

Effect of Cross-Sex Hormone Therapy on Hematological Parameters in Transmen: A 1-Year Follow-Up Study

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ABSTRACT

Objective: Testosterone is the primary cross-sex hormone therapy (CSHT) for the female-to-male (transmen) transition. However, there is a growing concern about the safety and long-term results of CSHT, including erythrocytosis and inflammation. We aimed to investigate the effects of testosterone therapy on hematological parameters and high-sensitive C-reactive protein (hsCRP) in transmen with a 1-year follow-up.

Methods: This was a single-center prospective study in 45 hormone-naïve transmen and 28 age- and body mass index (BMI)-matched ciswomen. Ciswomen were compared with hormone-naïve transmen. Testosterone ester preparation (250 mg) was prescribed to all transmen every 21 days. The transmen were evaluated before treatment and 6 and 12 months following CSHT. Sex steroids, complete blood counts, and hsCRP were analyzed.

Results: At initial assessment before CSHT, the transmen had higher total testosterone ($P=.002$), white blood cell count ($P=.013$), and neutrophil count ($P=.015$) than the ciswomen. The exogenous testosterone administration to transmen was associated with a significant increase in hematocrit ($P<.001$) and hsCRP ($P=.002$) at 12 months.

Conclusion: Testosterone administration to transmen was associated with a significant increase in hematocrit and hsCRP at 12 months. These parameters should be regularly monitored in line with current guidelines.

Keywords: Transmen, ciswomen, cross-sex hormone therapy, testosterone, hematological parameters, hematocrit

Introduction

Gender dysphoria (GD) has been defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as distress resulting from the incongruence between one's experienced gender identity and assigned biological sex at birth, along with a persistent and strong desire to be of another sex.¹ In Turkey, parallel to the world, the number of applications to endocrinology outpatient clinics for cross-sex hormone therapy (CSHT) among patients with GD is gradually increasing. Testosterone is the primary CSHT for the female-to-male (transmen) transition. For transmen on testosterone treatment, the physiological targets are to increase the level of serum testosterone to match that of the male gender and to suppress endogenous estradiol, while the physical targets include beard growth, muscle mass, and deepening of the voice.²

If transgender individuals can tolerate CSHT or do not develop side effects, CSHT should be continued for a lifetime. However, there is a growing concern about the safety and long-term results of testosterone administration to a female assigned at birth, including erythrocytosis. Since, it is basically known that there is an increased risk of erythrocytosis with testosterone replacement in men with androgen deficiency.³ On the other hand, hematocrit elevation that was shown with testosterone administration to hypogonadal men has not been observed in polycystic ovary syndrome (PCOS), which is characterized by hyperandrogenemia in women.^{4,5} Besides, it has been reported that testosterone usage in postmenopausal women with decreased sexual desire causes a slight increase in hematocrit but not erythrocytosis.⁶

There are various evidence that hyperandrogenism leads to a proinflammatory state.⁷ Androgen-related inflammation has been investigated in different trials and elevations in white blood cell (WBC) counts in women with PCOS have been demonstrated before.^{8,9}

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It has been reported that increased peripheral levels of WBC and C-reactive protein (CRP) are associated with chronic inflammation and early cardiovascular risk in PCOS.¹⁰ However, the results regarding whether increased WBC in PCOS is related to androgens are unclear. Although there are few studies reporting an increase in hematocrit with testosterone replacement in transmen^{11–13}, there is very limited data on the effects of testosterone on other hemogram parameters such as WBC differential counts and CRP in this cohort.¹⁴ It is crucial to understand the impacts of CSHT on the laboratory parameters used to determine the risks in order to provide optimal care and establish follow-up procedures for this population.

In this study, we aimed to analyze the effects of a supraphysiological dose of testosterone therapy on hematological parameters and CRP in transmen with a 1-year follow-up.

Materials and Methods

This single-center prospective research was approved by the Marmara University Faculty of Medicine Ethics Committee (number: 09.2022.241). Hormone-naïve transmen who were referred by a psychiatry outpatient clinic to the Marmara University outpatient clinics of endocrinology diagnosed with GD were included in the study. The inclusion criteria were ages 18–45 years and willingness to participate in the study. We excluded patients who were already being started with any hormone therapy; aged <18 or >50 years; on treatment for any concomitant disease; had any psychiatric, metabolic, endocrinologic, or neurologic disease during the study period; and had a history of oophorectomy or PCOS. A total of 45 drug-naïve transmen and 28 ciswomen were recruited. Written informed consent was obtained from all the participants.

Sustanon®, an intramuscular testosterone ester preparation containing 100 mg testosterone decanoate, 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, and 60 mg testosterone isocaproate was prescribed to the transmen as CSHT every 21 days. CSHT targeted the serum testosterone levels within the normal range for male adults and clinical response. The transmen were evaluated before the initiation of treatment and 6 and 12 months following CSHT. Comparison between ciswomen and transmen was made only before hormone therapy was initiated.

MAIN POINTS

- Data on the long-term results of testosterone therapy for the female-to-male transition, including erythrocytosis and inflammation, are limited.
- A single-center prospective study with a 1-year follow-up in 45 hormone-naïve transmen and 28 ciswomen was performed.
- Hormone-naïve transmen had higher total testosterone, white blood cell, and neutrophil count compared with ciswomen. Testosterone administration to transmen was associated with a significant increase in hematocrit and high-sensitive C-reactive protein (hsCRP) at 12 months.
- Complete blood counts and hsCRP should be monitored at regular intervals in line with current guidelines in the transmen population.

Age, smoking status, and body mass index (BMI) were recorded at the first visit. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, estradiol, androstenedione, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), high-sensitive C-reactive protein (hsCRP) levels, and complete blood counts (CBC) were analyzed between 2 and 5 days of the follicular phase of menstruation. After CSHT, these parameters were measured on the day that is the middle of the 2 injection sessions. The free androgen index (FAI) was calculated using the formula: total testosterone (µg/L)/SHBG (nmol/L) × 100.

FSH, LH, total testosterone, estradiol and DHEAS levels were measured using the electrochemiluminescence immunoassay (ECLIA, Modular Analytics E170, Roche Diagnostics, Mannheim, Germany). Serum androstenedione levels were measured with solid-phase enzyme-linked chemiluminescence immunometric assay (Immulite 2000, Siemens, PA, USA). CBC was determined using by a Unicel DxH800 Coulter Cell Analyzer (Beckman Coulter, CA, USA). HsCRP levels were analyzed by a nephelometric method (BN ProSpec, Dade Behring, IL, USA).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25.0 (IBM Corp.; Armonk, NY, USA) program. The conformity of the variables to the normal distribution was examined using histogram graphics and the Kolmogorov–Smirnov test. In addition to descriptive analysis, the mean and standard deviation (SD) were used for normally distributed parameters, and the median and interquartile range (IQR) values were used for non-normally distributed parameters. The categorical variables were compared with the Pearson chi-square test (n, %). Mann–Whitney *U*-test (median, IQR) and independent *t*-test (mean ± SD) were performed to compare non-normally distributed (nonparametric) variables and normally distributed variables between the 2 groups. Changes in the measured values were analyzed using the paired samples test for normally distributed parameters and the Wilcoxon test for non-normally distributed parameters. The change in more than 1 measured value was evaluated using the Friedman test. Spearman's correlation test was used to evaluate the measurement data with each other. Cases with a *P*-value below .05 were defined as statistically significant results.

Results

A total of 73 individuals (45 were transmen, and 28 were ciswomen) were evaluated. The median age and BMI were similar in the transmen and ciswomen groups. The rate of smoking in transmen was higher than in ciswomen (*P* < .001), while there was no difference in terms of pack-years smoked. Regarding androgens, transmen had higher total testosterone, FAI, androstenedione, and DHEAS levels than the ciswomen (*P* = .002, *P* = .015, *P* = .015, and *P* = .027, respectively). However, LH, FSH, estradiol, and SHBG levels were similar between groups. In hematological parameters, WBC and neutrophils (NEU) were significantly higher in transmen (*P* = .013 and *P* = .015, respectively); however, other parameters including hsCRP levels were similar between the groups (Table 1).

Table 2 shows the comparative evaluation of hormonal and hematological parameters at baseline and at 6 and 12 months following hormone therapy in transmen. BMI did not change significantly at either 6 or 12 months after CSHT. FSH levels decreased 6 months (*P* < .001)

Table 1. Basal Demographic and Hormonal Characteristics of Transmen and Ciswomen

Initial Measurements	Transmen (n = 48)	Ciswomen (n = 25)	P ^a
Age (years)	24 (21-29)	27 (23-29)	.077
BMI (kg/m ²)	24.73 (21.23-28.68)	22.10 (20.90-25.43)	.104
Smoking (n, %)	29 (72.5%)	7 (25%)	<.001 ^b
Cigarettes pack-year (n)	5 (3-6)	2.50 (2-5)	.408
FSH (U/L)	7.49 (6.19-8.38)	7.23 (5.45-8.20)	.278
LH (U/L)	6.01 ± 2.34	5.90 ± 2.40	.975 ^c
Estradiol (ng/L)	47.93 (38.13-63.87)	55.71 (39.75-62.72)	.672
Total testosterone	0.58 (0.45-0.79)	0.45 (0.33-0.55)	.002
SHBG (nmol/L)	55.09 ± 23.56	62.70 ± 29.28	.465 ^c
FAI	1.13 (.74-1.78)	0.87 (0.52-1.22)	.015
Androstenedione (µg/L)	3.24 (2.09-3.68)	2.52 (1.79-3.18)	.015
DHEAS (µg/L)	252.55 (198.40-329.55)	203.45 (171.60-253.60)	.027
WBC (/µL)	6850 (6050-7750)	6050 (4700-7200)	.013
NEU (/µL)	4100 (3500-4900)	3200 (2450-4550)	.015
LYM (/µL)	2090.00 ± 584.76	1846.43 ± 459.86	.251 ^c
NLR	2.00 (1.64-2.64)	1.80 (1.35-2.51)	.213
HGB (g/dL)	13.57 ± 0.99	12.93 ± 0.95	.695 ^c
HTC (%)	40.70 (37.65-41.30)	38.00 (36.80-39.85)	.063
MCV (fL)	87.70 (83.85-90.40)	86.20 (82.25-89.85)	.180
PLT (×10 ³ /µL)	250.50 (215.00-279.50)	237.50 (203.50-271.50)	.287
PLR	125.94 (99.00-147.50)	139.54 (109.50-156.06)	.159
MPV (fL)	9.10 (8.50-9.50)	9.10 (8.70-9.609)	.881
hsCRP (mg/L)	1.27 (0.33-2.09)	0.72 (0.36-2.74)	.866

DHEAS, dihydroepiandrosterone sulfate; FAI, free androgen index; FSH, follicle-stimulating hormone; HGB, hemoglobin; hsCRP, high-sensitive C-reactive protein; HTC, hematocrit; LH, luteinizing hormone; LYM, lymphocytes; MCV, mean corpuscular volume; MPV, mean platelet volume; NEU, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; SHBG, sex hormone-binding globulin; WBC, white blood count.

^aMann-Whitney *U*-test (median, IQR); ^bChi-square test (n, %); ^cIndependent *t*-test (mean ± SD). Statistically significant values (*P* < .05) are shown in bold.

and 12 months (*P* < .001) after CSHT. LH levels did not change significantly 6 months after CSHT, but they decreased significantly at 12 months compared to the baseline (*P* = .019). Estradiol and total testosterone levels increased 6 months (*P* = .032, *P* < .001, respectively) and 12 months (*P* = .009, *P* < .001, respectively) following CSHT. SHBG levels decreased at 6 (*P* < .001) and 12 months (*P* < .001) from the baseline. FAI values decreased at 6 (*P* < .001) and 12 months (*P* < .001) with CSHT. Androstenedione levels increased at 6 (*P* = .011) and 12 months (*P* = .029) compared to the baseline. After hormone therapy, hemoglobin (HGB) and hematocrit (HTC) gradually and significantly increased compared to the previous measurements (Table 2). Mean corpuscular volume (MCV) values decreased at 6 months compared to the baseline (*P* = .005) and then increased at 12 months (*P* = .001). Finally, there was no statistically significant difference between the baseline and 12-month values of MCV. Evaluation at 12 months showed no significant change in other hematological parameters, except HGB and HTC. Erythrocytosis was not observed in any participant. HsCRP did not significantly change at 6 months, but a significant increase was observed at 12 months following CSHT (*P* = .002).

Table 3 shows the correlations between hematological parameters and androgens. The relationship between hematological parameters and total testosterone or FAI initially before CSHT in the whole group (ciswomen and transmen) and in transmen at 12 months after CSHT was examined; however, no statistical significant correlation was found.

Discussion

In this study, we revealed that the transmen had higher androgen, WBC, and NEU compared with ciswomen at initial assessment before CSHT, and exogenous testosterone administration to transmen was associated with a significant increase in HGB/HTC and hsCRP at 12 months.

Recent studies in hormone-naïve transmen have indicated significantly higher androgen levels than ciswomen.^{15,16} In these studies, elevated androgen was generally associated with PCOS, which was more common in transmen. In another study we performed, when cases with PCOS were excluded, significant hyperandrogenemia persisted and androgen levels were significantly higher in transmen.¹⁷ In the present study, the significantly higher androgen levels in hormone-naïve transmen compared with ciswomen also support these findings.

The strong connection between androgens with erythropoiesis has been documented. Androgens exert their erythropoietic effects by stimulating erythropoiesis directly in the bone marrow or indirectly increasing erythropoietin.¹⁸ The increased hematocrit after testosterone administration, even in men with androgen deficiency, highlights the importance of testosterone on the proliferation of red blood cell.¹⁹ However, some studies have shown that in PCOS patients who are hyperandrogenic, erythrocytosis was not detected compared with healthy women.^{4,5} Thus, it can be considered that androgen

Table 2. Comparative Evaluation of Hormonal, Biochemical, and Hematological Parameters at Baseline and 6 and 12 Months Following Hormone Therapy in Transmen									
	Baseline			6 Months			12 Months		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	P ^a P ^b P ^c
BMI (kg/m ²)	25.34 ± 5.72	24.73 (21.23-28.68)	25.9 ± 4.68	25.46 (22.29-28.45)	25.96 ± 5.23	25.05 (22.39-30.39)	.328 [*]	.903 [*]	.119 [*]
FSH (U/L)	7.83 ± 2.23	7.49 (6.19-8.38)	5.53 ± 2.35	5.54 (4.03-7.44)	5.79 ± 4.14	5.02 (3.51-7.03)	<.001	.541	<.001
LH (U/L)	6.01 ± 2.34	5.76 (4.26-7.20)	5.17 ± 3.41	4.50 (2.43-7.04)	5.22 ± 4.65	4.65 (2.37-5.84)	0.066	0.788	.019
Estradiol (ng/L)	51.65 ± 18.47	47.93 (38.13-63.87)	70.3 ± 37.74	53.36 (43.68-87.93)	77.44 ± 72.85	55.70 (46.52-76)	.032	.840	.009
Total testosterone (µg/L)	.64 ± .29	.58 (.45-.79)	5.62 ± 2.35	5.55 (3.84-6.68)	5.72 ± 2.55	5.46 (4.04-6.81)	<.001	.682	<.001
SHBG (nmol/L)	55.09 ± 23.56	48.30 (37.40-73.35)	27.02 ± 10.93	26.30 (19.45-34.50)	37.12 ± 48.51	32.94 (20.85-35.80)	<.001 [*]	.082	<.001
FAI	1.44 ± 1.07	1.13 (.74-1.78)	.25 ± .16	.22 (.15-.30)	.9 ± 3.14	.30 (.14-.78)	<.001	.002	<.001
Androstenedione (µg/L)	4.23 ± 6.74	3.24 (2.09-3.68)	4.1 ± 2.25	3.80 (2.83-4.80)	3.9 ± 1.42	3.57 (3.10-4.48)	.011	.922	.029
DHEAS (µg/L)	284.8 ± 119.81	252.55 (198.40-329.55)	329.31 ± 131.40	323.00 (225.15-422.95)	300.7 ± 111.47	300.35 (208.20-331.30)	.006	.068	.102
WBC (/µL)	7035 ± 1586.25	6850.00 (6050.00-7750.00)	7127.5 ± 1656.38	6700.00 (6000-8200)	7509.75 ± 1757.72	7350.00 (6100-8850)	.902	.110	.111
NEU (/µL)	4237.5 ± 1094.90	4100.00 (3500.00-4900.00)	4227.5 ± 1210.00	3800.00 (3450-4800)	4487.5 ± 1332.62	4000.00 (3550-4950)	.638	.168	.459
LYM (/µL)	2090 ± 584.76	2000.00 (1800.00-2450.00)	2172.5 ± 616.44	2050.00 (1700-2650)	2243.8 ± 588.11	2238.50 (1700-2500)	.314 [*]	.417	.057
NLR	2.19 ± .89	2.00 (1.64-2.64)	2.09 ± .84	1.89 (1.48-2.41)	2.09 ± .65	2.04 (1.63-2.34)	.294	.717	.591
HGB (g/dL)	13.57 ± .99	13.70 (13.00-14.20)	14.67 ± 1.20	14.80 (13.70-15.60)	15.16 ± 1.12	15.25 (14.50-16.05)	<.001	.002	<.001 [*]
HTC (%)	39.58 ± 2.78	40.70 (37.65-41.30)	43.3 ± 3.21	43.60 (40.95-45.95)	45.05 ± 3.13	45.40 (43.85-47.45)	<.001	<.001	<.001
MCV (fL)	87.33 ± 4.82	87.70 (83.85-90.40)	85.99 ± 5.45	86.30 (82.10-90.20)	87.32 ± 4.68	87.20 (84.25-90.90)	.005 [*]	.001 [*]	.988 [*]
PLT (×10 ³ /µL)	252.27 ± 61.23	250.50 (215.00-279.50)	261.3 ± 61.75	257.50 (222-309.50)	255.49 ± 57.64	254.00 (214.50-284.50)	.069	.463 [*]	.379
PLR	12919 ± 43.72	12594 (99.00-147.50)	12776 ± 41.41	120.92 (98.23-152.96)	119.51 ± 34.27	117.75 (93.12-133.75)	.677	.187 [*]	.143
MPV (fL)	9.23 ± 1.07	9.10 (8.50-9.50)	9.57 ± 1.18	9.35 (8.90-10.05)	9.38 ± 1.21	9.10 (8.55-9.85)	.053	.422	.179
hsCRP (mg/L)	1.51 ± 1.36	1.27 (.33-2.09)	1.83 ± 1.78	1.60 (.54-2.24)	2.2 ± 1.48	2.04 (1.19-3.10)	.139	.147	.002

BMI, body mass index; DHEAS, dihydroepiandrosteredione sulfate; FAI, free androgen index; FSH, follicle-stimulating hormone; HGB, hemoglobin; hsCRP, high-sensitive C-reactive protein
HTC, hematocrit; LH, luteinizing hormone; LYM, lymphocytes; MCV, mean corpuscular volume; MPV, mean platelet volume; NEU, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; SHBG, sex hormone-binding globulin; WBC, white blood count.

^aP: Baseline to 6th month (Wilcoxon test, *paired samples test).
^bP: 6th month to 12th month (Wilcoxon test, *paired samples test).
^cP: Baseline to 12th month (Wilcoxon test, *paired samples test). Statistically significant values (p<0.05) are shown in bold.

Table 3. Correlations Between Hematological Parameters and Androgens

	All Individuals at Baseline				Transmen at 12th Months			
	Total Testosterone		FAI		Total Testosterone		FAI	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
WBC (/μL)	0.117	.342	0.167	.174	−0.178	.272	−0.213	.193
NEU (/μL)	0.154	.209	0.167	.174	−0.241	.134	−0.193	.239
LYM (/μL)	−0.033	.789	0.125	.311	−0.020	.901	−0.227	.164
NLR	0.165	.179	0.101	.413	−0.270	.092	−0.008	.963
HGB (g/dL)	0.235	.054	0.150	.222	−0.027	.868	−0.138	.402
HTC (%)	0.167	.173	0.095	.441	−0.072	.657	0.000	.999
MCV (fL)	0.158	.199	0.000	.998	0.241	.135	−0.177	.282
PLT ($\times 10^3/\mu\text{L}$)	−0.096	.437	0.018	.881	−0.113	.486	−0.212	.194
PLR	−0.094	.446	−0.088	.476	−0.127	.433	0.005	.976
MPV (fL)	−0.120	.331	−0.096	.434	0.237	.142	0.221	.176
hsCRP (mg/L)	−0.206	.093	0.081	.513	0.088	.589	0.047	.775

Spearman's correlation test.

FAI, free androgen index; HGB, hemoglobin; hsCRP, high-sensitive C-reactive protein; HTC, hematocrit; LYM, lymphocytes; MCV, mean corpuscular volume; MPV, mean platelet volume; NEU, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; WBC, white blood count.

elevation does not cause hematocrit increase in women with endogenous hyperandrogenemia. On the other hand, almost all studies indicate an increase in HGB and HTC levels in transmen during the first year of CSHT, with the most significant increase during the first 6 months.¹¹⁻¹³ In the prospective ENIGI study of 53 transmen treated with intramuscular testosterone for 12 months, the mean hematocrit was demonstrated to increase from 40.8% to 45.8% with statistical significance.¹² Chandra et al²⁰ showed an increase in hematocrit from 40% to 45% at 12 months in transmen with testosterone esters, cypionate, or enanthate administration ($P < .001$). A large cohort study reported HTC peaks at a mean of 31 months among transgender individuals receiving testosterone, and erythrocytosis occurs in up to 20%; despite the high rate of erythrocytosis, thromboembolic events were found to be rare.²¹ In the present study, HTC increased significantly with 12-month testosterone treatment in transmen ($P < .001$) in accordance with the literature, and no erythrocytosis occurred. Moreover, hemoglobin/hematocrit, which did not show a difference between transmen and ciswomen at the baseline, showed a significant increase after the supraphysiological dose of testosterone administration in transmen, suggesting that androgen-induced erythropoiesis is dose-dependent. It should be considered that the different testosterone formulations and the frequency of administration may lead to varying laboratory and clinical results. Further, it is still ambiguous whether altering the HGB/HTC in transmen has any effect on cardiovascular and thromboembolic outcomes.

In vitro studies have shown that androgen exposure in women is associated with inflammation and endothelial dysfunction.²² The expression of androgen receptors has been demonstrated in lymphoid and nonlymphoid cells of the bone marrow and thymus, proposing that androgens play a significant role in the development and activation of leukocytes.²³ It has been shown that women with PCOS have higher WBC levels than healthy ones.^{9,10} In a study of Chinese patients with PCOS, the serum androgen level was positively correlated with the total WBC count, indicating androgen-related chronic inflammation.⁸ Pergialiotis et al²⁴ have also shown a positive correlation between free testosterone and neutrophil-to-lymphocyte ratio (NLR) in PCOS, and furthermore, this association was independent of

obesity. On the contrary, Papalou et al²⁵ have stated that WBC elevation in PCOS is associated with obesity and insulin resistance, but not with hyperandrogenemia. In the present study, WBC and NEU were significantly higher in hormone-naïve transmen than in ciswomen, but other hemogram parameters were not significantly different. Regarding CSHT, only 1 research carried out in our country has shown that transmen had higher WBC levels after testosterone exposure than ciswomen; platelet-to-lymphocyte ratio, NLR, and MPV were similar between transmen receiving testosterone and ciswomen.¹⁴ In the present study, higher WBC and NEU levels, which were seen in hormone-naïve transmen than ciswomen, were not observed after 12-month CSHT in transmen. Therefore, we thought that the current WBC and NEU elevation may be related to the baseline higher smoking rate in transmen rather than the effect of testosterone. It is noteworthy that the smoking status of the patients was not included in most of the studies evaluating PCOS and transmen in the literature.

While investigating inflammation in PCOS patients, CRP was also used as an important marker.²⁶ It has been reported that CRP values in PCOS patients with hyperandrogenemia are higher than in healthy women.²⁷ However, data on the effect of testosterone administration on CRP in transmen are insufficient. Schutte et al²⁸ have found that a 12-month testosterone administration increases the hsCRP concentration in transmen but does not change the levels of other systemic inflammatory markers. The impact of testosterone treatment on inflammation parameters and endothelium has been assessed in a prospective observational study with 157 transmen using human umbilical vein endothelial cells. This study has revealed that 12 weeks of therapy with testosterone undecanoate increased proinflammatory cytokines and leukocyte-endothelium interplays. Also in this study, Iannantuoni et al²⁹ suggested that these effects warrant monitoring cardiovascular risk in these populations. Despite a significant increase in hsCRP in transmen compared with baseline at 12 months in our study, the clinical outcomes of testosterone administration on inflammation and endothelial dysfunction in transmen need to be supported with more studies.

The prospective evaluation of WBC differential counts in transmen before and after treatment is the strength of our study. The small

number of individuals and the relatively short follow-up period can be stated as limitations.

In conclusion, testosterone administration to transmen was associated with a significant increase in HGB/HTC and hsCRP at 12 months, and these parameters should be regularly monitored in line with current guidelines. More prospective research with an adequate sample size and follow-up period that assess hemoglobin/hematocrit and CRP levels are required to reach a clinical conclusion.

Ethics Committee Approval: The study was approved by Marmara University Faculty of Medicine Ethics Committee (number: 09.2022.241).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.E., Ö.Ü.; Design – O.E., Ö.Ü.; Supervision – Ö.Ü.; Materials – O.E.; Data Collection and/or Processing – O.E.; Analysis and/or Interpretation – O.E.; Literature Search – O.E.; Writing Manuscript – O.E.; Critical Review – O.E., Ö.Ü.

Declaration of Interests: The authors have no conflict of interest to declare.

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