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Surgical and pharmacological reassignment: influence on transsexual cardiovascular risk profile

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Abstract

Background/Aim: To evaluate and stratify early cardiovascular risk of transsexuals who underwent pharmacological and/or surgical gender reassignment.
Methods: Fifty-six transsexuals were divided into two groups: group 1 – underwent gonadectomy (orchiectomy for transwomen and hystero-annessiectomy for transmen); group 2 – hormone replacement therapy alone. All participants underwent carotid artery intima-media thickness (C-IMT) and flow-mediated vasodilation (FMD) of brachial artery evaluations.
Results: FMD was lower in patients who had undergone gonadectomy compared with non-surgically treated patients (Group 1: 5.711 vs Group 2: 7.339, $P < 0.0001$). Mean C-IMT was higher in group 1 than group 2 (group 1: 0.733 vs group 2: 0.582). The duration of hormone therapy correlates positively with mean C-IMT ($B = 0.001$) and negatively with FMD (%) ($B = -0.007$).
Conclusions: Cardiovascular risk, which is expressed in terms of endothelial (FMD) and morphological (C-IMT) dysfunction, increases in subjects undergoing gonadectomy compared with those receiving cross-sex reassignment therapy alone.

Introduction

The role of endogenous and exogenous sex hormones on cardiovascular risk profile is a controversial issue. Literature studies revealed different effects of exogenous sex hormones on different populations.[1–6] No definite data are available about the safeness or harmfulness of hormones substitute therapy. The exogenous administration of sex hormones in transsexual subjects is a further problem to be disclosed. Less and undetermined data exist of their effects on the cardiovascular profile of such individuals.[7–9]

In agreement with the Diagnostic and Statistical Manual of Mental Disorders (DSM) V new criteria,

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transsexuals [transwomen and transmen] are persons experiencing 'a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration'.[10,11] Those wishing to acquire the physical traits of the opposite sex can undergo hormonal treatment in order to modify their secondary sexual characteristics (voice, hair, etc.) or can consider surgical options for gender reassignment.

Therefore, hormonal pharmacological treatment is an important step in sex transition: transwomen are usually treated with oestrogen and antiandrogens, whereas transmen adopted testosterone hormone replacement therapy. Gynaecologists, urologists and psychiatrists assist transsexuals in this reassignment process, while the role of a cardiologist is still not considered due to non-assessed cardiovascular risk.

The aim of our study was to verify if gender reassignment (by hormone and surgical treatment) could influence cardiovascular status in transsexuals [operated or not transwomen and transmen].

Methods

This is an observational, population-based, matched cohort study. From January 2014 to June 2014, 56 transsexual patients were consecutively enrolled and studied at the Department of Cardiovascular Disease, University of Bari, Italy. Our sample was divided into: 6 operated transmen (o-transmen), 16 non-operated transmen (no-transmen), 13 operated transwomen (o-transwomen) and 21 non-operated transwomen (no-transwomen).

Inclusion criteria were: the condition of transsexualism in agreement with DSM-V criteria and hormonal treatment (i.e. oestrogen assumption associated with antiandrogen therapy for transwomen and testosterone for transmen).

Exclusion criteria were: prior history of myocardial infarction, angina, stroke, transient ischaemic attack, heart failure or other cardiovascular diseases (CVD, valvular heart diseases, cardiomyopathies, supraventricular or ventricular repetitive arrhythmias, pericardial diseases, myocarditis, etc); dyslipidaemia; hypertension; cigarette smoking (at least 10 cigarettes a day for the past 3 months[12]); chronic kidney disease; endocrinological diseases; systemic inflammatory diseases; chronic pulmonary diseases and corticosteroid treatment for the last 30 days.

The study was approved by the Institutional Review Board of Bari University General Hospital and carried out in accordance with the principles of the Helsinki Declaration. All patients provided written informed consent before entering the study.

Study population

The main characteristics of the study population are shown in Table 1.

All patients did not show any pathological level of SBP and DBP. Their body mass index (BMI) level was ≤25 kg/m^2. All patients were not hypertensive and did not take any antihypertensive drugs. This allows us to exclude confounding factors known to interfere with the cardiovascular risk profile of individuals. Furthermore, the absence of diabetic and insulin-resistant individuals in our research reduced the presence of a clear factor that is able to influence endothelial function.

All transwomen were on cross-sex hormone oestrogen therapy associated with antiandrogens until sex reassignment surgery (SRS); after reassignment surgery, o-transwomen were only treated with oestrogen therapy. Transmen were treated with testosterone before and after SRS.

All individuals underwent anthropometric [waist circumference, weight, height and the waist–height ratio (WHR)], laboratory and instrumental evaluations. All patients did not practise any physical activity.

Table 1 Characteristics of the study population

Total number: 56 patients	Mean	SD
Age	33.95	8.64
Height (cm)	180.80	8.2
Weight (kg)	73.26	14.52
BMI (kg/m^2)	22.3	3.13
Hormonal therapy duration (months)	28.49	43.21
Systolic blood pressure (mmHg)	121.88	11.97
Diastolic blood pressure (mmHg)	79.91	8.18
FMD %	6.78	1.64
Left IMT (mm)	0.65	0.15
Right IMT (mm)	0.63	0.14
White blood cells (×10^3/μL)	7.77	2.10
Haematocrit (%)	41.20	3.92
Platelets (×1000/μL)	252.75	65.12
Glycaemia (mg/dL)	85.57	8.47
Triglycerides (mg/dL)	95.96	46.48
Total cholesterol (mg/dL)	183.15	38.98
HDL cholesterol (mg/dL)	45.50	10.70
LDL cholesterol (mg/dL)	109.81	32.77
TSH (mU/L)	2.30	1.21
FT3 (pg/mL)	3.20	0.46
FT4 (ng/dL)	1,80	2.427
Cortisol (μg/L)	46.75	62.32
Oestrogen (pg/mL)	56.20	50.40
Total Testosterone (ng/dL)	2.40	3.15
Free Testosterone (%)	8.97	12.03

FMD, flow-mediated vasodilatation; FT3, Free triiodothyronine; FT4, Free thyroxine; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

Laboratory testing

Each patient underwent blood chemistry sampling to evaluate the following parameters: total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and glycaemia; white blood cells, platelets, haematocrit; sexual hormones: oestrogen, total testosterone, free testosterone; thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxin (fT4) and cortisol.

Instrumental evaluations

All subjects enrolled underwent ultrasound assessment of carotid artery intima-media thickness (C-IMT) and flow-mediated dilation (FMD) of the brachial artery in order to assess their vascular function and morphology and to establish the early change of vascular walls towards atherosclerosis. Patients underwent these evaluations 2–3 months after the reassignment procedures.

Ultrasound measurement of the carotid IMT

Ultrasonographic echo-colour Doppler studies of the left and right common carotid arteries were performed bilaterally by the same physician with a Philips Sonos 5500 using a 7.5 MHz high-resolution probe. Patients were placed in the supine position, with the neck extended and rotated contralaterally by 45°, and the common carotid arteries were examined on the sagittal axis with a lateral view. C-IMT was defined as a low-level echo grey band that does not project into the arterial lumen and was measured during end-diastole according to the method described by Pignoli.[13] The measurements were bilaterally performed thrice 1 cm proximally to the carotid bulb, and mean C-IMT was calculated. C-IMT measurements were always performed in an arterial segment devoid of atherosclerotic plaque, defined according to Mannheim carotid intima-media thickness consensus (2004–2006) as C-IMT greater than 1.5 mm or a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding C-IMT value.[14]

FMD of brachial artery

Temperature, food, stress, drugs and sympathetic stimuli influence the FMD. The study was performed with the subjects fasting for at least 8–12 h in a quiet, air-conditioned room (22–24°C) early in the morning. The subjects were asked not to exercise or take exciting substances like coffee, tea or chocolate, which could impair endothelial function, for at least 4–6 h before the exam. The right brachial artery was evaluated in a long axis projection between 5 cm and 10 cm above the elbow using a 7.0 MHz or higher linear probe. The study was performed using a high-resolution ultrasonograph (Philips Sonos 5500) connected to an image analysis system, certified by the CNR of Pisa (MVE II).[15] All the ultrasound examinations were performed by the same physician in order to reduce bias. With the subject in supine position for at least 10 min, the arm was positioned comfortably in order to get good images of the brachial artery. A sphygmomanometer cuff was placed in the distal site to the artery and on the forearm in cases of a humeral artery. After 1 min of flow image baseline acquisition, the artery was occluded by inflating the cuff to a pressure of 200–220 mmHg for exactly 5 min. After cuff deflation, a high-flow condition (reactive hyperaemia in the forearm microcirculation) developed. The resulting increased shear stress provided the stimulus for the dilatation of the humeral artery. Within 15 s from the end of ischaemia, the flow rate was measured, followed by the degree of hyperaemia. The image of the artery was then recorded continuously for 2–3 min after ischaemia. Reactive hyperaemia was calculated as the ratio of the change in diameter (maximal dilatation after deflation-baseline) divided by the baseline value, which corresponds to the maximum FMD recovery value. FMD was analysed as the percentage increase in brachial artery diameter after the application of a pressure stimulus.[16]

Statistical analysis

The examined variables were expressed as mean ± standard deviation. An analysis of variance using ANOVA test was therefore performed to highlight any statistically significant difference between the observed values in the two groups of study. We applied Levene test for non-parametric variables (which exploits the Kruskal-Wallis test) to verify the homogeneity of variance. A value of $P < 0.05$ was considered statistically significant. The intra-observer variability of ultrasound measurements was assessed by intraclass correlation coefficient (ICC good if > 0.80). In particular, the evaluation of C-IMT shows excellent reproducibility with an ICC of 0.98, as well as FMD with an ICC of 0.95.

Results

The main descriptive characteristics of the study population are shown in Table 1.

We divided the study population into two groups: [Group 1] transsexual patients who underwent gonadectomy (orchiectomy for trans-women and hystero-

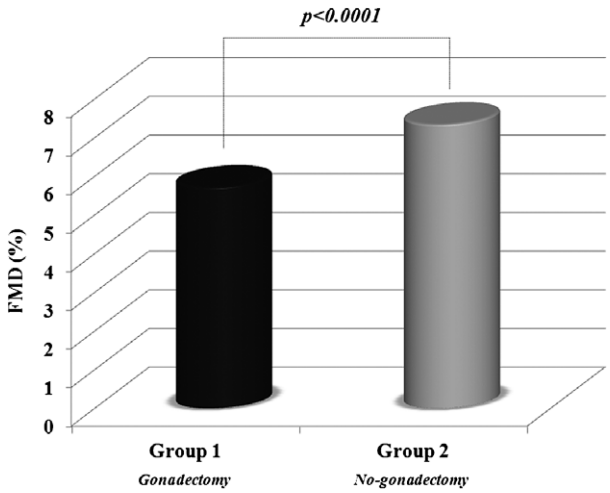

Figure 1 Comparison between the two groups of patients, transsexual who have undergone gonadectomy and transsexuals who have undergone hormone replacement therapy alone, according to endothelial function parameters (flow-mediated vasodilation (FMD)). Group 1 (■) = subjects with gonadectomy; group 2 (□) = subjects without gonadectomy.

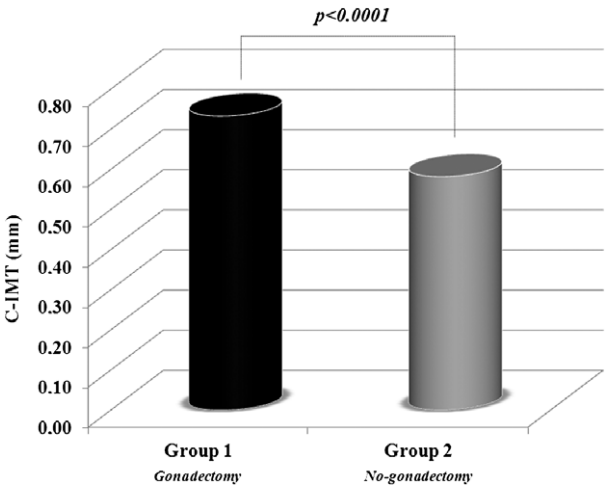

Figure 2 Comparison between the two groups of patients, transsexuals who have undergone gonadectomy and transsexuals who have undergone hormone replacement therapy alone, according to carotid intima-media thickness (C-IMT). Group 1 (■) = subjects with gonadectomy; group 2 (□) = subjects without gonadectomy.

annessiectomy for trans-men); [Group 2] transsexual patients treated only with hormone replacement therapy (oestrogen and antiandrogens for transwomen and androgens for transmen).

Our results showed a statistically significant difference ($P < 0.0001$) between patients of groups 1 and 2 – (Fig. 1) according to endothelial function. In fact, the mean value of FMD (%) in patients who underwent gonadectomy was lower than that of non-operated patients, who take only cross-sex hormones (5.711 in Group 1 and 7.339 in Group 2).

According to mean C-IMT, a statistically significant difference ($P < 0.0001$) between the two groups emerged. Mean C-IMT values were higher in patients treated with SRS than in non-operated patients (0.733 mm in Group 1; 0.582 mm in Group 2) (Fig. 2).

Dividing the two groups into two subgroups (transwomen and transmen), there were no statistically significant differences relating to FMD and C-IMT (Table 2). Furthermore, when comparing operated and non-operated groups, there were no differences in term of FMD and C-IMT modification (Table 2).

Table 3 shows the multivariate regression analysis of quantitative variables.

Discussion

The aim of our study was to verify how gender reassignment (by hormone and surgical treatment) could influence the inner alterations of vessel wall functions and morphology due to hormonal and/or physical changes in transsexuals. Transsexuals represent a particular population that usually undergoes cross-sex hormones.

Several studies demonstrated that hormone replacement therapy based on oestrogen supplementation improves the cardiovascular risk profile in postmenopausal women.[17] Others gave no definite results.[1–6,18] Oestrogen can influence vascular inflammation[19] and function[19–23] by reducing the former and increasing the latter. Hormones can counteract endothelial dysfunction through activation of endothelial cells by means of biochemical pathways related to their specific receptors,[24–26] such as ERα and ERβ for oestrogen.[19,20] Thus, the increased incidence of cardiovascular events in men may be due to the low levels of these hormones in their blood. An inverse correlation between serum estradiol levels and risk for CVD was found in older men, supporting the protective role of endogenous oestrogen on vascular

Table 2 Correlation between sex-flow-mediated vasodilatation (%) and sex-mean intima media thickness (mIMT)

		P-value
Transwomen vs Transmen	mIMT (mm)	0.629
	FMD (%)	0.746
Operated Transmen vs non-operated Transmen	mIMT (mm)	0.224
	FMD (%)	0.768
Operated Transwomen vs non-operated Transwomen	mIMT (mm)	0.818
	FMD (%)	0.385

FMD, flow-mediated vasodilatation; mIMT, mean intima media thickness.

Table 3 Multivariate regression of quantitative variables

		n	Mean	*P* value			*n*	Mean	*P* value
Systolic blood pressure (mmHg)	0	37	122.97 ± 11.69	0.343	Thyroid-stimulating hormone (mU/L)	0	37	2.55 ± 1.29	0.034
	1	19	119.74 ± 12.52			1	19	1.83 ± 0.90	
	Total	56	121.88 ± 11.97			Total	56	2.31 ± 1.21	
Diastolic blood pressure (mmHg)	0	37	80.27 ± 8.57	0.650	Free triiodothyronine (pg/mL)	0	37	3.22 ± 0.47	0.662
	1	19	79.21 ± 7.50			1	19	3.19 ± 0.47	
	Total	56	79.91 ± 8.17			Total	56	3.20 ± 0.45	
Height (cm)	0	37	179.99 ± 76.44	0.296	Free thyroxine (ng/dL)	0	37	1.61 ± 1.89	0.414
	1	19	182.89 ± 89.15			1	19	2.17 ± 3.26	
	Total	56	180.80 ± 80.98			Total	56	1.80 ± 2.43	
Weight (kg)	0	37	73.68 ± 14.34	0.767	Cortisol (μg/L)	0	37	54.12 ± 71.01	0.220
	1	19	72.45 ± 15.22			1	19	32.41 ± 38.17	
	Total	56	73.26 ± 14.52			Total	56	46.75 ± 62.32	
Total cholesterol (mg/dL)	0	37	165.93 ± 32.74	0.0001	Oestrogen (pg/mL)	0	37	67.54 ± 55.42	0.017
	1	19	216.68 ± 26.52			1	19	34,15 ± 29.02	
	Total	56	183.15 ± 38.99			Total	56	56.21 ± 50.40	
HDL cholesterol (mg/dL)	0	37	46.05 ± 11.27	0.593	Total testosterone (ng/dL)	0	37	2.87 ± 3.34	0.121
	1	19	44.42 ± 9.69			1	19	1.49 ± 2.591	
	Total	56	45.50 ± 10.69			Total	56	2.40 ± 3.1553	
LDL cholesterol (mg/dL)	0	37	104.34 ± 28.42	0.081	Free testosterone (%)	0	37	10.89 ± 13.0046	0.096
	1	19	120.47 ± 38.59			1	19	5.24 ± 9.0324	
	Total	56	109.81 ± 32.78			Total	56	8.97 ± 12.0283	
White blood cells ($\times 10^3/\mu L$)	0	37	8.12 ± 2.08	0.083	Glycaemia (mg/dL)	0	37	85.43 ± 8.68	0.866
	1	19	7.09 ± 2.04			1	19	85.84 ± 8.28	
	Total	56	7.77 ± 2.13			Total	56	85.57 ± 8.47	
Platelets (×1000/μL)	0	37	251.08 ± 63.44	0.792					
	1	19	256.00 ± 69.93						
	Total	56	252.75 ± 65.12						

0, subjects without gonadectomy; 1, subjects with gonadectomy; Total, total number of subjects.

walls structure and functions, whereas serum testosterone and dehydroepiandrosterone sulfate levels were not associated with cardiovascular events.[27] Zheng *et al.*[28] found that serum oestradiol levels were significantly lower in males suffering from ischaemic heart disease as compared to the controls; moreover, oestradiol was positively associated to triglycerides and HDL levels, whereas they were negatively related to LDL. Nevertheless, men who underwent coronary angiography had oestradiol values positively related to CVD; the prevalence of CVD significantly increased from the third highest tertiles to the first.[29] On the other hand, postmenopausal diabetic women who underwent coronary angiography showed low free testosterone levels that were independently associated with increased all-cause and cardiovascular mortality.[30] Nevertheless, our population was free from cardiovascular risk factors. The exclusion criteria did not allow us to include individuals complaining of cardiovascular risk factors (cigarettes smoking, hypertension, dyslipidaemia, etc). Although these criteria reduced the sample size, they allow us to avoid conditions that are able to influence negatively the final results.

Several publications agree about the different impact of testosterone on males and females. Low endogen levels of this hormone in males can be associated with CVD and coronary stenosis severity.[31,32] On the other hand, high levels of circulating androgens in women appear to be associated with higher cardiovascular risk, for example, in polycystic ovarian syndrome.[33,34] Ciccone *et al*. effectively demonstrated that polycystic ovarian syndrome increases infrarenal abdominal aortic diameter, an early marker of atherosclerosis.[35]

Moore *et al.*[36] proposed interesting hypotheses about the side-effects of sex hormone therapy in transsexuals. They outlined an increased incidence of deep venous thrombosis, myocardial infarction, stroke and pulmonary embolism, confirming the results of several previous clinical studies.[37–39] They correlated the increase in cardiovascular risk to a dose-dependent mechanism. They suggested a healthy lifestyle for transsexuals.

Moreover, the exogenous administration of testosterone induces a higher risk of weight gain, dyslipidaemia, decreased insulin sensitivity and an increase in haematocrit. These factors contribute to a higher

cardiovascular and thromboembolic risk.[40,41] However, a subsequent study by Medras[42] did not confirm these data. Wierckx *et al.*[43] evaluated the long-term side-effects of sex hormone treatment in gender reassignment. They concluded that transmen had lower risk than transwomen. No transmen experienced cardiovascular events, such as myocardial infarction and deep venous thrombosis. On the contrary, 20% of transwomen in this study demonstrated these adverse events.

Very few studies considered the evaluation of endothelial function in transsexuals who had or had not undergone surgical sexual reassignment therapy.

The endothelial function, evaluated through brachial artery FMD, and the vascular morphology, evaluated by means of C-IMT, are well-established biomarkers of CVD.[44–47] Literature points out the predictive value of these vascular indices within CVD progression and negative healthy effects, even in addition to previous predictive score, such as the Framingham one.[44–47] Nevertheless, few data exist about the role of these techniques when applied into a transsexual population.

New *et al.*[48] demonstrated that endothelial function assessed by means of FMD was similar between non-operated transwomen and women, which improved when the comparison between non-operated transwomen and male controls was considered, despite higher triglyceride and LDL levels in the transsexuals group. A further study by New *et al.*[49] corroborated such results by demonstrating that transwomen did not show an improvement in exercise-induced metabolic vasodilation despite oestrogen administration.

Our study pointed out that cardiovascular risk, which has been expressed in terms of endothelial function (FMD) and C-IMT, tends to increase in patients who underwent gonadectomy compared to those who underwent hormone replacement therapy.

We observed that the endogenous production of sexual hormones by gonads can represent a sort of protection for the cardiovascular system. In transwomen, we found a reduction in FMD values and an increase in C-IMT values. We believed that a sudden reduction in testosterone levels after orchiectomy surgery could promote such deterioration in cardiovascular risk markers. Therefore, we hypothesise that orchiectomy could reduce the protective effect of oestrogen exogenous administration on the cardiovascular risk profile in transwomen.[19]

Simultaneously, we found a similar worsening of cardiovascular risk in transmen who underwent hysteroannessiectomy. This surgical procedure, in fact, suddenly stops the endogenous production of oestrogen and exposes the endothelium to the potentially dangerous lone effect of testosterone by erasing the protective effect of the female sexual hormone.

Limitations

The small size of the sample is certainly a limitation to our study. The study population is very small, but this is due to the difficulty in the enrolment of the patients due to the small number of individuals who underwent such operations (both pharmacological and surgical) and to the resistance of being involved in research protocols. For this reason, we consider our research a 'pilot', only in relation to the limited number of patients that we could gather. Despite that, the few literary data about this topic lead us to promote the study and its results in order to create a dedicated trial to confirm or refute the obtained results.

The observational nature of our study could be considered a further limitation.

Some concerns can arise from the adopted instrumental evaluations (i.e. FMD of the brachial artery and C-IMT measurements). For this reason, all the instrumental evaluations were performed by the same physician. We calculated the intra-observer variability coefficients for both the evaluations: 0.98 (C-IMT) and 0.95 (FMD of brachial artery) according to the ICC (good if >0.80). Furthermore, the performance of a protocol based on a double evaluation of FMD and C-IMT before reassignment therapy and after a pre-specified follow-up period would certainly improve the evaluation of such patients.

The lack of a follow-up period that was able to outline any long-term outcome is a further limitation. Nevertheless, we are clinically following up those patients and monitoring their conditions in order to document any clinical variation.

Conclusions

Sexual reassignment surgery in transwomen or transmen is considered a fundamental step in the clinical course of subjects affected by gender identity crises. We demonstrated that such reassignment could be detrimental for endothelial function, causing a significant reduction in FMD and an increase in C-IMT. On the contrary, cross-sex hormones appeared not to worsen cardiovascular function. The results of this study may open the way to new investigations aimed at preventing the onset of atherosclerosis, even by its subclinical stages, in the delicate category of transsexual subjects who decide to undergo sexual reassignment surgery. Therefore, such patients should deserve screening for CVD and prevention/treatment programmes to prevent the progression of vascular alterations.

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