three features: i) oligo/anovulation, ii) clinical and/or biochemical hyperandrogenism, and iii) polycystic ovaries on ultrasonography (USG) (6). The control group consisted of healthy individuals in whom no clinical, laboratory, or USG signs of PCOS were present. Exclusion criteria were as follows: history of diabetes, hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, thyroid disorders, and hypertension. Patients who received oral contraceptives, anti-androgens, aspirin, statin, and insulin-sensitizing agents within the past six months were also excluded. A written informed consent was obtained from each participant. The study protocol was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital. (2011-KAEK-25 2018/06-31). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Biochemical analyses and hormone assays

Blood specimens were collected for biochemical and hormone analyses in the early follicular phase (between Day 2 and Day 5 of the menstrual cycle) with at least 12-h overnight fasting between 8.00 and 10.00 AM.Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone, dehydroepiandrosterone sulfate (DHEA), insulin, and 17-hydroxyprogesterone (17-OHP) were analyzed using the Abbott ARCHITECT® assay (Abbott Laboratories, Singapore). In addition, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were evaluated using the Synchron LX20, Beckman Coulter Diagnostics, USA. Insulin resistance was calculated using the Homeostatic Model Assessment Insulin Resistance (HOMA-IR) formula (fasting glucose (mg/dL) x fasting insulin (μU/mL)/405). The model of adipose distribution (MOAD) for women was calculated using the following formula: waist circumference/[36.58+(1.89xBMI)]. The visceral adiposity index (VAI) was calculated as MOADx(TG/0.81)x(1.52/HDL).

Anthropometric measurements

The body weight, height, and BMI were calculated for each participant. The waist circumference was measured at the narrowest part between the lower border of the rib cage and the iliac crest, while the hip circumference was measured at the greater trochanter while standing erect. The BMI was calculated as the weight in kilogram divided by height in meters squared.

Carotid intima-media thickness measurement

The carotid intima-media thickness (CIMT) was defined as the average of the three thickness measurements between the intimal and medial-adventitial interfaces and was measured in the supine position with head flexion. The CIMT measurements were performed by an experienced radiologist.

Adipose tissue measurement

The thickness of subcutaneous, preperitoneal,

intraperitoneal, and perirenal adipose tissues was measured using USG. The measurement was performed in the supine position in a fasting state by having the patient hold his/her breath to avoid any possible effect of respiration and abdominal wall tension. To avoid fat compression errors, the USG probe was placed above a given site without any pressure. Minimum subcutaneous and preperitoneal fat thickness were measured by longitudinal scanning with the use of (Toshiba Aplio 500, Japenese) 7 Mhz transducer from the xyphoid process, while maximum subcutaneous fat thickness was measured using the same transducer at the level of the umbilicus. Intraperitoneal fat thickness was measured by transverse scanning with the use of 5 Mhz probe in the midline of the abdomen, 2-cm above the umbilicus. Three measures were obtained based on the intraperitoneal fat thickness measurement: the distance from the fascia of rectus abdominis muscle to the vertebral column, the distance from the peritoneum to the vertebral column, and the distance from the linea alba to the vertebral column. Perirenal fat thickness was measured from the perirenal fascia to the renal surface on a long-axis view of the right kidney.

Statistical Analysis

Statistical analysis was performed using the SPSS version 23. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) values, and number and frequency. The Kolmogorov-Smirnov test was used to check the normality assumption. The Mann-Whitney U test was performed to compare variables between the patient and control groups. The Spearman's rank correlation analysis was used to investigate any relationship between serum PRL and other variables. After necessary adjustments for age, BMI, hip circumference, and waist-to-hip ratio were made, the partial Spearman's rank correlation analysis was performed. A multiple linear regression model was used to analyze the impact of potential variables on serum PRL levels. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 92 participants were included in this study. The study group consisted of 58 patients with PCOS and the control group consisted of 34 healthy individuals. However, as not every participant underwent all tests, the number of participants in both patient group and control group varied. The mean age was 27.07 ± 4.88 years in the patient group and 28.58 ± 4.78 in the control group, indicating no significant difference between the groups. Baseline demographic and clinical characteristics of the study population are shown in Table 1.

The median body weight ($p = 0.004$), BMI ($p = 0.001$), Ferriman-Gallwey Hirsutism (FGH) scores ($p = 0.001$), waist circumference ($p = 0.002$), hip circumference ($p = 0.003$), waist-to-hip ratio ($p = 0.013$), LH ($p = 0.012$), total testosterone ($p = 0.004$), DHEA-S ($p = 0.049$), 17-OHP ($p = 0.001$), insulin ($p = 0.001$), CIMT, minimum preperitoneal fat thickness ($p = 0.001$), maximum preperitoneal fat thickness ($p = 0.048$), and intraperitoneal fat thickness ($p = 0.018$) were significantly higher in the PCOS group compared to the control group. There was no significant difference in other variables between the groups.

Table 2 shows monotonic relationship between serum PRL and other variables. There was no significant correlation between serum PRL and any of the variables in the control group, while serum PRL significantly decreased with increasing age in the PCOS group ($p = 0.001$). However, there was no significant linear correlation between serum PRL and other variables in the PCOS group.

After necessary adjustments for age, BMI, hip circumference, and waist-to-hip ratio were made, correlation analysis was repeated. A positive and significant correlation was found between serum PRL levels and FGH scores ($p = 0.025$), TG levels ($p = 0.020$), and mid CIMT ($p = 0.039$) in the control group, while no significant correlation was found in the PCOS group (Table 3).

A multiple linear regression model was used to analyze the impact of potential variables on serum PRL levels. In the PCOS group, there was a significant correlation between age ($p = 0.020$), waist-to-hip ratio ($p = 0.044$), and HDL-C ($p = 0.049$) (Table 4).

DISCUSSION

Polycystic ovary syndrome is a reproductive endocrinopathy, predominantly accompanied by

Table 1. Demographic and clinical characteristics of the study population

Variable	Control group (n = 34)						PCOS group (n = 58)						*p* value
	N	Mean	SD	Percentiles			N	Mean	SD	Percentiles			
				1st	Median	3rd				1st	Median	3rd	
Age (years)	33	28.58	4.78	24.50	27.00	33.50	58	27.07	4.88	23.00	27.00	30.25	0.193
Height (cm)	33	160.30	17.13	157.00	164.00	169.00	57	162.72	5.77	160.00	162.00	167.00	0.890
Weight (kg)	33	70.94	18.21	56.00	64.00	79.50	57	81.34	16.93	70.00	78.00	94.50	**0.004**
BMI (kg/m^2)	33	31.26	29.61	21.87	25.80	30.22	57	30.61	5.46	26.98	30.85	34.43	**0.001**
FGH score	32	9.03	5.59	4.00	9.00	13.00	57	16.16	7.97	10.00	16.00	23.00	**0.001**
Waist circumference (cm)	33	86.79	15.26	73.50	83.00	100.50	57	96.39	12.17	88.50	97.00	105.00	**0.002**
Hip circumference (cm)	33	106.79	12.81	96.50	102.00	114.00	57	114.09	11,17	106.00	113.00	121.00	**0.003**
Waist-to-hip ratio	33	0.81	0.06	0.76	0.80	0.86	57	0.84	0.05	0.81	0.85	0.87	**0.013**
SBP (mmHg)	33	111.21	10.83	110.00	110.00	120.00	57	115,19	10.25	110.00	110.00	120.00	0.198
DBP (mmHg)	33	66.67	11.09	60.00	70.00	75.00	57	70,42	9.46	60.00	70.00	80.00	0.134
TSH (µU/ml)	34	2.38	1.55	1.44	1.79	2.94	58	1.97	1.00	1.23	1.77	2.55	0.528
PRL (ng/mL)	34	16.81	7.90	11.20	14.75	23.40	57	15.95	7.88	10.35	14.12	19.75	0.504
FSH (mIU/mL)	34	5.92	1.60	5.09	5.67	6.19	57	4.93	1.47	3.84	4.88	5.75	**0.003**
LH (mIU/mL)	34	4.01	1.46	3.05	3.61	4.98	57	5.63	3.37	3.53	4.68	6.50	**0.012**
Estradiol (pg/mL)	34	44.51	22.57	27.85	42.50	52.25	57	37.18	13.78	28.00	35.00	47.50	0.208
Total testosterone	33	1.16	0.45	0.88	1.09	1.30	56	1.39	0.44	1.05	1.34	1.70	**0.004**
DHEA-S (µg/dL)	33	198.36	95.97	130.50	172.00	235.00	55	227.44	86.04	155.00	239.00	292.00	**0.049**
17-OHP (ng/mL)	33	0.54	0.63	0.20	0.29	0.58	52	1.12	0.88	0.35	0.90	1.88	**0.001**
Insulin (µIU/mL)	33	11.05	13.85	5.00	7.00	11.50	55	12.14	6.66	7.30	10.10	16.00	**0.010**
FBG (mg/dL)	33	90.03	11.50	83.00	87.00	96.00	57	91.91	10.45	83.50	91.00	99.00	0.357
HDL-C (mg/dL)	32	50.22	10.81	42.25	47.00	58.00	57	50.81	16.54	41.00	46.00	58.50	0.666
LDL-C (mg/dL)	32	96.21	28.37	74.50	102.00	114.75	54	106.89	33.81	85.50	109.50	132.25	0.145
Total cholesterol (mg/dL)	33	173.18	30.95	162.00	176.00	191.50	56	180.02	35.48	157.25	177.50	204.75	0.405
TG (mg/dL)	33	107.00	65.44	60.00	87.00	130.00	56	120.45	57.84	78.25	112.50	157.50	0.136
CIMT (right) (mm)	26	0.50	0.12	0.43	0.46	0.56	38	0.56	0.11	0.46	0.58	0.63	**0.029**
CIMT (left) (mm)	26	0.50	0.12	0.43	0.46	0.60	38	0.56	0.10	0.46	0.58	0.63	**0.023**
CIMT (mid) (mm)	26	0.50	0.11	0.43	0.47	0.57	38	0.56	0.10	0.46	0.58	0.63	**0.036**
Min SAT thickness (mm)	26	17.16	6.78	12.43	17.50	21.55	38	19.28	6.20	13.45	19.20	23.70	0.180
Max SAT thickness (mm)	26	26.30	12.16	16.45	26.30	32.53	38	27.42	9.32	19.18	27.25	34.25	0.672
Min preperitoneal thickness (mm)	26	11.09	6.62	6.15	8.50	16.48	38	16.16	5.07	12.85	16.00	20.00	**0.001**
Max preperitoneal thickness (mm)	26	19.25	10.05	12,70	19.00	23.25	38	25.35	13.71	16.60	21.60	30.25	**0.048**
Intraperitoneal thickness (mm)	26	53.71	20.74	33.50	52.00	65.38	38	67.24	21.46	46.35	64.00	87.00	**0.018**
Perirenal thickness (mm)	26	5.66	4.73	1.95	5.35	7.60	38	7.48	5.08	4.38	5.50	9.55	0.124
VAI	31	4.47	3.49	2.17	3.21	5.58	55	5.24	3.24	2.77	4.74	7.12	0.141

PCOS = polycystic ovary syndrome, BMI = body mass index, FGH = Ferriman-Gallwey Hirsutism, SBP = systolic blood pressure, DBP = diastolic blood pressure, TSH = thyroid-stimulating hormone, PRL = prolactin, LH = luteinizing hormone, FSH = follicle-stimulating hormone, 17-OHP = 17-hydroxyprogesterone, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, CIMT = carotid intima-media thickness, DHEA-S = dehydroepiandrosterone s ulfate, Min = minimum, max = maximum, SAT = subcutaneous adipose tissue, VAI = Visceral Adiposity Index

Table 2. Monotonic relationship between serum prolactin and other variables

Variable	Serum PRL level					
	Control group (n = 34)			PCOS group (n = 58)		
	r	*p value*	N	*r*	*p value*	N
Age (years)	0.016	0.928	33	-0.525	0.001	57
Height (cm)	-0.159	0.376	33	0.121	0.375	56
Weight (kg)	-0.325	0.065	33	-0.090	0.512	56
BMI (kg/m^2)	-0.272	0.126	33	-0.108	0.429	56
FGH score	0.231	0.203	32	0.111	0.414	56
Waist circumference (cm)	-0.206	0.249	33	-0.047	0.730	56
Hip circumference (cm)	-0.221	0.216	33	-0.053	0.696	56
Waist-to-hip ratio	-0.046	0.798	33	-0.008	0.951	56
SBP (mmHg)	0.055	0.762	33	-0.050	0.715	56
DBP (mmHg)	-0.001	0.993	33	0.027	0.842	56
TSH (µU/ml)	-0.039	0.825	34	0.191	0.154	57
FSH (mIU/mL)	-0.123	0.487	34	-0.010	0.940	57
LH (mIU/mL)	0.152	0.390	34	-0.108	0.425	57
Estradiol (pg/mL)	0.180	0.308	34	-0.061	0.655	57
Total testosterone	-0.061	0.735	33	0.019	0.890	56
DHEA-S (µg/dL)	-0.167	0.352	33	0.166	0.229	54
17-OHP (ng/mL)	0.242	0.174	33	0.216	0.124	52
Insulin (µIU/mL)	0.055	0.763	33	-0.070	0.614	55
FBG (mg/dL)	-0.209	0.244	33	-0.152	0.258	57
HDL-C (mg/dL)	0.196	0.284	32	0.134	0.319	57
LDL-C (mg/dL)	-0.166	0.364	32	-0.022	0.873	54
Total cholesterol (mg/dL)	0.060	0.742	33	-0.073	0.93	56
TG (mg/dL)	0.239	0.181	33	-0.153	0.261	56
CIMT (right) (mm)	0.246	0.246	24	0.022	0.97	36
CIMT (left) (mm)	-0.085	0.693	24	-0.011	0.951	36
CIMT (mid) (mm)	0.079	0.715	24	0.007	0.966	36
Min SAT thickness (mm)	-0.042	0.844	24	0.252	0.37	36
Max SAT thickness (mm)	-0.211	0.322	24	0.042	0.809	36
Min preperitoneal thickness (mm)	-0.044	0.837	24	0.228	0.182	36
Max preperitoneal thickness (mm)	-0.226	0.288	24	0.058	0.735	36
Intraperitoneal thickness (mm)	-0.156	0.468	24	0.205	0.230	36
Perirenal thickness (mm)	-0.237	0.264	24	0.050	0.772	36
VAI	0.106	0.569	31	-0.077	0.578	55

PCOS = polycystic ovary syndrome, BMI = body mass index, FGH = Ferriman-Gallwey Hirsutism, SBP = systolic blood pressure, DBP = diastolic blood pressure, TSH = thyroid-stimulating hormone, PRL = prolactin, LH = luteinizing hormone, FSH = follicle-stimulating hormone, 17-OHP = 17-hydroxyprogesterone, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, CIMT = carotid intima-media thickness, DHEA-S = dehydroepiandrosterone sulfate, Min = minimum, max = maximum, SAT = subcutaneous adipose tissue, VAI = Visceral Adiposity Index

Table 3. Corrected correlation analysis with adjusted variables

Variable		Control group (n = 34)		PCOS group (n = 58)	
		Serum PRL level		Serum PRL level	
		r	*p value*	*r*	*p value*
BMI & waist-to-hip ratio	FGH score	0.499	**0.025**	0.210	0.302
	SBP (mmHg)	0.144	0.545	0.076	0.711
	DBP (mmHg)	-0.114	0.631	0.099	0.631
	TSH (µU/ml)	0.186	0.433	-0.218	0.285
	FSH (mIU/mL)	-0.136	0.569	-0.011	0.958
	LH (mIU/mL)	-0.020	0.933	-0.148	0.471
	Estradiol (pg/mL)	0.328	0.158	-0.026	0.901
	Total testosterone	0.268	0.253	-0.023	0.911
	DHEA-S (µg/dL)	0.219	0.353	-0.124	0.545
	17-OHP (ng/mL)	0.174	0.464	-0.014	0.947
	Insulin (µIU/mL)	0.297	0.204	0.099	0.629
	FBG (mg/dL)	-0.098	0.682	-0.193	0.344
	HDL-C (mg/dL)	0.354	0.126	0.203	0.319
	LDL-C (mg/dL)	-0.001	0.997	-0.078	0.706
	Total cholesterol (mg/dL)	0.182	0.442	-0.041	0.841
	TG (mg/dL)	0.516	**0.020**	-0.164	0.423
	CIMT_SAG	0.599	**0.005**	-0.181	0.377
	CIMT_SOL	0.296	0.205	-0.245	0.228
	CIMT_ORT	0.465	**0.039**	-0.224	0.271
	Min SAT thickness (mm)	0.108	0.651	0.190	0.351
	Max SAT thickness (mm)	-0.085	0.723	0.005	0.981
	Min preperitoneal thickness (mm)	0.188	0.427	0.087	0.671
	Max preperitoneal thickness (mm)	-0.071	0.767	-0.001	0.995
	Intraperitoneal thickness (mm)	0.002	0.994	0.245	0.228
	Perirenal thickness (mm)	-0.132	0.580	0.035	0.865
	VAI	0.387	0.092	-0.175	0.392

PCOS = polycystic ovary syndrome, BMI = body mass index, FGH = Ferriman-Gallwey Hirsutism, SBP = systolic blood pressure, DBP = diastolic blood pressure, TSH = thyroid-stimulating hormone, PRL = prolactin, LH = luteinizing hormone, FSH = follicle-stimulating hormone, 17-OHP = 17-hydroxyprogesterone, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, CIMT = carotid intima-media thickness, DHEA-S = dehydroepiandrosterone sulfate, Min = minimum, max = maximum, SAT = subcutaneous adipose tissue, VAI = Visceral Adiposity Index

Table 4. Multiple linear regression analysis

Group		Unstandardized Coefficients		Standardized Coefficients	*t*	*p value*
		β	SE	β		
PCOS	Age (years)	-1.362	0.529	-0.885	-2.572	**0.020**
	BMI (kg/m^2)	0.384	0.807	0.282	0.476	0.640
	FGH score	-0.231	0.275	-0.239	-0.839	0.413
	Waist-to-hip ratio	107.688	49.518	0.812	2.175	**0.044**
	SBP (mmHg)	-0.003	0.236	-0.004	-0.014	0.989
	DBP (mmHg)	0.037	0.238	0.048	0.156	0.878
	TSH (µU/ml)	0.268	1.821	0.045	0.147	0.885
	FSH (mIU/mL)	-0.443	1.668	-0.087	-0.266	0.794
	LH (mIU/mL)	-0.894	0.720	-0.322	-1,243	0.231
	Estradiol (pg/mL)	0.155	0.110	0.383	1.411	0.176
	Total testosterone	-3.806	5.265	-0.182	-0.723	0.480
	DHEA-S (µg/dL)	-0.012	0.026	-0.121	-0.467	0.647
	17-OHP (ng/mL)	-0.322	4.116	-0.030	-0,078	0.939
	Insulin (µIU/mL)	0.125	0.197	0.190	0.635	0.534
	HDL-C (mg/dL)	0.488	0.233	0.731	2.000	**0.049**
	TG (mg/dL)	-0.059	0.139	-0.384	-0423	0.677
	CIMT (mid) (mm)	6.249	25.749	0.083	0.243	0.811
	Min SAT thickness (mm)	0.462	0.605	0.399	0.764	0.455
	Max SAT thickness (mm)	-0.260	0.377	-0.333	-0.689	0.500
	Max preperitoneal thickness (mm)	-0.181	0.193	-0.330	-0.938	0.362
	Intraperitoneal thickness (mm)	-0.112	0.172	-0.321	-0.654	0.522
	Perirenal thickness (mm)	0.246	0.631	0.166	0.390	0.701

PCOS = polycystic ovary syndrome, BMI = body mass index, FGH = Ferriman-Gallwey Hirsutism, SBP = systolic blood pressure, DBP = diastolic blood pressure, TSH = thyroid-stimulating hormone, LH = luteinizing hormone, FSH = follicle-stimulating hormone, 17-OHP = 17-hydroxyprogesterone, HDL-C = high-density lipoprotein cholesterol, TG = triglyceride, CIMT = carotid intima-media thickness, DHEA-S = dehydroepiandrosterone sulfate, Min = minimu, max = maximum, SAT = subcutaneous adipose tissue

insulin resistance, obesity, and metabolic disorder [3]. Nearly 30 to 50% of lean patients with PCOS and those with obesity have insulin resistance and lipid metabolism disorders,suggesting that obesity is not the sole driver of metabolic alterations [7]. Several studies have demonstrated that metabolic disorders are more frequently associated with the distribution of adipose tissue rather than absolute amount of the body fat [8]. In the literature, some authors have reported no significant difference in the body composition and fat distribution between lean patients with PCOS and healthy controls [9], while some others have shown that PCOS patients have more visceral fat ratio proportionally to total body fat, suggesting a relationship between PCOS and glucose intolerance, type 2 diabetes, hypertension, and hyperlipidemia [10, 11]. Furthermore, although there are studies showing an increase in the subcutaneous adipose tissue in PCOS patients [12], some authors have not demonstrated such an increase [13]. Similarly,there are some studies showing an increase in the visceral adipose tissue [10, 14], whle some others have found no increase [13]. In

a study, Jena *et al*. [15] found increased subcutaneous adipose tissue in patients with PCOS and obesity, compared to BMI-matched healthy controls. However, in the aforementioned study, there was no significant difference in the subcutaneous adipose tissue between lean PCOS patients and controls. In addition, the authors reported increased visceral adipose tissue in PCOS patients with and without obesity compared to healthy controls [15]. In another study evaluating subcutaneous, preperitoneal, intraperitoneal, mesenteric, epicardial, and perirenal adipose tissue through USG, a significant increase in the visceral adipose tissue, particularly mesenteric and intraperitoneal, was observed in patients with PCOS with and without obesity, compared to the control group [16]. In our study, although we found no significant difference in the subcutaneous fat thickness between the groups, we observed a significant increase in the preperitoneal and intraperitoneal fat thickness in the patients with PCOS.

Visceral adipose tissue is a more active driver of metabolic alterations than subcutaneous adipose tissue and is more resistant to anti-lipolytic effects of insulin, thereby, increasing abnormal lipid production and insulin resistance [17]. Although preperitoneal adipose tissue is not a part of visceral adipose tissue, it has similar properties to visceral adipose tissue, as it is anatomically located close to peritoneal, omental, and retroperitoneal adipose tissues [18].

It has been well-established that PRL plays a central role in the reproductive system. In recent years, there are also several reports suggesting that PRL can be used as a useful biomarker for metabolic syndrome, diabetes mellitus, cardiovascular and all-cause mortality [19, 20]. It has been proposed that PRL exerts its effects on adipose tissue development and functions and pancreatic β cells [21]. There is a complex relationship between PRL and adipose tissue: PRL has not only an effect on adipogenesis and adipocyte functions, but also is produced in adipose tissues [2]. However, the effect of PRL on systemic circulation has not been clearly understood, yet. Some authors have suggested that PRL released by the adipose tissue shows an autocrine/paracrine effect [22].

In the literature, there are several reports showing a positive or negative or no correlation between the amount of adipose tissues and PRL levels [23-25]. The discrepancy among the studies can be attributed to the type of adipose tissue examined. In a study, Kok *et al*. [26] found a higher rate of basal and pulsatile PRL release in premenopausal women with visceral obesity, compared to lean controls. In another study, patients with obesity had a lower PRL release from subcutaneous adipose tissue, compared to visceral adipose tissue, indicating an inverse relationship between PRL release from subcutaneous adipose tissue and BMI [2] . On the other hand, the rate of PRL released from subcutaneous and visceral adipose tissues was similar in patients without obesity. Unlike this study, we found no significant relationship between PRL levels and subcutaneous and visceral adipose tissue in our study population. Similarly, in their study, Ernst *et al*. [25] found no significant difference in the serum basal PRL levels one year after gastric bypass in patients with obesity, compared to baseline, despite severe weight loss.

Adipose tissue dysfunction is considered an important contributor to obesity-related metabolic disorders. In patients with obesity, excessive fat deposition leads to insulin resistance, impaired adipogenesis, altered adipokine secretion, increased inflammation and fibrosis, and reduced angiogenesis [27]. Therefore, adipose tissue modeling is critical to prevent insulin resistance and associated metabolic disorders [28]. A healthy expansion of the adipose tissue is of utmost importance to maintain insulin sensitivity, while PRL is involved in the healthy expansion of the adipose tissue and maintenance of insulin sensitivity [19, 29].

On the other hand, PRL may have adverse metabolic effects in patients with high serum PRL levels due to prolactinoma or the use of antipsychotics, leading to type 2 diabetes(30). Bromocriptine, a dopamine agonist, inhibits PRL levels and increase insulin sensitivity and has been used in the treatment of type 2 diabetes in recent years [31]. However, there are several studies showing no direct correlation between corrected BMI and metabolic parameters and reduced PRL levels [32].

Review of the literature reveals controversial results regarding the relationship between serum PRL levels and metabolic parameters. Some authors reported an inverse correlation between PRL levels and diabetes, metabolic syndrome, HOMA-IR, and impaired lipid metabolism [19, 33], while some others found a positive correlation between PRL levels and

hypertension, insulin resistance, and aortic stiffness [20, 34, 35]. In a study, high physiological concentrations of PRL increased adiponectin release, showing a protective effect against metabolic dysfunction [28]. In another study, Albu *et al*. [5] found a positive correlation between adiponectin and PRL levels in patients with PCOS. In this study, VAI, but not adiponectin, was found to be a useful marker for predicting serum PRL levels. In our study, we found no significant correlation between serum PRL levels and metabolic parameters. Of note, we were unable to examine adipokine levels for adipose tissue dysfunction, although we used VAI. However, we found no significant correlation between serum PRL levels and VAI.

Limitations

Nonetheless, there are some limitations to this study. First, the study has a relatively small sample size. Second, only PCOS patients with obesity and BMI-matched healthy controls were included in this study and lean PCOS patients were unable to be evaluated. Third, thickness measurements of adipose tissues were made using USG. Finally, computed tomography and magnetic resonance imaging are more useful in the evaluation of subcutaneous and visceral adipose tissues(36), the outcomes of both methods are similar to USG [37, 38]. In our study, we used USG as it is an inexpensive, non-invasive imaging method in our study.

CONCLUSION

In conclusion, although there was an increase in the preperitoneal and intraperitoneal fat thickness in the PCOS group compared to the control group, no significant correlation was observed between PRL levels and visceral and subcutaneous adipose tissues. In addition, we found no significant correlation between serum PRL and metabolic parameters. We, therefore, recommend further large-scale studies to establish a definite conclusion on this topic.

Authors' contribution

GAA = designed the study, searched the literature, planned the concept, made statistical analysis, prepared and edited the manuscript, reviewed the manuscript and copy-edited the text and made contributions to improve the quality of the study. HGTÖ = designed the study, searched the literature, planned the concept, made statistical analysis, prepared and edited the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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