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The Association of Leukocyte Increase with Hyperandrogenism and Body Mass Index in Women with Polycystic Ovary Syndrome

Polikistik Over Sendromu Olan Kadınlarda Artan Lökosit Sayısının Hyperandrojenizm ve Vücut Kitle İndeksi ile İlişkisi

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Abstract
Objectives: The aim of this study was to compare the white blood cells (WBC) count in patients with polycystic ovary syndrome (PCOS) with the controls and to assess its relationship between metabolic markers and hormonal measures.
Materials and Methods: The study was conducted retrospectively. One hundred-thirty women with PCOS and 71 healthy women with regular menses were included in the study. General characteristics and anthropometric measures were analyzed. Hormonal, metabolic and inflammatory parameters were studied in all subjects at the follicular phase of the menstrual cycle.
Results: The average age and body mass index (BMI) of PCOS and the control groups were similar (*P*=0.071 and *P*=0.063, respectively). Inflammatory markers, WBC [6.00 (4.51-7.17) *vs.* 7.20 (5.91-8.41);(*P*<0.001)] and c-reactive protein (CRP) [3.45 (3.30-3.61) *vs.* 3.48 (3.45-4.98); (*P*=0.031)] were significantly higher in the PCOS group. In multiple regression analysis in a model when WBC is the dependent variable and total testosterone (TT), sex hormone binding globuline (SHBG), and homeostatic model assessment of insulin resistance (HOMA-IR) were the predictors, WBC was positively associated with TT levels and BMI even after adjustment for confounders (*P*=0.006; *P*=0.039, respectively).
Conclusion: WBC is an independent predictor of cardiovascular disease, is elevated in women with PCOS and is explained by both obesity and hyperandrogenemia.
Key words: PCOS, WBC, CRP, Free androgen index

Öz
Amaç: Bu çalışmanın amacı, polikistik over sendromlu (PKOS) hastalarla kontrol grubunun lökosit (WBC) sayılarını karşılaştırmak ve lökosit sayısı ile metabolik belirteçler ve hormonal değerler arasındaki ilişkiyi değerlendirmektir.
Materyal ve Metot: Çalışma retrospektif olarak yapıldı. Yüz otuz polikistik over sendromlu ve düzenli adet gören 71 sağlıklı kadın çalışmaya alındı. Genel özellikleri ve antropometrik ölçümleri analiz edildi. Tüm katılımcıların hormonal, metabolik ve inflamatuar parametreleri adet döngüsünün foliküler fazında çalışıldı.
Bulgular: PCOS ve kontrol grubunun yaş ortalaması ve vücut kitle indeksi (VKİ) benzerdi (sırasıyla, *P* = 0.071 ve *P* = 0.063). Inflamatuar belirteçler, WBC [6.00 (4.51-7.17) karşı 7.20 (5.91-8.41); (*P* <0.001)] ve c-reaktif protein (CRP) [3.45 (3.30-3.61) karşı 3.48 (3.45-4.98); (*P* = 0.031)] PKOS grubunda anlamlı olarak yüksek bulundu. WBC'nin bağımlı değişken; total testosteron (TT), seks hormon bağlayıcı globulin (SHBG) ve insülin direncinin homeostatik model değerlendirmesinin (HOMA-IR) belirleyici olarak konduğu bir çoklu regresyon analizinde, WBC'yi, karıştırıcı faktörlerin de göz önüne alınmasından sonra TT ve BMI'nin anlamlı olarak belirlediği bulundu (*P* = 0.006; *P* = 0.039, sırasıyla).
Sonuç: Kardiyovasküler hastalıklar için bağımsız bir belirleyici olan WBC, PCOS'u olan kadınlarda yüksektir ve bu durum obezite ve hiperandrojenemi ile açıklanabilir.
Anahtar kelimeler: PKOS, WBC, CRP, serbest androjen indeksi

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Introduction

The polycystic ovary syndrome (PCOS) is an important cause of both menstrual irregularity and excess androgen in women. It is one of the most common endocrinopathies in women of reproductive age and affects between 5 to 10 % of women. Its etiology is unknown, but it is obvious that, no single etiologic factor fully accounts for this syndrome.[1-3]

Chronic low grade inflammation is one of the accused factors, which in turn leads up to a cluster of risk factors for diabetes and cardiovascular diseases.[4-7] In PCOS patients, the occurence of inflammation has not yet been clarified; whether it is triggered by endocrine abnormalities associated with PCOS per se such as hyperandrogenemia or whether it is a consequence of obesity frequently observed in PCOS women is not clear yet. Hyperandrogenemia, which characterizes the syndrome, induces the maturation of adipocytes and causes central obesity. [8,9] The hypertrophy of adipocytes may cause compression in the stromal vessels and leads to hypoperfusion of adipose tissue and consequently hypoxia. Under hypoxic conditions, visceral adipocytes exert paracrine and endocrine, a number of molecules some of which are markers of inflammation. The continuous release of inflammatory mediators is associated with long-term metabolic and cardiovascular complications, while it also contributes to the maintenance of the syndrome concluding with excess ovarian androgen production and an endless vicious cycle starts.[10]

White blood cell (WBC) count and c-reactive protein (CRP) have been recognized as well known predictive markers of cardiovasculer events.[4-7] Even modest elevations of WBC are associated with multiple cardiovascular risk factors. Recent studies have observed that women with PCOS had higher levels of WBC, showing chronic inflammation.[11-16]

In this study, we aimed to investigate whether metabolic and inflammatory markers are different in patients with PCOS and in the control group, and whether inflammation process originates from obesity or hyperandrogenism.

Materials and Methods

Subjects

In this study, we retrospectively analyzed a routinely and systematically generated database of 18-40 years aged patients with PCOS, attended Kartal Dr. Lutfi Kirdar Training and Research Hospital, Endocrinology Clinic between July 2013 and July 2015. PCOS group consisted of 130 patients. Control group consisted of 71 subjects who attended family medicine policlinics for routine control. They had regular menstrual cycles and they did not have neither the signs of hirsutism nor the signs of hyperandrogenism. The study was conducted in agreement with the Declaration of Helsinki II. The hospital ethical committee approved the study protocol.

PCOS was diagnosed according to Rotterdam 2003 criterias.[2] At least two of the following criteria were required for PCOS diagnosis: 1) Oligo or anovulatory menstrual dysfunction (anovulation accepted as frequent bleeding at intervals <21 d or infrequent bleeding at intervals >35 d, occasionally, bleeding may be anovulatory despite falling at a normal interval, so a 21. day progesterone was documented for detection anovulation),

2) Clinical and/or biochemical signs of hyperandrogenism (clinical hyperandrogenism was defined according to Ferriman-Gallwey score at least 8, whereas biochemical hyperandrogenism was defined by more than 70 ng/dL serum testosterone level), 3) Typical ultrasonographic findings of PCO morphology (defined by the presence of 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL without a cyst or dominant follicle in either ovary). Other etiologies of similar symptoms were excluded.[2]

Subjects were excluded if they were pregnant or lactating, if they had a recent or any chronic illness (diabetes mellitus, cardiovascular/pulmonary diseases, rheumatologic diseases, thyroid dysfunction, Cushing's disease, congenital adrenal hyperplasia) and if they were taking any medications in the last three months of before hospital attendence (oral contraceptives, glucocorticoids, antiandrogens, insulin sensitizers, ovulation induction agents or antiobesity drugs).

Laboratory analysis

Fasting blood samples were drawn in all women 2-5 days after spontaneous or dydrogesterone induced withdrawal bleeding, total testosterone (TT), Sex hormone binding globuline (SHBG), Dehydroepiandrosterone-sulfate (DHEA-S), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), Estradiol (E2), thyrotropin (TSH), fasting glucose (FG), fasting insulin (FI), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) , low-density lipoprotein cholesterol (LDL-C), uric acid, CRP levels and complete blood count (CBC) were measured using these samples. Standard 75 g oral glucose tolerans test (OGTT) was performed to all participants.

Plasma venous glucose was measured using the hexokinase method. TC, TG and HDL-C levels were measured by an enzymatic colorimetric method on the AU5800 Clinical Chemistry System Analyzer (Beckmann Coulter, Florida, USA.). Serum insulin levels were measured by the immunoassay method (Abbott Diagnostics, USA). TT, SHBG, DHEA-S, E2, LH, FSH, PRL were measured by UniCel DXI 800 Access Immunoassay System (Beckmann Coulter, Florida, USA).

CRP was measured by the nephelometric method. WBC was measured by LH780 (Beckman Coulter, Mervue, Ireland).

LDL-C was calculated using the Friedewald calculation. Fasting glucose and fasting insulin values were used to calculate homeostatic model assessment of insulin resistance (HOMA-IR). To calculate insulin sensitivity index (ISI), glucose and insulin levels were used which obtained within 30 min intervals (0, 30, 60, 90 and 120 min) with standard 75 g OGTT. TT and SHBG levels were used to calculate free androgen index (FAI). Following formulas were used; HOMA-IR = [FI (μIU/ml) × FG (mg/dl)]/405 and ISI= [10,000/square root of ((FG × FI) × (mean glucose × mean insulin during OGTT))] and FAI= (TT (ng/dl)/ 28,84 x SHBG(nm/l)) x 100.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables or median (25% and 75% interquartiles) for non-normally distributed variables. Normality of data distribution was assessed by Kolmogorov–Smirnov test. Statistical significance was evaluated using the independent sample *t* test for normally distributed variables,

Mann–Whitney U test was used for non-normally distributed variables and chi-square test was used for categorical variables. In Table 3, multiple regression analysis was used. WBC and CRP were dependent variables. In Model 1, TT, SHBG, and HOMA-IR were predictors. In Model 2, results were adjusted for BMI and in Model 3, results were adjusted for age. For non-normally distributed variables, log was transformed before performing the analysis. A 5% type 1 error level defined statistical significance.

To have a mean WBC difference=0.5 between PCOS and control groups and if the standard deviation is accepted as =1.6 with 0.05 type 1 error and with 0.10 type 2 error, 42 subjects should be included in each groups.

Results

The comparative demographic and laboratory parameters of the PCOS (n=130), and the control group (n=71) are given in Table 1. The average age of PCOS and the control groups were respectively 25.08 ± 3.56 and 26.10 ± 4.19 years (*P*=0.071). Control group did not have oligomenorrhea, hirsutism and polycystic ovary view in ultrasonography. BMI and current smoking rate was similar in PCOS and control group (*P*=0.063, *P*=0.062, respectively).

TT, SHBG, FAI, DHEA-S levels and LH/FSH ratio were significantly higher in PCOS group than the control group (*P*<0.001; for all) (Table 1). FG level was found to be similar in both groups (*P*=0.955); however FI level was significantly higher in PCOS group (*P*=0.004). HOMA-IR was higher and ISI was lower in PCOS group than the control group [(2.49 (1.72-3.56) *vs.* 2.0 (1.38-2.98); (*P*=0.010) and 4.05 (2.70-5.84) *vs.* 5.12 (3.59-8.11); (*P*=0.001), respectively]. Inflammatory markers, WBC [6.00 (4.51-7.17) *vs.* 7.20 (5.91-8.41);(*P*<0.001)] and CRP [3.45 (3.30-3.61) *vs.* 3.48 (3.45-4.98); (*P*=0.031)] were significantly higher in PCOS group. Subgroups of WBC; i.e. neutrophil and lymphocyte counts were significantly higher in PCOS group (*P*<0.001; *P*=0.001, respectively) (Table 1).

Table 2 shows correlation analysis in all participants. BMI, TT, FAI, DHEA-S, HOMA-IR and TG had positive correlation with WBC count, although ISI and HDL-C had negative correlation with WBC count. BMI, HOMA-IR and TG had positively correlation with CRP, but PRL, ISI and HDL-C had negative correlation with CRP.

In multiple regression analysis in a model when WBC is the dependent variable and TT, SHBG, and HOMA-IR are predictors, WBC was positively associated with TT levels, even after adjustment for BMI and age (*P*=0.005) (Table 3).

Discussion

PCOS is one of the most common reproductive disorders, characterized by ovulatory dysfunction and androgen excess. Apart from the hormonal dysfunction, metabolic complications frequently accompany PCOS.[1-3] Although the pathogenesis of the syndrome has not been clarified yet, it is known that there is a low grade chronic inflammation in PCOS patients which triggers the initiation and progression of atherosclerosis. WBC count and CRP have been recognized as predictors of cardiovascular diseases.[4-7] The current study investigated that, WBC count and CRP were increased in PCOS patients compared to age and BMI matched controls. Additionally, multiple regression analysis showed that increased WBC in PCOS patients was positively associated with TT levels and BMI. However; HOMA-IR and SHBG was

not found to be associated with WBC after adjustment for age and BMI.

Table 1. General characteristics of all participants

	Control (n=71)	**PCOS (n=130)**	***P***
General characteristics			
Age (years)	26.10 ± 4.19	25.08 ± 3.56	0.071*
Menarche (years)	13.13 ± 1.83	13.42 ± 1.51	0.254*
FG Score (≥8)(%)	0	22	
Oligoamen.(%)	0	22	
PCO(%)	0	18	
Acanthosis(%)	4	10	0.183^
Current smoker(%)	4	24	0.062^
Anthropometric measures			
BMI (kg/m²)	26.65 ± 7.19	28.5 ± 6.90	0.063*
Weight (kg)	69.39 ± 19.41	73.91 ± 18.58	0.107*
WC (cm)	82.71 ± 17.29	86.94 ± 15.18	0.088*
Hormonal measures			
T. Testosterone	37.64 ± 12.94	61.19 ± 22.41	<0.001*
SHBG (nmol/L)	52.30 (31.00-71.60)	27.00 (16.90-40.25)	<0.001 ʿ
FAI	2.47 (1.51-4.04)	7.16 (4.72-12.17)	<0.001 ʿ
DHEA-S (ug/dL)	207.84 ± 84.48	296.01 ± 135.91	<0.001*
PRL (ng/mL)	15.66 (10.97-21.53)	17.00 (12.12- 22.23)	0.402 ʿ
LH (mIU/mL)	4.78 (3.99-6.25)	5.18 (3.28-8.29)	0.351 ʿ
FSH (mIU/mL)	6.55 ± 1.44	5.26 ± 1.49	<0.001*
LH/FSH	0.76 (0.56-1.04)	0.92 (0.70-1.66)	<0.001 ʿ
E2 (pg/mL)	43.00 (31.25-61.75)	42.00 (31.25-55.75)	0.536 ʿ
TSH (µIU/mL)	1.62 (1.25-2.72)	1.86 (1.33-2.70)	0.541 ʿ
Metabolic and inflammatory measures			
FG (mg/dL)	87.39 ± 10.18	87.31 ± 9.69	0.955*
FI (µU/mL)	9.00 (7.00-13.50)	12.00 (8.45-16.00)	0.004 ʿ
HOMA-IR	2.00 (1.38-2.98)	2.49 (1.72-3.56)	0.010 ʿ
ISI	5.12 (3.59-8.11)	4.05 (2.70-5.84)	0.001 ʿ
TC (mg/dL)	170.00 (155.00-207.00)	166.00 (151.7-197.00)	0.457 ʿ
LDL-C (mg/dL)	107.32 ± 32.31	106.30 ± 27.45	0.827*
HDL-C (mg/dL)	53.38 ± 11.28	48.28 ± 9.52	0.002*
TG (mg/dL)	73.00 (56.00-90.00)	83.00 (57.00-116.50)	0.052 ʿ
CRP (mg/L)	3.45 (3.30-3.61)	3.48 (3.45-4.98)	0.031 ʿ
WBC (/mm³)	6.00 (4.51-7.17)	7.20 (5.91-8.41)	<0.001 ʿ
Neutrophil	3.30 (2.66-4.11)	4.25 (3.50-4.92)	<0.001 ʿ
Lymphocyte	2.00 (1.56-2.30)	2.20 (1.91-2-80)	0.001 ʿ

*Student *t* test, ^Chi-square test, ʿMann-Whitney U test

It is widely known that WBC is increased in women suffering from PCOS.[11-16] In a large study, with a high number of PCOS patients (n=1016) compared with the control group (n=1016, age matched healthy women) it was found that total WBC and lymphocyte counts were elevated in PCOS patients even after adjustment for BMI.[15] In our study, total WBC count and both neutrophil and lymphocyte counts were increased in PCOS patients compared to the age&BMI matched control group.

Table 2. Correlation between metabolic, hormonal measures and inflammatory measures

	WBC		**CRP**	
	r	***P***	**r**	***P***
BMI	0.307	<0.001	0.398	<0.001
TT	0.282	<0.001	0.054	0.513
SHBG	-0.244	0.001	-0.134	0.113
FAI	0.343	<0.001	0.134	0.111
DHEA-S	0.171	0.023	0.011	0.894
PRL	-0.042	0.585	-0.254	0.002
LH/FSH	-0.047	0.549	0.044	0.609
HOMA-IR	0.218	0.004	0.256	0.002
ISI	-0.293	<0.001	-0.305	<0.001
TC	-0.088	0.255	0.053	0.531
LDL-C	-0.085	0.269	0.095	0.265
HDL-C	-0.342	<0.001	-0.209	0.012
TG	0.229	0.003	0.263	0.002

Spearman correlation

Increased adiposity in women with PCOS is a common finding. Although the mechanisms responsible for this association remain unclear, there are proofs about increased adiposity has a negative impact on several clinical features of these women.[17,18]

Table 3. Predictors of WBC by multiple regression analysis in all participants

	Model 1		**Model 2**		**Model 3**	
	β	***P***	**β**	***P***	**β**	***P***
TT	0.001	**0.003**	0.001	**0.004**	0.001	**0.006**
SHBG[a]	-0.073	**0.033**	-0.060	0.085	-0.049	0.173
HOMA-IR[a]	0.063	0.100	0.030	0.474	0.022	0.602
BMI			0.003	0.080	0.003	**0.039**
Age					-0.003	0.213

[a]Log transformed before performing the analysis.
WBC is the dependent variable
Model 1; Explanatory variables are T.testosterone, SHBG, and HOMA-IR
Model 2; model 1 adjusted for BMI
Model 3; model 2 adjusted for age.

Previous data showed that lean PCOS patients represent similar metabolic profile with healthy controls, although lean PCOS patients had higher serum androgen levels than controls. In our study, obese PCOS patients had higher FAI levels than lean PCOS patients. This shows obesity itself is responsible for increasing serum androgen levels, although this association turns into a vicious endless cycle. Thus, weight loss constitutes the main step of treatment.[19]

It is well known that obesity and insulin resistance are closely associated with low grade inflammation, but there is inconsistent data about hyperandrogenism, [20,21]so in order to evaluate the contribution of these fundamental factors to the inflammatory state observed in PCOS, we examined each one of them separately and in combination. BMI, TT and HOMA-IR were positively correlated with WBC count, although multiple regression analysis showed HOMA-IR was no more associated with WBC after adjustment for age and BMI. Contrarily, CRP did not have a significant correlation with hyperandrogenism. Other studies showed increased levels of serum CRP concentrations in women with PCOS compared to healthy women after adjustment for BMI. They also noted that serum CRP concentrations in both control group and PCOS group had a positive correlation with the degree of obesity and a negative correlation with insulin sensitivity, although TT concentrations were not similar to our study.

Adipose tissue is the resource of many cytokines, acute-phase proteins and other inflammatory mediators which exert influence on glucose metabolism. These products have been linked to the development of insulin resistance and type 2 diabetes mellitus in PCOS patients.[10] Moreover, according to recent data, glucose ingestion seems to activate oxidative stress and induce the release of TNFα, IL6, and CRP in PCOS patients.[21] Insulin resistance and hyperandrogenism may be the result of inflammation triggered by hyperglycemia and contribute to atherogenesis in PCOS.[10]

Interestingly, in our study, prolactin had a negative correlation with CRP, although it did not have an association with WBC count. It is known that prolactin is secreted not only by anterior pituitary gland but also by many extrapituitary cites including immune system cells and has a role in immune regulation.[22] Hyper and hypoprolactinemia are both associated with immunsupression, physiological levels of circulating prolactins are necessary to maintain basal immunocompetence.

Another issue is the strong association of elevated triglycerides and low HDL-C levels with increased WBC. In vitro studies demonstrated triglyceride-mediated activation of neutrophils.[23]

The limitations of our study is its cross-sectional design as we cannot identify the definite cause and affect the relationship.

In conclusion, WBC which is a potent predictor of cardiovascular disease is elevated in women with PCOS, and hyperandrogenism and BMI are closely related to the WBC counts.

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