

Relationship between androgen levels and neutrophil/lymphocyte ratio in patients diagnosed with hirsutism

Hirsutism and neutrophil-lymphocyte ratio

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Abstract

Aim: Hirsutism is a disease involving increased terminal hair growth in women with a male-type distribution pattern in androgen-sensitive areas such as the chin, upper lip, chest, abdomen, back, and thighs. Our review of the available literature revealed no previous studies concerning the role of the peripheral blood neutrophil/lymphocyte ratio (NLR), an easily calculated and noninvasive marker, in hirsutism. The purpose of this research was to determine the relationship between androgen levels and NLR in female patients diagnosed with hirsutism.

Material and Methods: The files of 392 patients presenting to the Bakırköy Dr. Sadi Konuk Education and Research Hospital due to hirsutism between 2018 and 2020 were included in this cross-sectional, retrospective study. Patients' hirsutism and menstrual cycles, age at menarche, number of pregnancies in the case of married women, number of living children, and history of infertility were investigated. Hyperandrogenemia findings, such as hair loss and acne, were also recorded. Patients' biochemical and complete blood count parameters were evaluated.

Results: The mean age of the participants was 26.27±6.37 years (min-max: 16-48), and their androgen levels were statistically significantly associated with high-density lipoprotein, hemoglobin, hematocrit, 17-hydroxyprogesterone, and HbA1c levels ($p<0.05$). However, no significant relationship was found between patients' androgen levels and NLR values ($p>0.05$).

Discussion: No significant relationship was determined in this study between androgen levels and NLR values in women diagnosed with hirsutism. Due to the limited numbers of previous similar studies, further research with larger patient numbers is now needed.

Keywords

Androgen, Hirsutism, Neutrophil/Lymphocyte Ratio

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Introduction

Hirsutism is a disease involving increased terminal hair growth in women with a male-type distribution pattern in androgen-sensitive areas such as the chin, upper lip, chest, abdomen, back, and thighs [1]. It affects approximately 10-15% of women of reproductive age [2,5]. Various diseases including polycystic ovary syndrome (PCOS), non-classic adrenal hyperplasia (NCAH), Cushing's syndrome, and acromegaly as well as certain drugs may be involved in the etiology. PCOS and idiopathic hirsutism have frequently been identified as etiological causes [1]. The blood neutrophil/lymphocyte ratio (NLR) has recently come to prominence as an easily measured and practical method providing valuable information in the diagnosis and prognosis of various diseases [2]. The principal causes implicated in the emergence of the manifestation of hirsutism are increased androgen secretion, a decrease in sex hormone-binding globulin concentrations, and a resulting increase in free androgen levels. The most important androgens in this context are androstenedione, testosterone, and dihydrotestosterone [3]. Adrenal diseases are a rarer cause of hirsutism. One of the most common causes of adrenal hirsutism is NCAH. This can develop in association with deficiencies of 21- α hydroxylase, 11- β hydroxylase, or 11- β hydroxysteroid dehydrogenase enzymes [4]. The patient's history and physical examination findings yield important clues in the determination of virilizing diseases, PCOS or other endocrinopathies, and androgenic drug use. The investigation of PCOS findings, one of the most frequent causes of hirsutism, is important in the approach to the condition. Examination of anovulation, one of the important findings of PCOS and frequently manifesting with menstrual cycle irregularity, is also important in terms of the investigation of insulin resistance findings such as obesity, metabolic syndrome, acanthosis nigricans, or familial type 2 diabetes mellitus. Investigation of androgenic drug use is also important in the differential diagnosis [6]. Hyperprolactinemia-related hirsutism should be considered during examination in the event of thyroid dysfunction symptoms together with galactorrhea, since hyperprolactinemia can result in increased adrenal androgen secretion [7]. Comorbidity of hyperprolactinemia and polycystic ovaries is also frequently seen, and hirsutism is detected in 59% of these patients [8]. Moon face, muscular atrophy, stria, and thinning of the skin with easy bruising are suggestive of the presence of Cushing's syndrome. The upper total plasma testosterone limit in women is 70-90 ng/dL. Dehydroepiandrosterone sulfate (DHEA) elevations may be observed in approximately 15% of women with normal total and free testosterone levels. Idiopathic hirsutism may be determined in women with normal total testosterone levels or levels above the threshold and no other findings. Laboratory findings in cases of PCOS include high luteinizing hormone (LH) in blood collected on the third day of the menstrual cycle, normal or low follicle-stimulating hormone (FSH) levels, and moderately increased testosterone, androsterone, and DHEA levels with polycystic ovaries upon pelvic ultrasound. A significantly increased 17-hydroxyprogesterone (17-OHP) and 11-deoxycorticosterone (11-DOC) response to the adrenocorticotrophic hormone (ACTH) stimulation test is diagnostically important in cases of NCAH [7].

Since the physiological response to the stress of circulating leukocytes causes an increase in neutrophil numbers and a decreased leukocyte count, the ratio between these two subgroups is employed as an inflammatory marker [9, 10]. Neutrophils activated with tissue destruction release enzymes such as myeloperoxidase, acid phosphatase, and elastase [11, 12]. Changes in leukocyte rates occur during inflammatory responses. Relative lymphopenia accompanies neutrophilia. The NLR has been proposed as a simple inflammatory response marker and has been used as an inflammatory marker in several cardiac and noncardiac diseases [13]. An increased mortality rate in cases of acute coronary syndromes has been recently shown with elevation in the NLR [14, 15]. Higher NLR compared to the attack-free period has also been reported during attacks in patients with familial Mediterranean fever [16].

The presence of T lymphocytes in a tumor indicates a significant immune response to the lesion. Recent data have shown that a low lymphocyte count in colorectal tumors is associated with poor prognosis. The NLR has been identified as a prognostic factor for survival in colorectal and ovarian cancers [17, 18]. It has also been suggested that preoperative NLR may be a simple tool for identifying colorectal cancer patients with poor prognosis [19].

An increased inflammatory response and oxidative stress are also thought to occur in patients with hirsutism. The NLR in peripheral blood is also used as a parameter providing information about the relationship between the inflammatory environment and physiological stress. Our review of the available literature revealed no previous studies concerning the role of the peripheral blood NLR, an easily calculated and noninvasive marker, in hirsutism. The purpose of this research was therefore to determine the relationship between androgen levels and the NLR in female patients diagnosed with hirsutism.

Material and Methods

The files of 458 female patients presenting to the Bakırköy Dr. Sadi Konuk Education and Research Hospital's Internal Diseases Clinic in İstanbul, Turkey, due to hirsutism in 2018-2020 were examined retrospectively. Women with missing sociodemographic data and test results, women using drugs such as antidepressants, and pregnant and menopausal women were excluded from the study. Patients' Ferriman-Gallwey scores were not available. The files of 392 (85.5%) women containing full data were included in the study. Women's hirsutism and menstrual histories, age at menarche, number of pregnancies in the case of married women, number of living children, and infertility history were investigated. Hyperandrogenemia findings such as loss of hair and acne were also recorded. Results for hormone analysis performed in the follicular phase (days 2-5 of the menstrual cycle) were recorded. Evaluations were performed for FSH, LH, estradiol (E2), prolactin (PRL), dehydroepiandrosterone sulfate (DHEA-S), 17-OHP, androstenedione, total testosterone, free testosterone, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, uric acid, ferritin, glucose, insulin, and HbA1c levels and all complete blood count parameters. The research commenced following receipt of approval from the Gümüşhane University Education

and Research Hospital Ethics Committee (Date: 04.02.2021, No: E-95674917-108.99-8026) and the study complied with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed with SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive methods (mean, standard deviation, median, frequency, and percentage) were applied in the evaluation of the study data. The Mann-Whitney U test and Spearman correlation analysis were employed in the evaluation of nonnormally distributed data. Correlation coefficients (r) were regarded as weak correlations at 0.00-0.24, moderate at 0.25-0.49, powerful at 0.50-0.74, and very powerful at 0.75-1.00. Results were expressed at 95% confidence intervals with significance set at p<0.05.

Table 1. Complete blood count and biochemistry findings

	Min-Max	Mean±SD
WBC	3 - 13	7.36±1.92
Lymphocyte	0 - 6	2.30±0.73
Neutrophil	1 - 10	4.38±1.64
Neutrophil/ Lymphocyte ratio (NLR)	0.56 - 24.54	2.14±1.81
HB	9- 16	12.75±1.20
HCT	29 - 49	38.91±3.32
MPV	6 - 13	8.88±1.07
PCT	0 - 0.05	0.24±0.05
PDV	10 - 24.80	17.52±15.15
PLT	141 - 495	275.92±65.59
KOL	92 - 315	180.96±38.49
LDL	43 - 200	105.86±30.36
HDL	15 - 117	53.17±13.12
TG	11-679	97.00±65.96
Insulin	2 - 82.20	12.37±10.17
Glucose	63 - 185	88.67±12.17
HbA1c	4.50 - 9.70	5.41±0.41
Uric acid	2.1 - 7.7	4.25±1.06
Ferritin	0 - 125	20.34±15.40
FSH	0.10 - 137.45	8.63±12.46
LH	0.03 - 61.49	8.19±8.01
T. testosterone	0.03 - 11.12	0.71±0.91
Free testosterone	0.35 - 22.01	2.80±2.35
17-OHP	0.04 - 13.85	1.25±7.57
PROG	0 - 25.77	2.79±4.52
DHEA-S	9.3 - 806.0	274±138.73
Prolactin	0.37 - 177	15.04±12.26

Results

The mean age of the patients in this study was 26.27±6.37 years (min-max: 16-48). Complete blood count and biochemistry findings are shown in Table 1.

Lymphocyte, glucose, HbA1c, and 17-OHP levels were found to be significantly higher in patients with high s-testosterone levels (p<0.05). Hemoglobin (Hb), hematocrit (HCT), triglycerides, glucose, HbA1c, and 17-OHP levels were found to be significantly higher in patients with high t-testosterone levels. HDL levels were found to be significantly higher in patients with normal s-testosterone and t-testosterone levels (Table 2).

The correlations between the androgen levels of the patients and some other parameters are shown in Table 3. There was a positive correlation between DHEA-S levels and s-testosterone and t-testosterone levels in these patients, while a weak but significant negative correlation was found with the level of HbA1c. There was a positive correlation between the patients' t-testosterone levels and their s-testosterone, Hb, and HCT levels while a significant negative correlation was found

Table 2. Comparison of some variables according to Free Testosterone and Total Testosterone levels

	Free Testosterone (pg/mL)		Total Testosterone (ng/dL)	
	Normal Mean±SD	Abnormal Mean±SD	Normal Mean±SD	Abnormal Mean±SD
Lymphocyte	2.20±0.67 p=0.025	2.55±0.73	2.27±0.71 p=0.220	2.43±0.85
NLR	2.32±2.36 p=0.258	1.97±0.87	2.26±2.05 p=0.251	1.86±0.84
Hb	12.64±1.16 p=0.061	13.00±1.38	12.66±1.12 p=0.025	13.15±1.53
HCT	38.54±3.19 p=0.053	39.56±3.89	38.66±3.10 p=0.018	40.08±4.26
HDL	54.17±12.87 p=0.005	49.50±13.22	53.76±13.11 p=0.008	47.97±11.53
Triglyceride	93.95±65.23 p=0.301	102.95±73.34	93.40±60.08 p=0.006	123.43±95.13
Glucose	11.24±9.16 p=0.001	15.78±12.78	11.86±9.81 p=0.027	15.85±13.20
HbA1c	5.40±0.34 p=0.044	5.51±0.60	5.40±0.33 p=0.019	5.56±0.81
17-OHP	0.71±0.96 p=0.036	2.68±14.33	0.75±0.99 p=0.002	4.63±21.01

Table 3. Correlation coefficients between patient's androgen levels and some parameters

Characteristic	1	2	3	4	5	6	7	8	9	10
(1) DHEA-S (µg/dL)	1									
(2)Total testosterone (ng/dL)	0.131**	1								
(3) Free testosterone (pg/mL)	0.170**	0.679*	1							
(4)Triglyceride (mg/dL)	-0.013	0.059	0.117**	1						
(5)HDL (mg/dl)	-0.013	-0.172*	-0.212*	-0.294*	1					
(6)Hb (gram/dL)	0.105	0.275**	0.386*	0.034	-0.064	1				
(7)HCT	0.089	0.296**	0.409*	0.043	-0.119	0.945*	1			
(8)17-OHP (ng/mL)	-0.076	0.052	0.115**	-0.026	0.073	-0.011	-0.054	1		
(9) NLO	-0.014	-0.039	-0.039	-0.019	-0.160**	-0.092	-0.047	-0.001	1	
(10) HgA1c	-0.208*	0.051	0.115**	0.154**	-0.121**	-0.038	0.008	-0.008	-0.059	1

*p<0.001 **p<0.05

with HDL level. There was a positive correlation between the patients' s-testosterone levels and triglyceride, Hb, HCT, HbA1c, and 17-OHP levels while a significant negative correlation was found with HDL level.

Discussion

Levels of inflammatory markers are known to increase in patients with PCOS. Several studies have suggested an increased inflammatory response in patients hospitalized due to PCOS [20]. Some of these studies have employed high-sensitivity C-reactive protein (hs-CRP), mean platelet volume (MPV), and NLR as inflammatory markers [21]. For example, Yılmaz et al. reported higher NLR and MPV values in patients with PCOS compared to healthy controls, although hs-CRP levels were similar between the two groups [22].

No significant difference was observed in NLR values in idiopathic hirsutism patients in the present study. Meanwhile, lymphocyte, glucose, HbA1c, and 17-OHP values were significantly higher in patients with elevated free testosterone levels. These findings show that there is no correlation between NLR and clinical or laboratory parameters.

Zhao et al. compared androgen and lipid levels in PCOS patients with high LH/FSH ratios and determined increased LDL and triglyceride levels and decreased HDL levels compared to a control group [23]. In the present study, Hb, HTC, triglyceride, glucose, HbA1c, and 17-OHP levels were significantly higher in patients with total testosterone elevation.

Salman et al. compared fasting blood sugar, insulin, total cholesterol, LDL, HDL, and triglyceride levels between a patient and a control group, but only fasting blood sugar levels in the patient group were higher than those in the control group. This difference was statistically significant, although values in both groups were within normal limits [24]. In the present study, fasting blood sugar levels were significantly higher among patients with total testosterone elevation.

Celikbilek et al. reported higher neutrophil and lymphocyte counts and NLR values in a patient group with Behçet disease compared to a control group. Neutrophil counts and NLR values during attack periods were significantly higher than post-attack values [25].

Walsh et al. determined significant NLR elevation in the preoperative period in a study of colorectal cancer patients [19]. In their study of acute coronary syndrome patients, Öztürk et al. reported no significant difference in NLR values between stable and unstable angina pectoris groups [25]. In the present study, no statistically significant difference was determined in NLR values according to androgen levels.

This study was conducted in a single center and involved a single diagnosis. Therefore, as a limitation of this study, the results cannot be generalized.

Conclusion

Our study results revealed no statistically significant association between androgen levels in hirsutism patients and NLR and MPV values or leukocyte counts. On the basis of these findings, we conclude that a diagnosis of idiopathic hirsutism has no significant impact on these biomarkers. However, we also think that further studies on this subject will provide sounder evidence and will enhance our current levels of understanding.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

- Somani N, Harrison S, Bergteld WF. The clinical evaluation of hirsutism. *Dermatol Ther* 2008; 21: 376-391.
- Adanas Aydın G, Gülsüm Turan Özsoy H, Ankaralı H, Özgen G, Neselioglu S. The association of dynamic thiol-disulfide homeostasis and inflammatory markers in patients with polycystic ovary syndrome 2020 Jan; 59[1]: 7984. doi:10.1016/j.tjog.2019.11.012.
- Price VH. Testosterone metabolism in the skin. *Arch Dermatol* 1975; 111:1496-1502.
- Keleştimur F. Hirsutism of adrenal origin in adolescents: Consequences in adults. *J Ped Endocrinol Metabol* 2001; 14: 1309-1315.
- Azziz R, Carmina E, Sawaya ME. Idiopathic hirsutism. *Endocr Rev* 2000; 21: 347-362.
- Nelson-DeGrave VL, Wickenheisser JK, Coc-krell JE, Wood JR, Legro RS, Strauss JF, et al. Valproate potentiates androgen biosynthesis in human ovarian theca cells. *Endocrinology* 2004; 145:799-808.
- Yıldız BO. Diagnosis of hyperandrogenism: clinical criteria. *Best Pract Res Clin Endocrinol Metab* 2006; 20: 167-176.
- Rosenfield RL. Hirsutism. *N Engl J Med* 2005; 353: 2578- 2588.
- Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B, et al. Regulation of adhesion molecules during human endotoxemia. No acute effects of aspirin. *Am J Respir Crit Care Med* 1999; 159: 857-63.
- Zahorec R. Ratio of neutrophil to lymphocyte counts Rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 2001; 102:5-14.
- Reichlin T, Socrates T, Egli P, Potocki M, Bredthardt T, Arenja N, et al. Use of myeloperoxidase for risk stratification in acute heart failure. *Clin Chem* 2010; 56: 944-51.
- Tousoulis D, Antoniadis C, Koumallos N, Stefanadis C. Proinflammatory cytokines in acute coronary syndromes: from bench to bedside. *Cytokine Growth Factor Rev* 2006; 17:225-33.
- Demirkol S, Balta S, Kucuk U, Kucuk HO. The neutrophil lymphocyte ratio may be useful inflammatory indicator before applying other expensive and invasive procedures. *Indian J Nephrol*. 2014; 24(1): 65-6.
- Tamhane UU, Aneja S, Montgomery D, Rogers RN, Eagle KA, Hitinder S, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol* 2008; 102: 653-7.
- Duffy BK, Gurm HS, Rajagopal V, Ritesh G, Stephen GE, Bhatt DL, et al. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. *Am J Cardiol* 2006; 97: 993-6.
- Celikbilek M, Dogan S, Akyol L, Borekci E, Zararsiz G, Kozan M, et al. Neutrophil:Lymphocyte Ratio in Patients with Familial Mediterranean Fever. *J Clin Lab Anal*. 2014 Mar 28. Doi: 10.1002/jcla.21732. [Epub ahead of print]
- Tsujimura A, Kawamura N, Ichimura T, Honda KI, Ishiko O, Ogita S. Telomerase activity in needle biopsied uterine myoma-like tumors: differential diagnosis between uterine sarcomas and leiomyomas. *Int J Oncol* 2002; 20:361-5.
- Blake-Mortimer JS, Sephton SE, Carlson RW, Stites D, Spiegel D. Cytotoxic T lymphocyte count and survival time in women with metastatic breast cancer. *Breast J* 2004; 10:195-9.
- Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ: Neutrophil- lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg On- col* 2005; 91:181-4.
- Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al. Cardiometabolic aspects of the polycystic ovary syndrome. *Endocr Rev* 2012;33(5):812e41.
- Kahal H, Aburima A, Ungvari T, Rigby AS, Dawson AJ, Coady AM, et al. Poly-cystic ovary syndrome has no independent effect on vascular, inflammatory orthrombotic markers when matched for obesity. *Clin Endocrinol* 2013;79(2):252e8.
- Yılmaz MA, Duran C, Basaran M. The mean platelet volume and neutrophil tolymphocyte ratio in obese and lean patients with polycystic ovary syndrome. *J EndocrinolInvestig* 2016;39:45e53
- Zhao Y, Fu L, Li R, Wang LN, Yang Y, Liu NN, et al. *BMC Med*. 2012 Nov 30;10:153. doi: 10.1186/1741-7015-10-153.
- Salman S, Demirsoy EO, Bilen N, Cantürk Z, Aktürk AŞ, Bayramgürler D, et al.

Androjenetik alopesili kadınlarda insülin direnci ve metabolik sendrom. Archives of the Turkish Dermatology & Venerology/Turkderm, 2015, 49.2
25. Öztürk S, Erdem A, Özlü MF, Ayhan S, Erdem K, Özyaşar M, et al. *Türk Kardiyol Dern Arş - Arch Turk Soc Cardiol* 2013;41(4):284-289

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