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Tenascin-C levels in polycystic ovary syndrome and polycystic ovarian morphology

Mustafa Kemal Koksal,[1] Ugur Kemal Ozturk,[2] Esra Keles,[2] Burak Arslan,[3] Yaprak Engin Ustun[4]

[1]Department of Obstetric and Gynecology, Izmir Torbali State Hospital, Izmir, Turkiye

[2]Department of Gynecologic Oncology, University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkiye

[3]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at The University of Gothenburg, Mölndal, Sweden; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[4]Department of Obstetric and Gynecology, University of Health Sciences, Ankara Etlik Zubeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkiye

ABSTRACT

OBJECTIVE: It is considered that the underlying reason for metabolic anomalies and ovarian dysfunction in polycystic ovary syndrome (PCOS) is low-grade chronic inflammation. Therefore, we aimed to investigate Tenascin-C (TN-C) levels in PCOS. This is the first study to document the impact of inflammation with TN-C in this specific population.

METHODS: A total of 90 participants, consisting of 30 PCOS patients, 30 polycystic ovarian morphology (PCOM) patients, and 30 matched healthy controls between September 2018 and April 2019 enrolled. All participants were randomized by age and body mass index. Demographic, clinical characteristics, ultrasonographic features, lipid profile, hormonal and metabolic parameters were collected.

RESULTS: When comparing serum TN-C levels between PCOS, PCOM and control subjects, a statistically significant difference was observed only between subjects with PCOS and control subjects (p=0.009). ROC analysis demonstrated that PCOS could be predicted with 89.7% sensitivity and 45.5% specificity when TN-C levels are cut off at 1.87 ng/ml.

CONCLUSION: This study indicated that TN-C level was higher in the PCOS group compared to PCOM and control groups, while it was similar between the PCOM and the control groups. It may be suggested that TN-C levels may contribute to the differentiation between PCOS and PCOM.

Keywords: Inflammation; PCOM; PCOS; tenascin.

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Polycystic ovary syndrome (PCOS) is a disease characterized by clinically or biochemically demonstrated hyperandrogenism, ovulatory dysfunction (oligo-anovulation), and ultrasonographic polycystic ovaries [1]. PCOS patients are at risk for reproductive and metabolic long-term complications [2].

Polycystic Ovarian Morphology (PCOM) is defined by ultrasound (US) as the presence of 12 or more follicles with a diameter of 2 to 9 mm or an ovarian volume greater than 10 mm^3 [3]. PCOM is the excess androgen synthesized from the ovary that causes premature luteinization leading to thecal and cortical stromal hy-

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Correspondence: Esra KELES, MD. Saglik Bilimleri Universitesi, Kartal Lutfi Kirdar Sehir Hastanesi, Jinekolojik Onkoloji Klinigi, Istanbul, Turkiye.
Tel: +90 216 391 06 80 e-mail: dresrakeles@hotmail.com

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perplasia in the follicles. It also generates a polycystic appearance in the ovaries. It affects approximately 6-14% of reproductive-aged women worldwide [4].

In 2006, the link between PCOS phenotypes and independent disease rates was determined by the Androgen Excess and PCOS Society (AE-PCOS). In 2012, National Institutes of Health guidelines (NIH) recommended a phenotypic approach [5]. Recently, studies on the role of increased oxidative stress and secondary chronic inflammation in the pathophysiology of PCOS have been conducted [6]. Higher levels of inflammation markers have been observed in PCOS patients [7].

Many studies have reported an association between polycystic ovary syndrome (PCOS) and low-grade chronic inflammation [8]. Based on available data, it has been observed that PCOS patients have higher levels of inflammatory markers [9]. Tenascin-C (TN-C), which is an extracellular matrix glycoprotein composed of 6 monomers, has been found to play a role in inflammation. TN-C has been shown to indicate early stages of cell damage and correlate with the degree of inflammation [10]. However, there is a lack of data regarding the potential of serum TN-C in patients with PCOS.

It is considered that the underlying reason for metabolic anomalies and ovarian dysfunction in PCOS is low-grade chronic inflammation. Therefore, we aimed to investigate TN-C levels in PCOS. To our knowledge, this is the first study to document the impact of inflammation with TN-C in this specific population. In addition, we compared TN-C levels in PCOS, PCOM, and healthy controls to determine whether there is a distinguishing feature between PCOS and PCOM.

Highlight key points

- Triglyceride levels were significantly higher in the PCOS group compared to controls.
- Total and free testosterone levels were significantly higher in the PCOS group compared to controls.
- Insulin levels were significantly higher in the PCOS group compared to controls.
- Insulin resistance was significantly higher in the PCOS group compared to controls.
- Serum TN-C level could predict PCOS with 89.7% sensitivity and 45.5% specificity when TN-C is >1.87 ng/ml.

MATERIALS AND METHODS

Patient Population

This research has been granted by Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Clinical Research Ethics Committee (approval number and date: 62/2018, 15.11.2018) and follows the Declaration of Helsinki. After obtaining informed consent from all participants, comprising 30 PCOS patients, 30 PCOM patients, and 30 matched healthy controls between September 2018 and April 2019, participants were randomized by age and body mass index (BMI). Detailed data, including age at menarche, marital status, symptoms at admission, history of drug use, past medical and surgical histories, grading of hirsutism, lipid profile, hormonal and metabolic parameters were collected. Ultrasonographic examinations were performed in the early follicular phase by a single practitioner using an ultrasonography device (Toshiba APLIO 300, California, USA). Transabdominal convex probe and transvaginal probe were used for examinations. All patients underwent transabdominal examination. Longitudinal, anteroposterior, and transverse dimensions of the uterus were measured. Following the transabdominal examination, the procedure was continued transvaginally. The ovaries were evaluated in terms of number and location of cysts, and echogenicity of the stroma. Ovarian dimensions were measured as length, width, and thickness on the longest axis. Ovarian area and ovarian circumference were calculated by applying the area and circumference mode to the ultrasonography device. A total of six patients whose hormone levels could not be reached, who lost follow-up, and whose ultrasonographic examination did not have a typical polycystic ovary appearance were excluded. A total of 84 patients were evaluated for final analyses.

Inclusion Criteria

All patients underwent physical and pelvic examinations at the first clinical visit. PCOS was defined according to the 2004 Rotterdam criteria. PCOS group consisted of patients who did not use oral contraceptives or other hormonal drugs and whose ovaries had a polycystic appearance and/or increased ovarian volume. The PCOM group consisted of patients who also had not used oral contraceptives and/or any other hormonal drugs, and whose ovaries also had a polycystic appearance and/or increased ovarian volume (>10 ml) on ultrasound but without oligomenorrhea, amenorrhea or hirsutism. For detailed analysis, patients were classified into four categories according to phenotype classification. Phenotype

A: Hyperandrogenism (with clinical or biochemical markers) + Ovulatory Dysfunction + PCOM. Phenotype B: Hyperandrogenism (with clinical or biochemical markers) + Ovulatory Dysfunction. Phenotype C: Hyperandrogenism (with clinical or biochemical markers) + PCOM. Phenotype D: Ovulatory Dysfunction + PCOM [5]. The women who applied to the gynecology outpatient clinic right after each PCOS patient, who were informed about the study and volunteered to participate, and who had not received any treatment were included in the study as the control group.

Exclusion Criteria

Women who used drugs, smoked cigarettes, had a BMI of 35 kg/m^2 and over, received medical treatment to regulate insulin secretion or sensitivity, had an infectious disease, had systemic diseases, or had endocrinological disorders were excluded.

Clinical and Laboratory Evaluation

Blood samples were taken from all patients and control groups from 8 am to 9 am on cycle day 3. Basal hormone levels and biochemical values were studied. Approximately 10 ml of antecubital venous blood was drawn from each patient in a sitting position. Collected blood samples were placed in yellow-capped, vacuumed, plastic gel tubes. The samples were transferred to the laboratory within 30 minutes and centrifuged at 4000 rpm for 10 minutes in NF800 centrifuge devices (Nuve Industry Materials Manufacturing and Trade Inc., Ankara, Turkey). Next, serum samples were taken into Eppendorf tubes and stored at -80°C until analysis. Serum basal hormone and insulin levels were determined using Roche Cobas ® 6000 analyzer (Roche Diagnostics). Free Androgen Index (FAI) was calculated as the percentage ratio of total testosterone to SHBG level.

Collected serum samples were kept in Makrosel-Private Contemporary Laboratory at room temperature for half an hour. Tenascin-C (SinoGeneClon Biotech Co., Ltd., Cangxin Road, YuHang) ELISA kits were washed with Mikroplate Washer RT 2600C (China) device. Then, evaluations were carried out with a Rayto Microplate Reader (RT 2100C, China) at a 450 nm wavelength. Based on the manufacturer's instructions, the lowest concentration the used kits could reliably detect was 10 pg/ml. The Tenascin-C levels in the samples were calculated using Microsta, a statistical software program.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 22 (Armonk, New York: IBM Corp.) was employed. To verify normal distribution, both Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted. Independent-Sample T-test and Mann-Whitney U test were utilized to compare two independent groups. Pearson Chi-Square and Fisher's exact test were performed to analyze categorical data comparison. Spearman and Pearson Correlation tests were carried out to investigate correlations between variables. Normally distributed data are given as meanstandard deviation, while non-normally distributed data are given as median (minimum-maximum). Categorical data are expressed in numbers (n) and percentages (%). Optical density values were subjected to regression correlation. The role of TN-C in predicting PCOS was investigated using ROC analysis.

RESULTS

Study groups were formed with 29 PCOS patients, 28 PCOM patients, and 27 matched healthy controls. The participants were age- and BMI-matched and were followed up by our institution between September 2018 and April 2019. No statistically significant difference was found between the groups in terms of age, body mass index (BMI), and the number of abortions. A significant difference was found between groups for gravida, parity, and living children (all $p<0.001$) (Table 1).

Based on comparisons between groups, a statistically significant difference was observed in terms of luteinizing hormone (LH), estradiol (E_2), total testosterone, triglycerides, low-density lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL), total cholesterol, insulin, HbA1c, HOMA-IR, CRP, and TN-C levels (all $p<0.05$). A statistically significant difference was found between PCOM and control groups in terms of luteinizing hormone (LH), total testosterone, triglycerides, HDL, HbA1c, and HOMA-IR values (all $p<0.005$). A significant difference was found between PCOS and control groups regarding TSH, E_2, total testosterone, Triglyceride, VLDL, Total Cholesterol, C-reactive protein (CRP), TN-C, insulin, HbA1c, and HOMA-IR values (all $p=0.05$). In comparisons between PCOM and PCOS, statistically significant differences were found in LH, E_2, total testosterone, LDL, and VLDL values (all $p<0.05$) (Table 2).

The distribution of subgroups according to PCOS phenotype were as follows: Phenotype A group 10

Table 1. Anthropometric measurements of polycystic ovarian morphology, polycystic ovary syndrome and control cases

	PCOM (I)	PCOS (II)	Control (III)	p	p (I-II)	p (I-III)	p (II-III)
Age (years) Mean±SD	24.8±4.2	25.8±5.2	26.8±3.5	0.227	0.664	0.198	0.644
BMI (kg/m^2) Mean±SD	28.1±6.3	28.4±5.5	27.8±4.6	0.915	0.978	0.974	0.907
Gravida, Median (Min–Max)	1 (0–4)	0 (0–4)	3 (0–7)	**<0.001**	0.086	**<0.001**	**<0.001**
Parity, Median (Min–Max)	1 (0–2)	0 (0–3)	2 (0–7)	**<0.001**	0.110	**<0.001**	**<0.001**
Living children, Median (Min–Max)	1 (0–2)	0 (0–3)	2 (0–7)	**<0.001**	0.079	**<0.001**	**<0.001**
Abortus, Median (Min–Max)	0 (0–2)	0 (0–2)	0 (0–2)	0.147	**0.047**	0.564	0.149

SD: Standard deviation; BMI: Body mass index; PCOM: Polycystic ovarian morphology; PCOS: Polycystic ovary syndrome; Min: Minimum; Max: Maximum.

Table 2. Comparison of hormonal characteristics and metabolic parameters in PCOS, PCOM and control cases

Variables	PCOM (I)	PCOS (II)	Control (III)	p	p (I-II)	p (I-III)	p (II-III)
FSH (mIU/ml)	5.9±1.6	5.3±1.3	5.6±1.0	0.274	0.242	0.712	0.696
LH (mIU/ml)	8.6±3.1	7.4±3.1	6.0±1.3	<0.001	0.012	<0.001	0.104
DHEA-S (mcg/dl)	226.1±70.1	231.3±11.6	231.8±64.6	0.493	0.708	0.631	0.207
AMH (ng/ml)	5.2±2.4	6.1±3.1	4.7±1.4	0.162	0.930	0.259	0.171
TSH (mIU/ml)	2.5±1.3	2.4±0.9	1.9±0.6	0.084	0.994	0.113	0.024
E_2 (pg/mL)	63.9±62.0	45.1±17.5	51.0±7.8	0.017	0.018	0.637	0.012
Total testosterone, (ng/ml)	0.3±0.1	0.5±0.5	0.2±0.1	<0.001	0.018	<0.001	0.102
Triglyceride (mg/dL)	96.0±51.0	125.3±75.2	64.6±13.9	<0.001	0.136	0.004	<0.001
LDL (mg/dL)	84.5±23.8	99.5±27.5	96.5±11.2	0.032	0.034	0.116	0.872
HDL (mg/dL)	52.1±12.2	47.3±10.1	46.6±5.2	0.095	0.083	0.043	0.837
VLDL (mg/dL)	19.5±10.5	25.1±15.0	14.8±4.7	0.009	0.114	0.131	0.002
Total cholesterol (mg/dL)	161.8±26.4	171.3±32.2	120.1±19.4	<0.001	0.373	<0.001	<0.001
CRP (mg/dl)	1±0+5.5	30–9.5	0.40–4.5	0.040	0.034	0.370	0.001
Tenascin-C (ng/ml)	2.2±1.3	3.2±2.6	2.2±1.5	0.009	0.011	0.966	0.006
Insulin (µIU/mL)	17.5±19.0	17.1±8.5	10.93.1	0.026	0.110	0.674	0.004
HbA1c (%NGSP)	5.60.5	5.30.3	5.00.5	<0.001	0.111	<0.001	0.045
HOMA-IR	5.2±6.2	5.6±3.4	2.1±0.9	<0.001	0.678	0.003	<0.001

FSH: Follicular stimulating hormone; LH: Luteinizing hormone; E_2: Estradiol; AMH: Anti-mullerian hormone; TSH: Thyroid Stimulating Hormone; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; CRP: C-Reactive Protein; SHBG: Sex hormone binding globulin; DHEA-S: Dehydroepiandrosterone sulfate; PCOM: Polycystic ovarian morphology; PCOS: Polycystic ovary syndrome; CRP: C-Reactive protein; HOMA-IR: homeostatic model assessment of insulin resistance.

(34.5%), Phenotype B group 3 (10.3%), Phenotype C group 2 (7%), Phenotype D group 14 (48.3%). In the comparison between phenotype A and phenotype D subgroups, a statistically significant difference was found between E_2 (p=0.023) and DHEA-S values (p=0.031) (Table 3).

It was found that only the free androgen index ratio correlated statistically with TN-C levels between phenotypes A and D. There was no significant correlation with other parameters, including age, BMI, total cholesterol, triglycerides, anti-Müllerian hormone (AMH), HOMA-IR, HbA1c, dyhdyroepiandrostene-

Table 3. Comparison of hormonal and biochemical parameters between phenotype A and group D

Variables	Phenotype A Mean±SD	Phenotype D Mean±SD	p
FSH (mIU/ml)	5.01±1.95	5.37±1.10	0.659
LH (mIU/ml)	6.65±2.75	7.80±3.30	0.190
E_2 (pg/ml)	55.0±20.0	38.3±14.0	**0.023**
AMH (ng/ml)	5.8±3.2	7.2±3.2	0.297
TSH (mIU/ml)	2.68±1.21	2.05±0.69	0.122
Free T_4 (ng /dL)	1.81±0.41	2.14±0.49	0.094
DHEA-S, (mcg/dl)	296±141.2	197±65.9	**0.031**
Total testosterone (ng/ml)	1.488±0.928	0.90±0.170	0.103
Free testosterone (pg/ml)	0.60±0.27	0.48±0.33	0.085
Androstenedione (mosm/kg)	8.51±4.38	3.57±1.30	0.196
SHBG (nmol/L)	85.1±49.7	63.2±18.2	0.824
Total Cholesterol (mg/dL)	175±39	169±31.2	0.659
Triglyceride (mg/dL)	154±106	110.4±54.8	0.197
LDL (mg/dL)	98±19.6	99.6±34.4	0.895
HDL (mg/dL)	44.5±14.2	50±8.5	0.254
VLDL (mg/dL)	30.5±21.1	22.6±11.2	0.247

SD: Standard deviation; FSH: Follicular stimulating hormone; LH: Luteinizing hormone; E_2: Estradiol; AMH: Anti-mullerian hormone; TSH: Thyroid stimulating hormone; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; CRP: C-Reactive protein; SHBG: Sex hormone binding globulin; DHEA-S: Dehydroepiandrosterone sulfate.

dione-sulfate (DHEA-S), androstenedione, free testosterone, and insulin (Table 4).

The mean TN-C value was 2.2 ng/ml (±1.3) in the PCOM group, 3.2 ng/ml (±2.6) in the PCOS group, and 2.2 ng/ml (±1.5) in the control group (Fig. 1). There was statistical significance between PCOS and the control group (p=0.009), while no significant difference was found between PCOM and control.

ROC analysis demonstrated that when a cut-off for TN-C level of 1.87 ng/ml was used, PCOS could be predicted with an 89.7% sensitivity and 45.5% specificity. The optimal cut-off point was >1.87 ng/ml, and the area under the curve was 0.705, with a standard error of 0.058, and a p-value of 0.002 (Fig. 2).

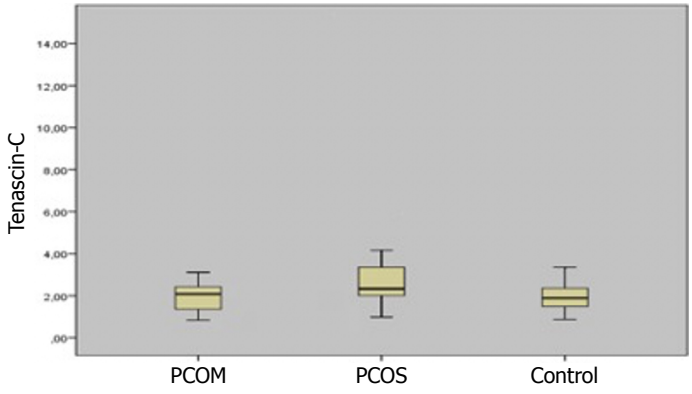

Figure 1. Tenascin-C value ranges in polycystic ovarian morphology group, polycystic ovary syndrome group and control group.

DISCUSSION

The etiology of PCOS is still not completely elucidated. It is believed to arise as a result of dysregulation in steroidogenesis caused by one or more congenital or environmental factors as well as one or more ovarian genetic traits. The most common environmental factor is obesity. In the pathophysiology of PCOS, an increase in oxidative stress and secondary chronic inflammation are some of the issues emphasized in recent years. Systemic inflammation frequently occurs in women with PCOS. Chronic inflammatory processes, especially the

TABLE 4. Evaluation of the correlation between Tenascin-C and all parameters in phenotype A and D groups

PCOS grup	Variables	Tenascin-C (mg/dl)	
		Correlation	p
Phenotype A (n=10)	Age (years)	0.687	0.552
	BMI	0.637	0.856
	Total cholesterol (mg/dL)	0.687	0.659
	Triglyceride (mg/dL)	0.197	0.197
	AMH (ng/ml)	0.297	0.297
	Free Androgen Index (FAI)	0.578	**0.021**
	HOMA-IR	0.687	0.502
	HBa1c (%NGSP)	0.436	0.436
	DHEA-S (mcg/dl)	0.061	0.061
	Androstenedione (mosm/kg)	0.196	0.196
	Free testosterone (pg/ml)	0.103	0.103
	Insulin (µIU/mL)	0.734	0.734
Phenotype D (n=14)	Age (years)	0.597	0.554
	BMI	0.587	0.852
	Total cholesterol (mg/dL)	0.531	0.671
	Triglyceride (mg/dL)	0.564	0.252
	AMH (ng/ml)	0.184	0.298
	Free Androgen Index (FAI)	0.527	**0.045**
	HOMA-IR	0.597	0.434
	HbA1c (%NGSP)	0.207	0.450
	DHEA-S (mcg/dl)	0.231	0.057
	Androstenedione (mosm/kg)	0.062	0.296
	Free testosterone (pg/ml)	0.154	0.182
	Insulin (µIU/mL)	0.373	0.733

FAI: Free androgen index; AMH: Anti-mullerian hormone; DHEA-S: Dehydroepiandrosterone sulfate; BMI: Body mass index.

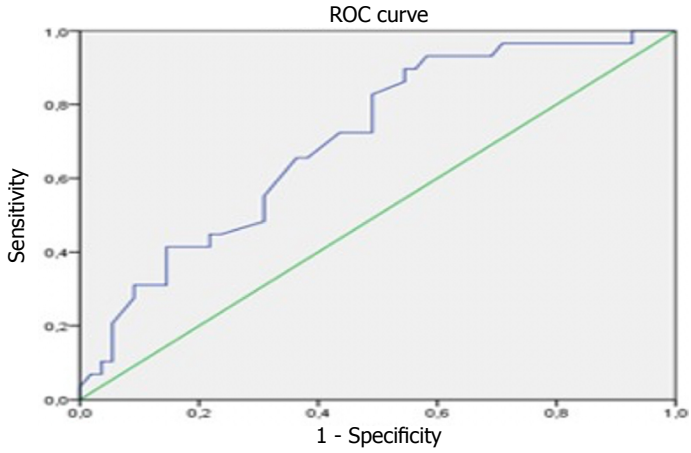

FIGURE 2. ROC curve analysis of Tenascin-C level in polycystic ovarian morphology group, polycystic ovary syndrome group and control group.

increased production of proinflammatory cytokines and the activation of innate immunity are associated with obesity and are also implicated in the pathophysiology of metabolic diseases [11, 12].

To date, this is the first study of blood TN-C values of PCOS and PCOM patients compared with healthy controls. There are also no studies evaluating the relationship of TN-C with BMI. In our study, TN-C levels were higher in the PCOS group than in the PCOM and control groups, whereas they were similar between the PCOM and the control groups. Our study demonstrated that serum TN-C level could be used to predict PCOS with 89.7% sensitivity and 45.5% specificity when TN-C is >1.87 ng/ml. Combined with other biochemical markers, we believe these results will guide the differentiation between PCOS and PCOM.

PCOS is associated with an increase in inflammatory biochemical markers that measure CVD risk [13, 14]. Existing evidence shows that increased levels of CRP, leukocyte count, and pro-inflammatory cytokines point to low-grade inflammation in PCOS [15]. As of yet, it is unclear whether the inflammatory process is associated only with obesity or also related to other features of PCOS [16]. Our study found that the CRP value was higher in the PCOS group. In addition, TN-C was positively correlated with CRP which is another acute phase reactant in PCOS. Similarly, in a study conducted in 2015, high CRP values were reported in the PCOS group [17]. Recently, adipose tissue has emerged as a valuable source of pro-inflammatory mediators [18]. TNF-α, IL-6, white blood cell (WBC), and neutrophil levels were higher in PCOS women than in healthy controls. It is proposed that the coexistence of PCOS and obesity increases the inflammation and hyperandrogenism [18]. Aytan et al. [18] showed that the levels of inflammatory mediators (CRP) were higher in obese PCOS patients compared to the healthy control group and also higher in lean PCOS patients compared to the healthy lean control group patients. Levels of anti-inflammatory cytokines were significantly lower in the PCOS group than the control group [18]. Based on these results, we can conclude that TN-C is an effective indicator of PCOS.

Dyslipidemia is the most common metabolic abnormality in PCOS. The most prominent lipid profile disorder in PCOS is high non-HDL cholesterol [19]. Based on the available literature, there are studies demonstrating that the LDL level does not change in women with PCOS. A key study by Kim et al. [20] comparing PCOS with the general population also showed no difference in serum LDL levels in PCOS patients [20, 21]. In line with the current literature, our findings also indicated no significant differences in HDL and LDL cholesterol levels among all three groups. Additionally, we observed a statistically significant increase in triglyceride, VLDL cholesterol, and total cholesterol levels in the comparison of PCOS and PCOM patients with the control group.

This study found elevated levels of triglycerides and HOMA-IR values in the PCOS group compared to control groups. Prior studies have demonstrated that high triglycerides levels, increased insulin levels and insulin resistance are associated with PCOS, which coincides with the present results [22]. In addition, studies have established that insulin resistance increases in PCOS. This can be explained by the fact that each PCOS phenotype has different characteristics. Some patient groups exhibit severe insulin resistance, while others do not exhibit a change in insulin sensitivity. It is well established that age and BMI are substantial contributing factors to decreased insulin sensitivity. In our study, when we compared age- and BMI-matched PCOS and control groups, a significant increase in insulin resistance was observed in the PCOS group.

Hyperandrogenism is indicated by the persistent elevation of serum testosterone. In the presence of clinical risk factors for PCOS, serum testosterone levels should be measured as part of a routine evaluation. Serum-free testosterone concentrations are 50% more sensitive than total testosterone in detecting hyperandrogenism [23]. In line with the available literature, we also observed significantly higher serum total and free testosterone levels in the PCOS group compared to controls. However, our study could not demonstrate a significant difference in DHEA-S levels in PCOS cases compared to control cases. This finding is contrary to previous studies suggesting DHEA-S levels are increased in PCOS. These differences can be explained in part by age differences among women participating in the study and the literature. Although DHEA-S elevation is an indicator of functional adrenal hyperandrogenism in PCOS, DHEA-S evaluation is mostly used to detect unexpected adrenal disorders, such as adrenal tumors causing virilization [24].

Prior research has indicated that PCOS patients with a high free androgen index exhibit higher insulin resistance and lower SHBG levels compared to those with a low free androgen index. This relationship has been attributed to the underlying pathogenesis of PCOS [25]. The findings of our study suggest that the accompaniment of TN C elevation with elevated free androgen index in the PCOS group may be due to similar pathophysiological mechanisms.

A limitation of our study is based on a limited number of cases per phenotype of PCOS. Notwithstanding the relatively small sample, the present research explores, for the first time, serum TN-C levels in PCOS and PCOM. So far, numerous factors have been proposed for the pathogenesis of PCOS, but the exact mechanism remains unclear. Consequently, studies on TN-C stabilization and molecular characteristics in serum can lead to new treatment options for PCOS. TN-C has emerged as a promising marker for the differentiation of PCOM and PCOS due to its potential for cost-effectiveness and easy accessibility. Its widespread clinical use is anticipated in the near future.

Conclusion

The study's findings showed a significant increase in TN-C levels in the PCOS groups compared to controls. The research has also shown that serum TN-C level could predict PCOS with 89.7% sensitivity and 45.5% specificity when TN-C is >1.87 ng/ml. In addition, we observed a statistically significant increase in triglycerides, VLDL cholesterol, total cholesterol, total and free testosterone, insulin levels, and insulin resistance.

Ethics Committee Approval: The Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Clinical Ethics Committee granted approval for this study (date: 15.11.2018, number: 62/2018). This study obtained permission from the EuroQol Research Foundation.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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