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Hyperandrogenism-related metabolic changes in drug-naïve transmen compared to cisgender women: a case-controlled study

Pınar Erel[1], *Onur Elbasan*[2], *Neşe Yorguner*[3], *Eren İmre*[2], *Özlem Üstay*[1]

[1]*Department of Internal Medicine, Marmara University School of Medicine, Istanbul, Türkiye*
[2]*Department of Endocrinology and Metabolism, Marmara University School of Medicine, Istanbul, Türkiye*

Abstract

Introduction: The aetiology of gender dysphoria is still unclear. Although prior studies have shown that trans men have higher androgen levels than cisgender women, they all concluded unselected populations. Our reason for performing this study is to evaluate trans men's hormone profile and metabolic status to compare with cisgender women in a more selected population. This is the first case-controlled study to compare anthropometric, metabolic, and endocrinological parameters of drug-naïve trans men with those of cisgender women.

Material and methods: We designed this study as a single-centre observational cohort study. We included 70 drug-naïve trans men, and the control group comprised 34 healthy cisgender women. We measured and compared hormone profiles and metabolic parameters in the 2 groups.

Results: Of the 70 trans men individuals, 16 (22.85%) met the Rotterdam criteria and were diagnosed with polycystic ovary syndrome (PCOS); 4 individuals in the control group met the criteria (11.7%). Although we matched body mass index in the groups, total testosterone, free androgen index, androstenedione, 17 hydroxyprogesterone, muscle strength, triglyceride, and homeostatic model assessment of insulin resistance levels were significantly higher in the trans men than in the cisgender women ($p < 0.05$). Even after were excluded PCOS patients, hyperandrogenaemia was apparent in the trans men.

Conclusion: Our study showed that trans men have clearly higher androgen levels, which may have been the reason for metabolic changes compared to cisgender women. However, the main reason for hyperandrogenism in drug-naïve trans men is still not known, and more comprehensive studies are needed.

Key words: *androgen; cisgender women; metabolic syndrome; trans men*

Introduction

The American Psychiatric Association defined gender dysphoria (GD) in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) as distress experienced due to incongruence of gender identity and designated (biological) sex [1]. "Biological sex" refers to the reproductive organs' anatomic characteristics and hormone profile, which are determined by genetic factors in the intrauterine period. "Gender identity" refers to an inner sense of being a man or a woman, and "gender presentation" refers to how one expresses gender on a feminine to masculine scale [2].

The size of the transgender population varies in many societies, but according to a meta-analysis published in the *European Psychiatry Journal* in 2015, the population of trans women is 6.8/100,000 and trans men is 2.6/100,000 [3]. The influencing factors of gender dysphoria are still unclear. Studies have shown that trans men have higher androgen levels than cisgender women, probably due to polycystic ovary syndrome (PCOS) [4]. PCOS is characterized by chronic anovulation, polycystic ovarian morphology, and biochemical and/or biological signs of hyperandrogenism. Most women with PCOS also exhibit insulin resistance and hyperinsulinism, which occur independent of obesity [5]. In addition, insulin resistance is associated with hypertension, dyslipidaemia, obesity, and atherosclerotic cardiovascular disease [6].

Prior studies have shown a conflict regarding PCOS prevalence among trans men [4, 7, 8]. In some studies that included cisgender women as a control group, hyperandrogenaemia in trans men was detected, but researchers have not compared trans men to cisgender women, as PCOS patients have been excluded.

We aimed to evaluate metabolic parameters and hormonal profiles of drug-naïve trans men compared to those of cisgender women.

Assoc. Prof. Özlem Üstay, MD, Department of Endocrinology and Metabolism, Marmara University School of Medicine, Fevzi Cakmak Mah. Muhsin Yazicioglu Cad. No:10, Kaynarca/Pendik/Istanbul, Türkiye, tel: 00 90 216 625 45 45; e-mail: drozlemustay@gmail.com

Material and methods

We designed this study as a single-centre, case-controlled, cross-sectional study. The study population consisted of assigned female at birth (AFAB) transgender individuals who had been referred to Marmara University Hospital's Department of Endocrinology Outpatient Clinic from psychiatry outpatient clinics. We assessed these individuals for eligibility and included 70 drug-naïve trans men, and the control group comprised 34 cisgender women. We informed the subjects that their participation in the study was completely voluntary and that they could withdraw their consent at any time. We obtained written informed consent from all study subjects. The Marmara University School of Medicine Ethics Committee approved the study (Ethics Committee approval number: 09.2018.554). Inclusion criteria were being between the ages of 18 and 45 years and willingness to participate in the study. Our exclusion criteria were having already started any hormone therapy, being under 18 or over 50 years old, ongoing psychiatric disease, any ongoing metabolic and endocrinological disease (such as metabolic syndrome, hypertension, and dyslipidaemia), or neurological disease, history of oophorectomy, undergoing treatment for any metabolic disease, and low intellectual capacity. We asked participants about their age, comorbidity, chronic medical treatments, smoking, and drinking.

We measured height, weight, and body mass index (BMI) at the first visit. We conducted handgrip strength tests (HSTs) to evaluate muscle strength with a handheld dynamometer (T.K.K.5401; Takei Scientific Instruments, Tokyo, Japan). We took 3 measurements one minute apart in each hand. We used the mean value of all measurements as the score for each patient, and applied the measurement according to the NHANES Muscle Strength/Grip Test Procedure [9]. We used the Ferriman-Gallwey (F-G) scoring system to determine our participants' hirsutism status. The same physician evaluated hair growth in 9 areas of the body and determined the F-G scoring.

We measured oral glucose tolerance, follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, 17-OH progesterone, total testosterone, sex hormone-binding globulin (SHBG), prolactin (PRL), androstenedione, dehydroepiandrosterone sulphate (DHEAS), thyroid-stimulating hormone (TSH), lipid profile, and highly-sensitive C-reactive protein (HsCRP) levels between days 2 and 5 of the follicular phase of menstruation. We evaluated all the participants regarding the 2003 Rotterdam criteria [10].

Laboratory assessment

We measured FSH, LH, PRL, total testosterone, and oestradiol using electrochemiluminescence immunoassay (ECLIA). The intra- and inter-assay coefficients of variation were 1.67–3.93% and 4.67–8.1% for total testosterone, respectively, and the inter-assay coefficients of variation were 2.2–12.3% for oestradiol. The inter-assay coefficients of variation were 3.1–4.3% for FSH and 1.6–2.2% for LH. We measured serum insulin-like growth factor 1 (IGF-1) levels using the Immulite solid-phase, enzyme-labelled chemiluminescent immunometric assay (Roche, Immulate, 2000). The intra- and inter-assay coefficients of variation were 3.0–7.6% for IGF-1. We analysed total cholesterol, high-density lipoprotein (HDL), and triglycerides following the enzymatic colour method and measured fasting glucose level employing the enzymatic UV test (hexokinase method) with an AU5800 Clinical Chemistry Analyzer (Beckman Coulter, United States). We analysed insulin following the immunoassay method in a Unicel DXI 800 automated analyser (Beckman Coulter, United States).

We used the following formulas:

$$\textit{Free Androgen Index (FAI)} = \frac{\textit{Total Testosterone } (\mu g/L)}{\textit{SHBG } (nmol/L)} \times 100$$

$$\textit{HOMA-}\beta = 360 \times \frac{\textit{Fasting Insulin } (mU/L)}{\textit{Fasting Glucose } (mg/dl) - 63}$$

$$\textit{HOMA-IR} = \textit{Fasting Insulin [Mu/L]} \times \textit{Fasting Glucose [mg/dl]}/405$$

We calculated area under the curve (AUC) values for glucose and insulin using the following formula:

$$[\textit{Plasma Fasting Glucose} + (\textit{30-minute Plasma Glucose} \times 2) + (\textit{1-hour Plasma Glucose} \times 3) + (\textit{2-hour Plasma Glucose} \times 2)]/4$$

We evaluated all the participants for PCOS, using Rotterdam 2003 criteria. We accepted individuals who had 2 of the 3 criteria as having PCOS.

Statistical analysis

We analysed data using SPSS 20.0 software (SPSS Inc., Chicago, IL). We presented data as mean ± standard error (SE) or median (interquartile range) for continuous variables and as percentages for categorical variables. We compared the 2 groups (trans men and control groups) using Student's *t* test, the Mann-Whitney U test, or the chi-square test. We used the general linear model to calculate and compare the corrected means. We conducted Pearson correlation and Spearmen correlation analyses for total testosterone and FAI with muscle strength, IGF-1, HsCRP, low-density lipoprotein (LDL), 17 OH progesterone, BMI, AUC, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) according to the distributions of these parameters. We set statistical significance at $p < 0.05$. We conducted a post hoc power analysis and calculated the study's power as 89% by considering the 5% error rate of the post hoc power analysis method based on the average of total testosterone levels in the groups, which contained a total of 104 subjects.

Results

The case group included 70 trans men, and the control group consisted of 34 cisgender women. The trans men group's mean age was 24.70 ± 4.80 years, and the control group's mean age was 26.52 ± 3.77 years ($p = 0.026$). The trans men group's mean weight was 62.94 ± 12.82 kg, and the control group's mean weight was 64.81 ± 14.97 kg ($p = 0.767$). We found no significant differences between the 2 groups' BMI or systolic and diastolic blood pressure (p-values were 0.529, 0.325, and 0.644, respectively). However, waist circumference measurements were significantly higher in the trans men group than in the control group ($p = 0.008$). We found no significant difference in F-G scores between the 2 groups ($p = 0.333$).

Total testosterone, triglyceride, FAI, androstenedione, 17-OH progesterone, muscle strength, and HOMA-IR levels were significantly higher in the trans men group, but HDL levels were significantly higher in the control group. AUC (insulin) levels were also higher in the case group, but the difference was not statistically significant (Tab. 1, 2).

Of the 70 trans men, 16 met the Rotterdam criteria and were diagnosed with PCOS (22.9%). On the other hand, 4 individuals in the control group met the criteria (11.7%). When we re-analyzed the 2 groups after excluding PCOS patients, we found that waist circumference, triglycerides, IGF-1, total testosterone,

Table 1. *Comparison of female-to-male individuals' and control group's mean values*

	GD (n = 70)	Control (n = 34)	p-value
Age [Years]	24.70 ± 4.80	26.52 ± 3.77	0.026
Weight [kg]	62.94 ± 12.82	64.81 ± 14.97	0.767
BMI	23.82 ± 4.53	23.73 ± 5.16	0.529
Waist circumference [cm]	79.20 ± 11.42	73.78 ± 10.67	0.008
Systolic blood pressure [mmHg]	115.33 ± 14.94	112.54 ± 14.76	0.325
Diastolic blood pressure [mmHg]	74.25 ± 11.70	73.29 ± 10.84	0.644
F-G Score	3.78 ± 3.25	4.45 ± 3.56	0.333

BMI — body mass index; F-G — Ferriman-Gallwey; GD — gender dysphoria; statistically significant p values ($p < 0.05$) are shown in bold

Table 2. *Comparison of the 2 groups' metabolic and hormonal parameters*

	GD (n = 70)	Control (n = 34)	p-value
Fasting glucose [mg/dL]	83.82 ± 7.13	82.15 ± 7.13	0.225
Triglyceride [mg/dL]	85.47 ± 62.10	61.97 ± 24.22	0.007
Total cholesterol [mg/dL]	172.21 ± 32.28	178.79 ± 21.11	0.251
LDL [mg/dL]	105.93 ± 25.87	106.55 ± 18.45	0.675
HDL [mg/dL]	52.95 ± 10.43	59.85 ± 11.07	0.003
IGF-1 [μg/L]	189.59 ± 53.76	168.77 ± 51.56	0.045
FSH [U/L]	7.41 ± 2.29	7.29 ± 2.12	0.920
LH [U/L]	6.16 ± 2.83	6.14 ± 2.25	0.933
Oestradiol [ng/L]	47.85 ± 18.16	55.74 ± 33.72	0.230
Total testosterone [μg/L]	0.63 ± 0.30	0.46 ± 0.21	0.001
SHBG [nmol/L]	53.58 ± 23.91	63.59 ± 30.13	0.158
FAI	1.57 ± 1.33	1.01 ± 0.87	0.013
Androstenedione [μg/L]	4.06 ± 5.21	2.72 ± 1.41	0.009
DHEAS [μg/L]	280.80 ± 115.68	219.84 ± 89.34	0.007
Prolactin [μg/L]	17.42 ± 9.93	19.07 ± 9.88	0.332
17-OH progesterone [μg/L]	1.23 ± 0.62	0.93 ± 0.60	0.011
HsCRP [mg/L]	2.19 ± 2.27	1.78 ± 1.91	0.373
Mean muscle strength	27.16 ± 4.30	23.97 ± 4.01	0.001
HOMA-IR	2.17 ± 0.98	1.76 ± 1.38	0.004
HOMA-β	184.58 ± 94.04	164.59 ± 95.24	0.197
AUC (glucose)	200.16 ± 48.75	198.38 ± 50.16	0.830
AUC (insulin)	96.58 ± 53.48	87.81 ± 80.97	0.074

LDL — low-density lipoprotein; HDL — high-density lipoprotein; IGF-1 — insulin-like growth factor; SHBG — sex hormone binding globulin; FAI — free androgen index; DHEAS — dehydroepiandrostenedione sulphate; HsCRP — high-sensitive C-reactive protein; HOMA-IR — Homeostatic Model Assessment for Insulin Resistance; HOMA-β — Homeostatic Model Assessment of β-cell function; AUC — area under the curve; statistically significant p-values (< 0.05) are shown in bold

FAI, DHEAS, androstenedione, 17 OH progesterone, HOMA-IR, and AUC (insulin) levels were still significantly higher in the trans men group than in the control group. HDL levels were also significantly higher in the control group, aligning with our first full group analysis, but we did not find a significant difference in muscle strength between the 2 groups after excluding PCOS patients (p = 0.087) (Tab. 3).

When we conducted correlation analysis of total testosterone and FAI with muscle strength, IGF-1, HsCRP, LDL, 17 OH progesterone, BMI, AUC, and HOMA-IR, we found that total testosterone was positively correlated with IGF-1, 17 OH progesterone, muscle strength, and hip and neck circumference (r = 0.334, 0.302, 0.305, 0.281, 0.230; p = 0.002, 0.006, 0.002, 0.034, 0.035). On the other hand, we found no correlation in total

Table 3. *Comparison of the 2 groups' parameters after patients with polycystic ovary syndrome were excluded*

	GD (n = 54)	Control (n = 30)	p
Age [years]	25.09 ± 5.02	26.86 ± 3.81	**0.044**
Weight [kg]	60.18 ± 9.68	65.05 ± 15.62	0.368
BMI	22.88 ± 3.48	23.71 ± 5.39	0.863
Waist circumference [cm]	77.87 ± 9.56	73.21 ± 11.12	**0.009**
F-G Score	3.15 ± 2.28	3.76 ± 2.52	0.341
Fasting glucose [mg/dL]	83.77 ± 7.41	82.44 ± 7.37	0.477
Triglyceride [mg/dL]	86.75 ± 66.40	57.86 ± 19.81	**0.002**
Total cholesterol [mg/dL]	171.53 ± 31.56	176.70 ± 19.26	0.436
LDL [mg/dL]	104.30 ± 25.01	105.30 ± 18.10	0.595
HDL [mg/dL]	53.07 ± 8.56	59.83 ± 11.06	**0.005**
IGF-1 [μg/L]	188.30 ± 57.09	161.55 ± 49.84	**0.024**
FSH [U/L]	7.73 ± 2.33	7.40 ± 2.20	0.881
LH [U/L]	6.03 ± 2.16	6.25 ± 2.36	0.798
Oestradiol [ng/L]	48.39 ± 18.11	58.21 ± 35.15	0.132
Total testosterone [μg/L]	0.59 ± 0.28	0.43 ± 0.18	**0.004**
SHBG [nmol/L]	58.27 ± 22.32	67.03 ± 29.88	0.227
FAI	1.25 ± 0.97	0.81 ± 0.44	**0.032**
Androstenedione [μg/L]	4.02 ± 5.91	2.40 ± 0.87	**0.012**
DHEAS [μg/L]	268.98 ± 113.95	202.81 ± 72.10	**0.008**
Prolactin [μg/L]	17.48 ± 9.90	19.43 ± 10.38	0.384
17-OH progesterone [μg/L]	1.25 ± 0.66	0.81 ± 0.33	**0.005**
HsCRP [mg/L]	1.88± 1.87	1.73 ± 2.02	0.465
Mean muscle strength	26.37± 4.37	24.51 ± 3.96	0.087
HOMA-IR	2.14± 0.90	1.80 ± 1.48	**0.011**
HOMA-β	180.52± 85.80	159.39 ± 99.88	0.124
AUC (glucose)	203.61± 39.68	197.59 ± 51.47	0.571
AUC (insulin)	94.75± 47.75	87.14 ± 86.54	**0.032**

LDL — low-density lipoprotein; HDL — high-density lipoprotein; IGF-1 — insulin like growth factor; SHBG — sex hormone binding globulin; FAI — free androgen index; DHEAS — dehydroepiandrostenedione sulphate; HsCRP — high-sensitive C-reactive protein; HOMA-IR — Homeostatic Model Assessment for Insulin Resistance; HOMA-β: Homeostatic Model Assessment of β-cell function; AUC — area under the curve. Statistically significant p-values (< 0.05) are shown in bold

testosterone and LDL, HsCRP, AUC (insulin), waist circumference, weight, or BMI.

We found that FAI was also correlated with IGF-1 and muscle strength ($r = 0.402, 0.456$; $p = 0.000, 0.000$). It was also correlated with BMI, waist circumference, weight, and AUC (insulin) ($r = 0.423, 0434, 0.445, 0.245$; $p < 0.001, < 0.001, < 0.001, 0.018$).

A post hoc power analysis showed that we had an adequate sample size and met the requirement to attain 80% power. A post hoc power calculation also revealed that this study achieved power of 80% at the 5% alpha level.

Discussion

Our study showed that trans men have clearly higher androgen levels, which may have been the reason for their metabolic changes, compared to cisgender women.

Studies have shown that hyperandrogenism is common in trans men, and it is thought to be related to PCOS. Studies on the relationship between trans men and PCOS showed that the PCOS ratio is between 11% and 91% in the trans men population [4, 8, 11–13]. Although studies have linked hyperandrogenaemia in trans men with PCOS, Cesta et al. showed that the size of gender dysphoria/gender incongruence is not high in PCOS cases [14].

Becerra-Fernandez et al. showed that androgen levels and PCOS rates were higher in trans men [7]. In this study, we found that 49.4% of the 77 participants had hyperandrogenaemia (n = 38), and 36.4% were diagnosed with PCOS according to the Rotterdam criteria (n = 28). We did not include a control group

in this study to compare parameters. Another study showed that the hyperandrogenaemia rate was significantly higher in trans men (44.3%) than in cisgender women (20.2%) (p = 0.002) [8]. Also, the PCOS rate was higher in trans men, but the difference was statistically insignificant. Even though they included trans men before the onset of their hormone therapy, they did not question participants about self-medication. Therefore, the use of non-prescribed medication could not be ruled out as a cause of underlying hyperandrogenaemia [8]. Baba et al. found that 58% of trans men have PCOS and 39.1% of them have hyperandrogenism [4]. They reported that hyperandrogenism was associated with PCOS and obesity, but theirs was a descriptive study and therefore did not include a control group.

In our study, the PCOS rate was 22.9% among trans men and 11.7% among cisgender women. We found that levels of androgen, such as total testosterone, FAI, androstenedione, and DHEAS, were significantly higher in trans men than in cisgender women. When we define hyperandrogenaemia as total testosterone higher than 0.59 μg/L, 30 of 70 trans men (42.8%) had testosterone levels significantly higher than those of cisgender women (20.5%) (p = 0.04). After we excluded PCOS cases, trans men still had a higher hyperandrogenism rate (37%; n = 20) than cisgender women (16.7%; n = 5), but the difference was not statistically significant. According to the Turkish Endocrinology and Metabolism Association's (TEMD's) guideline, the prevalence of PCOS in women of childbearing age in Turkey is between 16 and 20%, and the prevalence of PCOS in our study is consistent with the average in our country [15]. The difference in PCOS rates in trans men populations in different studies may be related to the prevalence of PCOS in the countries studied. However, even when we exclude PCOS cases, the presence of PCOS does not explain the high androgen levels in trans men. Although there are many hypothesized causes of hyperandrogenism in trans men, such as hormone type, the level of the foetus's exposed to intrauterine life, the possible effect of endocrine disrupters in pregnancy, and the effect of fraternal birth order, which has been recently discussed, none of these hypotheses have provided clarity [16, 17].

In terms of metabolic parameters, all group analyses in our study showed dyslipidaemia (higher triglyceride and lower HDL levels) and increased HOMA-IR in trans men compared to cisgender women. AUC (insulin) was also higher in this group, but the difference was not statistically significant. After we excluded PCOS cases, the analysis showed similar metabolic parameters. Although BMI values among cisgender women were higher when we excluded PCOS cases, dyslipidaemia (high triglyceride, low HDL) and higher HOMA-IR numbers persisted in trans men. In addition, AUC (insulin) was significantly higher in trans men, unlike in all-group analysis. This was interpreted as a finding showing that insulin resistance was significantly higher in trans men than in cisgender women.

Studies have shown that metabolic syndrome parameters are significantly higher in women with high androgen levels. A recent meta-analysis to evaluate the metabolic parameters of 9556 women with PCOS showed that incidences of metabolic syndrome and insulin resistance (HOMA-IR) were significantly higher in the PCOS/hyperandrogenic (HA) group than in the PCOS/non-hyperandrogenic (NHA) group. The HDL value in the PCOS/HA group was lower than in the PCOS/NHA group, although TC, TG, and LDL were not significantly different between the groups. The lack of case-control studies was another limitation of this study [18]. A recent study showed that PCOS, higher androgen levels, and greater insulin resistance are closely related [19].

In the case of PCOS subtypes, hyperandrogenism was strongly related to metabolic risk profile, especially in women diagnosed with PCOS according to the NIH 1999 classification [20]. Another recent study showed that hyperandrogenism increases the risk of metabolic dysfunction regardless of the presence of PCOS [21]. Therefore, the presence of these metabolic syndrome-like findings in trans men can be a result of hyperandrogenism.

We found a positive correlation between handgrip strength, total testosterone (r = 0.305, p = 0.002), and FAI (r = 0.456, p < 0.001). In a case-control study that included 40 women with PCOS and 40 healthy women, total testosterone (p < 0.01) and FAI (p < 0.01) levels were higher in the PCOS group; likewise, HST results were significantly higher (p = 0.03) [22]. In another study designed in Taiwan, researchers evaluated the relationship between HST in people older than 50 years and found that FAI and testosterone are correlated with muscle strength [23]. Based on previous studies, we believe that increased HST in trans men occurs due to hyperandrogenaemia.

Our study had some limitations. We had a limited number of cases, and our study had a retrospective nature. Studies performed in larger populations are needed.

Conclusion

This is the first case-controlled study to compare anthropometric, metabolic, and endocrinological parameters in drug-naïve trans men and cisgender women. We showed that trans men have higher androgen, HOMA-IR, HST, and dyslipidaemia lev-

els than age- and BMI-matched cisgender women, even after we excluded PCOS patients. Trans men clearly have higher androgen levels than cisgender women, which may have been the reason for their increased muscle strength, insulin resistance, and dyslipidaemia. But the main cause of hyperandrogenism in drug-naïve trans men is still not known, and more comprehensive studies are needed.

Conflict of interest

None declared.

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