Transmen Individuals Have Hyperandrogenism Related Metabolic Changes Compared Ciswomen: Case Controlled Study

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Abstract

Introduction

: This study aims to evaluate metabolic parameters and hormonal profiles of transmen individuals who are referred from psychiatry outpatient clinic, compared to natal women.

Method

This study is designed as a single-center observational cohort study. Seventy drug-naive female to male transgender individuals (FtoM) and 34 healthy natal women for the control group were included. Hormone profile and metabolic parameters were measured and compared between the two groups.

Results

Sixteen of the 70 FtoM individuals meet Rotterdam criteria and are diagnosed with PCOS (22,85%), on the other hand in 4 individuals in the control group meet the criteria (11,7%). Although there wasn't any significant difference between the two groups weight and BMI; total testosterone, triglyceride, FAI, androstenedione, 17-OH progesterone, muscle strength, HOMA-IR levels were significantly higher in the transmen group and HDL levels were significantly higher in the control group (p values 0.001, 0.007, 0.013, 0.011, 0.001, 0.004 respectively.)

Conclusion

This is the first case-controlled study that compared anthropometric, metabolic, and endocrinological parameters of transmen individuals with cis women. In our study, we showed that even when PCOS patients were excluded, hyperandrogenemia continues in these individuals compared to cis women. It is clear that transmen individuals have higher androgen levels which may have been the reason for increased muscle strength, insulin resistance, and dyslipidemia compared to natal women. But the main reason for hyperandrogenism in drug-naïve transmen individuals is still not known and more comprehensive further studies are needed.

Introduction

Gender dysphoria (GD) is defined by the American Association of Psychiatry 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 reproductive organs’ anatomic characters 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” to how one expresses gender on a feminine to masculine scale (2).

Gender dysphoria appeared in DSM-3 for the first time in 1980 as “Transsexualism”. This term was followed by the “Gender Identity Disorder” in DSM 4, 1994 (3). “Gender Identity Disorder” definition, which was previously used by DSM, is left nowadays to leave the term of “disorder” to prevent these individuals feel left out or discriminated (4).

The prevalence of transgenderism varies in many societies but according to a meta-analysis published in European Psychiatry Journal in 2015, transwomen prevalence is 6,8/100.000, and transmen prevalence is 2.6/100.000 (5). There are many theories on the etiology of transgenderism. However, there is no consensus about it, endocrinological, neuroanatomical and psychosocial factors appear to be involved in some cases (6).

Several studies showed that FtoM individuals have higher hyperandrogenism levels than *cis* women and it's thought to be related to PCOS. A retrospective and descriptive study designed by Becerra-Fernandez et al. showed increased hyperandrogenism and PCOS rates in transmen (6). On the other hand, another study designed by Mueller et al. in 2016, which compares 61 FtoM individuals with 94 *cis* women, showed that FtoM individuals have significantly higher androgen levels, but there wasn’t any significant difference between the two groups’ PCOS ratio (p = 909) (7).

This study aims to evaluate metabolic parameters and hormonal profiles of transmen individuals who are referred from psychiatry outpatient clinics, compared to natal women.

Material And Method

This study is designed as a single-center observational cohort study. The study population consists of individuals that have been referred to Marmara University Hospital Department of Endocrinology Outpatient Clinic diagnosed with gender dysphoria. These individuals were assessed for eligibility and 70 drug-naive females to male transgender individuals (*transmen*) and 34 healthy natal women (*cis women*) for the control group were included. The subjects are informed that their participation in the study is completely voluntary and that they could withdraw their consent at any time. Written informed consent is obtained from all study subjects. Ethical approval was obtained by Marmara University School of Medicine ethics committee (Ethical committee approval number: 09.2018.554).

Inclusion criteria were being between age 18–45 and willingness to participate in the study. Our exclusion criteria were being already started with any hormone therapy, being under age 18 or above age 50, ongoing psychiatric disease, ongoing any metabolic, endocrinologic, or neurologic disease, history of oophorectomy, being on treatment because of any metabolic disease, and low intellectual capacity. Age, comorbidity, chronic medical treatments, smoking, and alcohol status were questioned among included individuals.

Height, weight, and body mass index (BMI) were measured at the first visit. Handgrip strength test was performed to evaluate muscle strength. To measure hand and forearm muscle strength, the test was performed three times, and mean muscle strength levels were noted. We used Ferrimann-Gallwey (F-G)

scoring system to evaluate our participants' hyperandrogenism status. Hair growth in 9 different areas of the body was evaluated by the same researcher and noted.

Oral glucose tolerance test (OGTT), FSH, LH, estradiol, 17-OH progesterone, total testosterone, sex hormone-binding globulin (SHBG), prolactin, androstenedione, dehydroepiandrostenedione sulfate (DHEAS), thyroid stimulating hormone (TSH), lipid profile, high sensitive CRP (hsCRP) levels were measured between 2.-5. days of the follicular phase of menstruation. Free androgen index (FAI) was calculated by these measures using the formula "total testosterone (µg/L)/ SHBG(nmol/L) x 100". HOMA-β was calculated with the "360 x fasting insulin (mU/L)/ [fasting glucose (mg/dl) -63]" and HOMA-IR was calculated 'fasting insulin (Mu/L) x fasting glucose (mg/dl)/ 405" formulas.

Area under the curve (AUC) values were calculated for glucose and insulin using the formula "[plasma fasting glucose + (30min plasma glucose x 2) + (1h plasma glucose x 3) + (2h plasma glucose x 2)] / 4 ". All of the participants were evaluated about polycystic ovary syndrome(PCOS) due to Rotterdam 2003 Criteria. Individuals who have 2 among 3 criteria were accepted as PCOS.

Statistical Analysis

Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL). Data are presented as mean ± SE or median (interquartile range) for continuous variables and as percentages for categorical variables. Comparisons between the two groups (transmen and control groups) were performed using the Student's t-test, Mann-Whitney U-test, or chi-squared test. The general linear model is used to calculate and compare the corrected means. Pearson correlation and Spearmen correlation analyses were performed for correlation analysis of total testosterone and FAI with muscle strength, IGF-1, hsCRP, LDL, 17 OH progesterone, BMI, AUC, and HOMA-IR according to the distributions of these parameters. Statistical significance was defined by a P value less than 0.05.

Results

The case group consists of 70 transmen individuals and the control group consists of 34 natal (cis) women. Transmen group's mean age was 24,70 ± 4,80 and the control group mean age was 26,52 ± 3,77 (p = 0.026). Transmen group's mean weight was 62,94 ± 12,82 and control group's mean weight was 64,81 ± 14,97 (p = 0.767). Likewise, there were no significant differences between the two groups' BMI, systolic, and diastolic blood pressure (p values 0,529; 0,325; 0,644 respectively). But waist circumference measurements were significantly higher in the transmen group than in the control group (p = 0.008). There was not any significant difference in F-G scores between the two groups (p = 0,333). As total testosterone, triglyceride, FAI, androstenedione, 17-OH progesterone, muscle strength, HOMA-IR levels were significantly higher in the transmen group; HDL levels were significantly higher in the control group. AUC (insulin) levels were also higher in the case group but not statistically significant.

Sixteen of the 70 FtoM individuals meet Rotterdam criteria and are diagnosed with PCOS (22,85%), on the other hand in 4 individuals in the control group meet the criteria (11,7%). When we reanalyzed the two

groups after excluding PCOS patients, we found that waist circumferences, triglyceride, IGF-1, total testosterone, FAI, DHEAS, androstenedione, 17 OH progesterone, HOMA-IR, and AUC (insulin) levels were still significantly higher in the transmen group than the control group. HDL levels were also significantly higher in the control group, compatible with our first full group analysis. But muscle strength did not show a significant difference between the two groups after PCOS patients were excluded (p = 0,087).

When correlation analysis of total testosterone and FAI with muscle strength, IGF-1, hsCRP, LDL, 17 OH progesterone, BMI, AUC, and HOMA-IR were evaluated; we found total testosterone was positively correlated with IGF-1, 17 OH progesterone, muscle strength, 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, there was no correlation between total testosterone and LDL, hsCRP, AUC insulin, waist circumference, weight or BMI.

FAI was also correlated with IGF-1, muscle strength like total testosterone (r = 0.402, 0.456; p = 0.000, 0.000) but it was additionally found correlated with BMI, waist circumference, weight, AUC insulin (r = 0.423, 0434, 0.445, 0.245; p = 0.000, 0.000, 0.000, 0.018 respectively).

Discussion

This study aims to evaluate metabolic and hormonal parameters of individuals who are diagnosed with transmen gender dysphoria by psychiatry and referred to our outpatient clinic before cross-sex hormone therapy and compare to natal women's parameters.

Prior literature shows us hyperandrogenism is seen in transmen individuals often and it's thought to be related to PCOS. A retrospective and descriptive study designed by Becerra-Fernandez et al. showed increased hyperandrogenism and PCOS rates in transmen (6). In this study, cases that have free testosterone levels higher than 0.028 nmol/L are accepted as hyperandrogenemia. 49,4% of 77 participants were found hyperandrogenic (n = 38) and 36.6% were diagnosed with PCOS according to Rotterdam criteria (n = 28). Additionally, they have reported this higher LH levels found in the hyperandrogenemia group may be because of increased androgen secretion from ovaries. The lack of a control group was added as a limitation of the study.

Another study (Mueller et al. in 2008), which compared 61 FtoM individuals to 94 cis women has reported free testosterone levels higher than 0.028 nmol/L in the case group, hyperandrogenemia rate was 44,3% (n = 27) significantly higher than control group whose rate was 20,2% (n = 19). On the other hand, PCOS rates were in case group 14.8% (n = 9) and in control groups 12.8% (n = 12) (p values: 0,002; 0,909). Even though they included FtoM individuals before the onset of their hormone therapy, they added self-medication wasn’t questioned and this may be the reason for underlying hyperandrogenemia and this may be the limitation of their study (7).

In our study, androgen levels such as total testosterone, FAI, androstenedione, DHEAS were found significantly higher in the transmen group and muscle strength was directly correlated with these androgen levels. These findings continued in the second analysis that is done after the exclusion of

PCOS patients. This hyperandrogenic status of transmen individuals who don't have a history of cross-sex hormone therapy may indicate another underlying cause of hyperandrogenemia. This study has the largest number of cases among case-control studies about gender dysphoria in current literature and it proves that transmen still have significant hyperandrogenemia after exclusion of PCOS and other causes. Our study confirms the previous studies and it is more powerful in terms of study method.

In our study, muscle strength was found significantly higher compared to the control group. In a case-control study designed by Kogure et al. including 40 PCOS and 40 healthy women, total testosterone ($p < 0.01$) and FAI ($p < 0.01$) levels were found higher in the PCOS group likewise isometric handgrip stress test results were significantly higher too ($p = 0.03$)(8). Another study designed in Taiwan evaluated the relationship between muscle strength in people older than 50 years and showed that FAI and testosterone are correlated with muscle strength. Despite lower testosterone levels in women compared to men, muscle strength and testosterone correlation were similar between the two genders (9). In our study findings, we showed a positive correlation between muscle strength, total testosterone ($r = 0.305$, $p = 0.002$) and FAI ($r = 0.456$, $p = 0.000$). Higher muscle strength in the case group was thought to be due to hyperandrogenemia in this group. Since there is no prior case-control study that compares transmen's muscle strength to a control group, our study is the first study in this field.

We found IGF-1 levels significantly higher in the case group in our all group analysis and PCOS patients excluded analysis (p values 0.045; 0.024). Total testosterone was also found to be correlated with IGF-1 levels ($p = 0.002$). Francomano et al. designed a study with 20 men diagnosed with hypogonadism and metabolic syndrome. Testosterone undecanoate was started once in 12 weeks for 60 weeks' period and IGF-1 levels were compared with the control group. As there were no significant differences between the two groups' IGF-1 levels at the start, by the end of 60 weeks period IGF-1 levels were found significantly higher in the testosterone group ($p = 0.01$) (10). In our study total testosterone and IGF-1 levels' correlation coefficient was 0.334 which indicates a strong correlation. Likewise, FAI and IGF-1 levels were correlated and the coefficient was 0.402 ($p = 0.000$). Since there is no prior study that evaluates IGF-1 levels in transmen individuals our study shows a new aspect in this field. More studies are needed to be done in this area.

In terms of metabolic parameters, all group analyses showed higher triglyceride, HOMA-IR, and lower HDL levels in the FtoM group. AUC (insulin) was also higher in this group but not statistically significant. After PCOS cases were excluded, the analysis showed the same metabolic parameters before. Although the BMI values of the control group were higher after PCOS cases were excluded, dyslipidemia (high triglyceride, low HDL) and higher HOMA-IR numbers continued in the case group. In addition, AUC-insulin was significantly higher in the case group which was not before. This was interpreted as a finding supporting that insulin resistance was significantly higher in the case group compared to the control group. The presence of these metabolic syndrome-like findings in the case group can be explained by the high androgen levels in this group. In previous studies, it has been shown that metabolic syndrome parameters are significantly increased in women with high androgen levels.

In a meta-analysis that evaluates the effect of hyperandrogenism in polycystic ovary syndrome on metabolic parameters, 32 observational studies were included comprising 9556 females with PCOS. Incidences of metabolic syndrome, HOMA-IR value, the incidence of IR were significantly higher in the PCOS/HA group compared with the PCOS/NHA group and the HDL value in the PCOS/HA group was smaller than that in the PCOS/NHA group, while TC, TG, and LDL were not significantly different between the PCOS/HA and PCOS/NHA groups. Lack of case-control studies was added as a limitation of this study(11). In another study investigates whether biochemical hyperandrogenism, represented by elevated serum free testosterone, resulted in an aberrant circulating microRNA (miRNAs) expression profile and whether miRNAs can identify those PCOS women with metabolic syndrome, 42 PCOS and 20 healthy women were included. Although there were no significant differences between the two groups' age, height, weight, BMI, and waist-to-hip ratios, F-G score, total testosterone, and androstenedione levels were significantly higher in the PCOS group. PCOS group was divided into two groups according to whether they are hyperandrogenic or not. Fasting serum insulin, HOMA-IR, triglyceride levels, and metabolic syndrome incidence were significantly higher and HDL levels were significantly lower in the hyperandrogenic group(12).

In conclusion, this is the first case-controlled study that compared anthropometric, metabolic, and endocrinological parameters of transmen individuals with cis women. Various studies had shown significant hyperandrogenemia in FtoM individuals before. In our study, we showed that even when PCOS patients were excluded, hyperandrogenic status continues in these individuals compared to cis women. Since there was no significant difference between the groups according to age, BMI or weight, these findings did not seem to be due to obesity or other metabolic situations. It is clear that transmen individuals have higher androgen levels which may have been the reason for increased muscle strength, insulin resistance, and dyslipidemia compared to natal women. But the main reason for hyperandrogenism in drug-naïve transmen individuals is still not known and more comprehensive further studies are needed.

Declarations

Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Tables

Table 1
Comparison of anthropometric findings between FtoM individuals and control group.

	GD (n = 70)	Control group (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 BP (mmHg)	115,33 ± 14,94	112,54 ± 14,76	0,325
Diastolic BP (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)			

Table 2
Comparison of Hormonal and metabolic parameters of the groups.

	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
Estradiol (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 Globuline, FAI: Free Androgen Index, DHEAS: Dihidroepiandrosetenedione Sulfate, 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)

Table 3
Comparison of GD and control group parameters after PCOS patients 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
Estradiol (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

(LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, IGF-1: Insulin Like Growth Factor, SHBG: Sex Hormone Binding Globuline, FAI: Free Androgen Index, DHEAS: Dihidroepiandrosetenedione Sulfate, 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)

	GD (n = 54)	Control (n = 30)	P
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 Globuline, FAI: Free Androgen Index, DHEAS: Dihidroepiandrosetenedione Sulfate, 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)