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ORIGINAL ARTICLE

Hormone therapy in female-to-male transgender patients: searching for a lifelong balance

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Abstract

Background Reassignment of a female-to-male (FtM) person requires gender-affirming, androgenic hormonal treatment that is planned to induce appropriate structural changes. This therapy must be prolonged long term, even after the sex reassignment surgery (SRS). The purpose of this study is to evaluate the effects of hormone therapy with testosterone in FtM subjects during a 24-month follow-up in order to highlight the occasional need for early decompensation and to make adequate hormone therapy modulations.

Methods Fifteen out of 23 FtM persons had been previously treated with SRS, while eight were still awaiting surgery. During hormone therapy, both groups were followed for 24 months, with evaluation of desired changes, adverse effects, and functional or metabolic indicators.

Results In the group of operated FtM subjects (15/23), a significant increase of total testosterone (total T) and free testosterone (free T) was found after 24 months. Luteinizing hormone (LH) maintained a low level, decreasing after ovariectomy, while FSH increased. Voice deepening, facial and body hair variation, male-pattern balding, and body mass index (BMI) increase are all physical changes due to androgenization. In both groups of patients who have been closely monitored, the side effects and thromboembolic, metabolic, and cardiovascular risks of androgen therapy, even in the long term, appear to be irrelevant.

Conclusion Total T, free T, and LH dosages are shown to be reliable markers of correct androgenization. Strict monitoring of lipid profile, evaluation of BMI and hematocrit, avoidance of self-initiated therapeutic modifications, adherence to a healthy lifestyle, and avoidance of excessive daily calorie intake can limit risks linked to long-term testosterone administration.

Trial registration Retrospectively registered

Keywords Health · Long-term therapy · Testosterone · Transgender

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Background

Gender reassignment for the female patient affected by "gender dysphoria" (FtM—female-to-male transgender patient) is preceded by and associated with androgenic hormonal treatment in order to induce appropriate structural changes and to obtain a male phenotype [1]. To correctly manage the *gender dysphoria*, it is essential to verify that the criteria put forth in the DSM 5 [2] are completely fulfilled. At the same time, a period of up to 12 months (reversible gender reassignment) is sometimes necessary to assess the severity of the gender dysphoria and to determine if the patient will benefit from a definitive transition process, including sex reassignment surgery (SRS), which is an irreversible gender change [3]. Therefore, hormonal therapy is an essential step during the reversible phase of the sexual transition process and must be prolonged for many years even after the SRS [4]. Periodic monitoring of metabolic and hormonal changes during the hormonal treatment allow a determination of the correlation between type and dose of testosterone administered, serum hormonal levels, and the clinical phenotypic changes so as to achieve a personalized adjustment of testosterone dosage [5]. The purpose of this study is to describe how hormone treatment can change metabolic and hematological indices so that periodic clinical monitoring may ensure the safety and efficacy of long-term hormone therapy.

Methods

The transgender register of the University of Bari, Italy, was consulted from 2015 to 2018, selecting 23 FtM transgender patients, average age 27 years, with a psychiatric diagnosis of "gender dysphoria" (formerly "gender identity disorder") and who are followed at the clinic dedicated to transgenderism collaborating with the Gynecology and Obstetrics Unit-Department of Interdisciplinary Medicine of University of Bari "Aldo Moro," currently the only regional referral center. Before being placed on the list, each patient was given an explanation of the study and was formally invited to participate in it. The patients who agreed to participate in the study signed an informed consent form.

All procedures performed in this study were in accordance with the Declaration of Helsinki, as revised in 2013. In addition, the patients were also informed that the data collected for this study are protected by the Privacy Act; the data were thus collected and used after each patient had signed a further informed consent form to authorize the use of personal data for scientific purposes only. Fifteen of 23 FtM subjects had previously undergone surgical treatment for SRS using hysterectomy, mastectomy, and phalloplasty, while eight of the 23 FtM transgender persons were still awaiting surgery. Both groups were followed up for 24 months. The results of the blood chemistry tests of both groups of patients from baseline values up to 24 months were collected in special databases dedicated to periodic follow-up, reporting all values recorded during follow-up in both patient groups. The base value of the operated subjects represents the value at the time of the oophorectomy, while in the unoperated patients, it is the value at the first visit. Hormonal treatment was performed with a testosterone enanthate 250 mg IM, at one dose every 21 days for the first year, in order to induce the appropriate structural changes. After the first year, the maintenance dose is quite different, since, as reported in the literature [3], hormonal treatment of gender reassignment is not standard but must be personalized on the basis of hormonal treatment response and on individual symptoms such as hypertension, erythrocytosis with thrombotic risk, and liver dysfunction. Absolute contraindications to initiation of testosterone therapy were preliminarily excluded, such as pregnancy, sensitivity/allergy to any of the ingredients in the testosterone formulation, unstable coronary artery disease, hematocrit ≥ 55, and past breast cancer. Relative contraindications were also considered, such as mildly increased hematocrit, untreated obstructive sleep apnea, advanced congestive heart failure, liver disease, and cardiovascular or cerebrovascular disease, with the aim of consulting the appropriate specialists before initiation of treatment. Follow-up was performed every 3 months comprising evaluation of desired effects, including facial hair and body hair distribution using the Ferriman-Gallwey score, changes of voice, seborrhea, alopecia, body weight and body mass index (BMI = weight in kg/height in m^2) changes, and cessation of menses, as well as adverse effects of therapy, like hypertension, erythrocytosis, venous thromboembolism, liver dysfunction, destabilization of mental health, acne, male-pattern balding, migraines, and clitoral pain. Moreover, blood sampling to evaluate the level of functional or metabolic indicators, such as hematocrit (HCT, %), low-density lipoprotein (LDL, mg/dl), high-density lipoprotein (HDL, mg/dl), and serum hormones, as follows: total testosterone (total T, ng/ml), free testosterone (free T, pg/ml), 17-β-estradiol (pg/ml), follicle-stimulation hormone (FSH, mU/ml), luteinizing hormone (LH, mU/ml), and sex hormone-binding globulin (SHBG, nmol/l), was performed during every follow up.

Statistical analysis

Results are presented as median (min, max) for each group (operated and non-operated). To investigate possible differences between groups, we used Friedman test. InStat3® (GraphPad Software Inc., 2000) has been used for the statistical analysis. The level of statistical significance has been set to $p < 0.001$

Results

In the group of operated FtM subjects (15/23), median basal testosterone level was 0.55 (0.20–9.80) ng/ml, while after 24

months of therapy, a significant increase in total T (p value = < 0.001) to 5.00 (0.18–10.90) ng/ml was found. In non-operated FtM subjects (8/23), the increase in total T was non-significant (p value = 0.066), from 0.50 (0.20–5.00) to 3.43 (0.20–12.00) ng/ml. Similarly, regarding free T level, in 15/23 operated FtM subjects, the increase was significant (p value < 0.001) from 1.90 (0.10–9.90) to 14 (0.90–35.00) pg/ml, while in 8/23 non-operated FtM subjects, it was non-significant (p value = 0.015) from 1.55 (0.40–6.40) to 12.00 (1.90–54.00) pg/mL. Regarding the dosage of gonadotropins, testing of basal levels of FSH and LH was performed irrespective of the day of the menstrual cycle. In operated FtM subjects (15/23), FSH showed a statistically significant increase (p value < 0.001) from 7.10 (4.27–58.00) to 40.00 (3.50–110.00) mIU/ml after 24 months. LH was significantly reduced (p value < 0.001) from 25.80 (5.50–64.40) to 10.10 (0.30–26.00) mIU/ml, while LH levels appeared to be influenced early on by ovariectomy (within 6–12 months). In non-operated FtM subjects (8/23), FSH levels showed a non-significant increase (p value = 0.1778) from 5.50 (0.90–8.90) to 7.65 (4.40–8.60) mIU/ml. In 8/23 non-operated subjects, reduction of LH was non-significant (p value = 0.9246) from 6.15 (0.20–30.40) to 4.45 (1.50–6.70) mIU/ml. Concerning SHBG, in 15/23 operated FtM subjects, a statistically significant reduction (p value < 0.001) of SHBG from 27.00 (21.00–87.30) to 21.00 (6.20–38.70) nmol/l was registered, while 8/23 non-operated FtM subjects showed a non-significant decrease (p value = 0.062) from 21.25 (15.00–43.00) to 15.40 (9.50–35.20) nmol/l. On the other hand, in 15/23 operated FtM subjects, 17-β-estradiol decreased significantly (p value < 0.001) from 85.80 (10.00–296.00) to 26.00 (10.00–40.00) pg/ml, while in 8/23 non-operated subjects, the variation was non-significant (p value = 0.754) from 58.95 (10.00–124.00) to 50.20 (14.40–72.00) pg/ml. Therefore, in this experience, ovariectomy makes an early and significant difference between the two groups. Furthermore, BMI in operated FtM subjects showed an increase of median values from 23.45 (20.19–28.80) to 24.20 (21.90–29.00), which is statistically significant (p value < 0.001). Non-operated FtM subjects had a non-significant increase in BMI median values (p value = 0.433) from 28.07 (18.75–34.62.) to 28.60 (18.30–33.32). Moreover, with regard to cholesterol LDL and HDL, the results were as follows: operated FtM subjects showed a statistically significant increase (p value = 0.0121) of median LDL from 111 (69–169) to 129 (90–150) mg/dl, while non-operated FtM subjects showed an increase of LDL from 115 (60–129) to 130.5 (67–139) mg/dl, which was non-significant (p value = 0.130). As concerns HDL median levels, in operated FtM subjects, we observed a statistically significant decrease (p value < 0.001) of HDL from 58 (47–67) to 50 (41–57) mg/dl, while in non-operated subjects, a non-significant variation (p value = 0.951) of HDL from 43 (28–56) to 42.5 (36–50) mg/dl was reported. In conclusion, in operated FtM subjects, HTC demonstrated a significant increase from 41.0 (37.4–45.0) to 44% (49.7–47.0), (p value < 0.001), while non-operated FtM subjects did not have any significant increase (p value = 0.319), from 45.4 (36.9–50.1) to 45.7% (39.6–49). All these results are summarized in a Table 1.

Discussion

The beginning of use by transsexual people of hormones of the opposite sex (cross-sex hormone therapy) goes back to the late 1960s. After about 60 years of this treatment, a number of questions have arisen, including whether, for instance, in the case of hormone replacement therapy, long-term cross-sex hormone therapy may be harmful for transgender users [6]. It is clear that for transsexuals, no large population, randomized, longitudinal studies are available due to the rarity of the condition, the impossibility of sex change without cross-sex replacement therapy, and the scarcity of long-term follow-up studies. Of note, reports concerning an increased incidence of tumors after menopause following hormone replacement therapy have little relevance in the case of cross-sex hormone therapy, the available data showing no increased malignancy rate, even in subjects of the age of 70 [7–12]. More interesting are the findings concerning cardiovascular disorders and quality of life [13, 14]. Indeed, as also confirmed in the present study devoted to long-term androgen activity in FtM transgender people, total T level before therapy starts with normal values, particularly among women, and rises to optimal values after 24 months of therapy both in operated and non-operated patients. After surgery, total T increases and remains high even as long as 2 years after gonadectomy (Fig. 1). Free T fraction increases in both groups of FtM subjects after 24 months of therapy, this being due in particular to the inhibitory effect of androgens on the hepatic synthesis of SHBG (Fig. 2). This protein, in fact, decreases after androgen administration. 17-β-estradiol undergoes a drastic reduction after gonadectomy, though in non-operated people it shows a slight increase, probably because of residual ovarian activity and/or because of the peripheral aromatization of exogenously administered T [11, 15–18]. Moreover, in non-operated FtM individuals, FSH level increases after hormonal therapy, confirming the suppressive activity of androgens on ovarian function, followed by anovulation and amenorrhea after a mean time of 6 months from the beginning of treatment before surgery. Subsequently, FSH shows a substantial peak after annessiectomy, as after menopause, implying that there is minimal hypothalamic-hypophyseal suppression in the absence of ovulation. Interestingly, LH in operated FtM subjects from an initial value of 25 mIU/ml after 24 months of therapy decreases to 10 mIU/ml. This datum demonstrates direct modulation by androgens of the hypothalamic-pituitary axis, reaching optimal androgenization (with reduction of LH) only after

Table 1 Results of blood chemistry tests of operated and non-operated FtM

		Testosterone		Gonadotropins (mUI/ml)		SHBG (mmol/L)	17-β-Estradiol (ng/ml)	Cholesterol (mg/dl)	
		total (ng/ml)	free (pg/ml)	FSH	LH			LDL	HDL
15/23 operated FtM TGs	Baseline (*)	**0.55** (0.20-9.80)	**1.90** (0.10-9.90)	**7.10** (4.27-58.00)	**5.70** (2.40-12.40)	**26.00** (15.40-87.30)	**85.80** (10.00-296.00)	**112** (69-169)	**49** (35-67)
	6 mm. FU	**7.83** (0.30-19.90)	**15.90** (1.60-46.00)	**70.00** (7.00-152.00)	**13.00** (1.50-36.40)	**20.00** (10.80-79.40)	**31.40** (17.90-83.70)	**117** (65-186)	**49** (30-65)
	12 mm. FU	**6.90** (1.35-11.70)	**16.50** (5.00-33.20)	**50.00** (1.40-142.00)	**33.10** (1.20-64.500)	**19.50** (13.40-50.30)	**29.00** (12.70-82-40)	**116** (71-162)	**53** (29-79)
	18 mm. FU	**6.70** (2.00-38-9)	**17.80** (5.00-41.30)	**42.60** (2.00-116.00	**19.00** (0.50-58.70)	**25.00** (11.00-56.00)	**31.30** (14.40-46.00)	**121** (70-183)	**47** (39-57)
	24 mm. FU	**5.00** (0.18-10-90)	**14.00** (0.90-35.00)	**40.00** (3.50-110.00)	**12.00** (0.18-36.90)	**21.00** (6.20-38.70)	**26.00** (10.00-40.00)	**121** (71-150)	**50** (41-72)
Friedman test ANOVA		**Fr =23.181**	**Fr = 32.548**	**Fr = 20.854**	**Fr = 14.667**	**Fr = 8.227**	**Fr = 21.813**	**Fr = 7.307**	**Fr = 5.120**
P value		**P = 0.0001**	**P < 0.0001**	**P = 0.0003**	**p = 0.0054**	**P = 0.0836 (n.s.)**	**P = 0.0002**	**P = 0.1205 (n.s.)**	**P = 0.2752 (n.s.)**
8/23 not-operated FtM TGs	Baseline	**0.50** (0.20-5.00)	**1.55** (0.40-6.40)	**5.50** (0.90-8.90)	**4.45** (0.20-8.80)	**21.25** (15.00-43.00)	**50.20** (10.00-124.00)	**115** (60-129)	**43** (28-56)
	6 mm. FU	**5.73** (2.28-10.20)	**19.00** (6.00-24.00)	**5.15** (1.20-9.20)	**4.30** (0.30-10-80)	**18.10** (10.00-25.50)	**62.85** (34.20-143.00)	**103.5** (56-130)	**43** (29-50)
	12 mm. FU	**5.83** (0.18-14-10)	**16.00** (0.30-48.10)	**5.05** (1.40-15.80)	**3.60** (0.30-30.40)	**17.00** (11.00-22.00)	**56.20** (27.40-160.00)	**101** (52-148)	**41.5** (35-54)
	18 mm. FU	**4.43** (0.22-14.00	**17.25** (1.30-44.00)	**5.25** (2.80-11.609	**5.30** (0.90-17.10)	**18.80** (10.00-26.00)	**65.65** (20.80-136.00)	**118.5** (61-142)	**42** (33-53)
	24 mm. FU	**3.43** (0.20-12.00)	**12.00** (1.90-54.00)	**7.65** (4.40-8.60)	**5.70** (2.80-6.70)	**15.40** (9.50-35.20)	**58.95** (14.40-72.00)	**130.5** (67-139)	**42.5** (36-50)
Friedman test ANOVA		**Fr = 8.800**	**Fr = 12.200**	**Fr = 6.300**	**Fr = 1.700**	**Fr = 8.937**	**Fr = 1.900**	**Fr = 7.100**	**Fr = 0.700**
P value		**P = 0.0663 (n.s.)**	**P = 0.0159 (n.s.)**	**P = 0.1778 (n.s.)**	**P = 1.7907 (n.s.)**	**P = 0627 (n.s.)**	**P = 0.7541 (n.s.)**	**P = 0.1303 (n.s.)**	**P = 0.9513 (n.s.)**

		TAG (mg/dl)	BMI	Transaminases (U/L)		Hematocrit (%)
				AST	ALT	
15/23 operated FtM TGs	Baseline (*)	**84** (42-154)	**23.45** (20.19-28.80)	**17** (12-37)	**23** (14-54)	**44.60** (37.40-48.80)
	6 mm. FU	**97** (54-162)	**24.17** (20.95-31.20)	**18** (12-38)	**25** (17-58)	**44,20** (40.20-47.60)
	12 mm. FU	**94** (50-154)	**23.52** (18.00-32.45)	**21** (14-33)	**25** (16-45)	**44.70** (40.30-46.50
	18 mm. FU	**91** (51-174)	**23.19** (21.00-30.02)	**19** (11-36)	**26** (17-42)	**44.80** (42.00-48.90)
	24 mm. FU	**101** (57-144)	**24.20** (21.90-29.00)	**21** (11-36)	**27**(19-39)	**44.00** (39.70-48.70)
Friedman test ANOVA		**Fr = 3.413**	**Fr = 11.573**	**Fr = 9.565**	**Fr = 0.9498**	**Fr = 1.707**
P value		**P = 0.9412 (n.s.)**	**P = 0.0208**	**P = 0.0484**	**P = 0.9173 (n.s.)**	**P = 0.7895 (n.s.)**
8/23 not-operated FtM TGs	Baseline	**99** (46-147)	**28.07** (18.75-34-62)	**17** (11-26)	**22.5** (14-34)	**45.65** (38.80-50.10)
	6 mm. FU	**101.5** (34-138)	**26.76** (18,35-35.00)	**18** (13-21)	**23.0** (16-32	**45.55** (38.40-47-30)
	12 mm. FU	**119.5** (37-185)	**26.65** (19.00-34.60)	**17** (15-26)	**25.5** (18-33)	**45.25** (37.00-47.40)
	18 mm. FU	**107** (32-163)	**28.00** (18.50-34.179	**19** (10-35)	**23.0** (15-29)	**46.90** (41.80-52.10)
	24 mm. FU	**108**.5 (76-155)	**28.60** (18.30-33.32)	**20** (16-23)	**24.0** (19-34)	**46.10** (39.60-50.00)
Friedman test ANOVA		**Fr = 1.600**	**Fr = 3.799**	**Fr = 3.195**	**Fr = 0.7.723**	**Fr = 8.800**
P value		**P = 0.8088 (n.s.)**	**P = 0.4339 (n.s.)**	**P = 0.5257 (n.s.)**	**P = 0.1023 (n.s.)**	**p = 0.0663 (n.s.)**

(*) Baseline for operated patients means at time of surgery

N mm. FU = Follow-up after N months.

Data are reported as **median (min-max)**.

Statistical analisys: Friedman Test (Nonparametric Repeated Measures ANOVA) . **n.s.** = not significant

FtM:female to male

TGs:trans-gender

SHBG:sex hormone binding globin

LDL: low-density lipoprotein

HDL: high-density protein

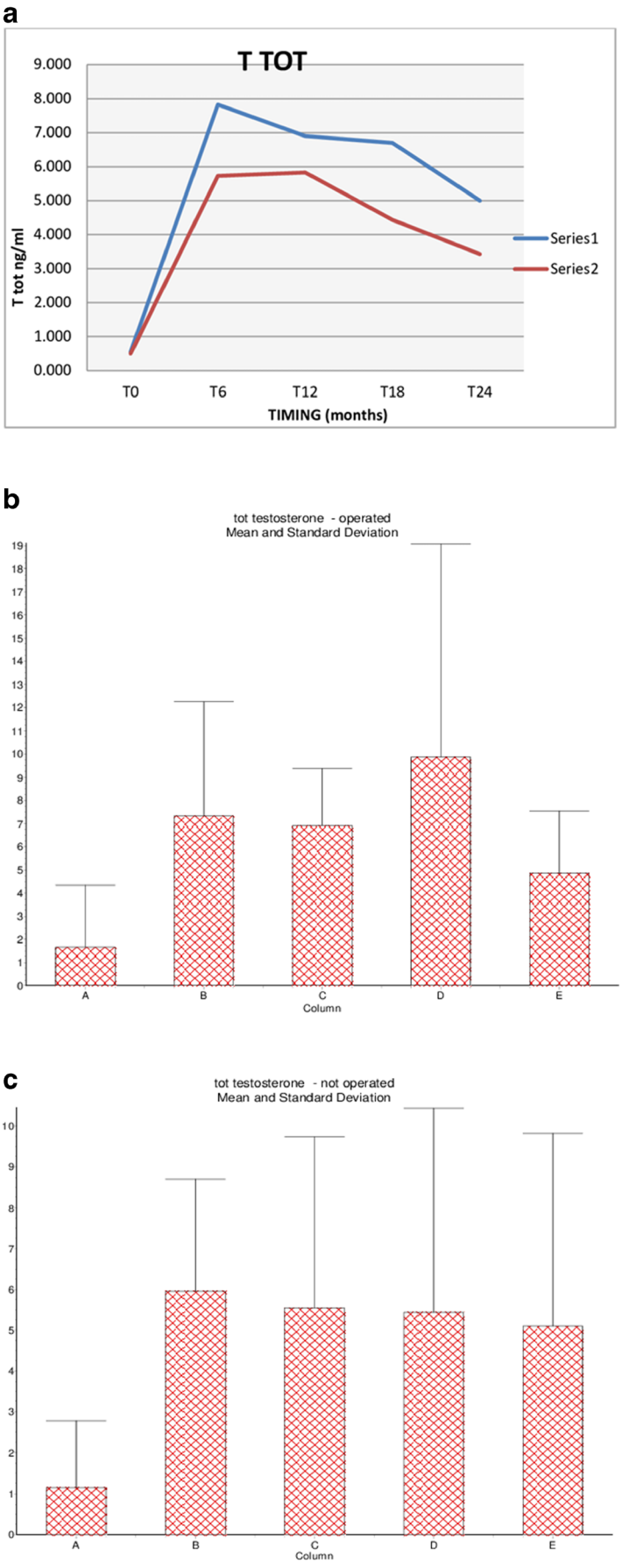
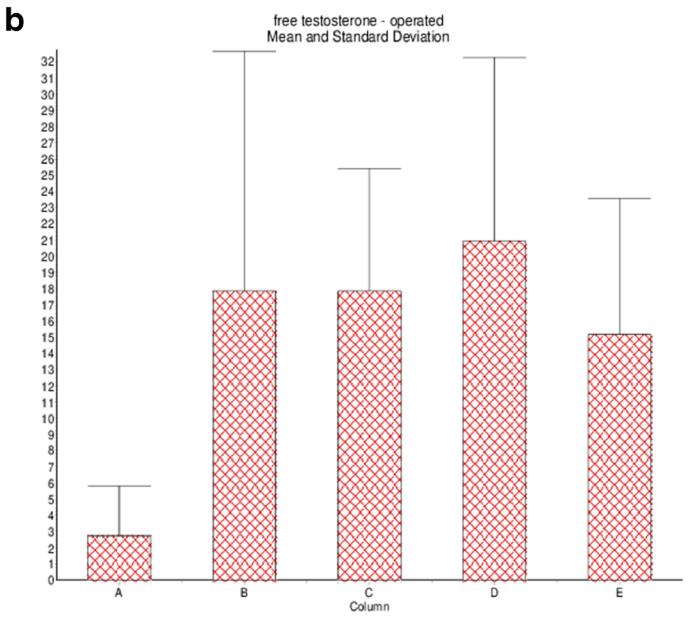


Fig. 1 **a** Total testosterone (T tot) changes after surgery (blue) and before surgery (red) over a period of 24 months, **b** T tot operated mean levels and standard deviation, **c** T Tot not operated mean levels and standard deviation



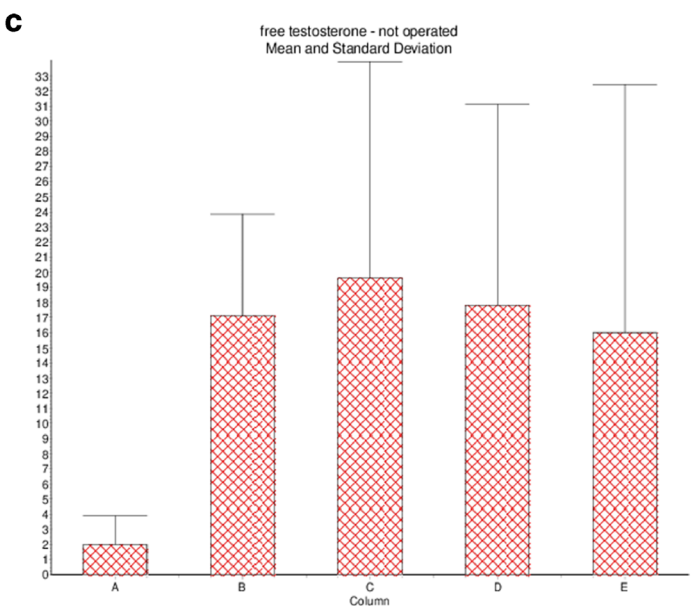


Fig. 2 Free testosterone (T free) changes after surgery (blue) and before surgery (red) over a period of 24 months, **b** T free operated mean levels and standard deviation, **c** T free not operated mean levels and standard deviation

ovariectomy. During this androgenization process, we have also noted some changes of metabolic indicators, namely: in operated FtM subjects, BMI rises from 23.45 to 24.20, while also in operated FtM subjects, LDL values are observed to rise, suggesting a synergic negative anabolic and adipogenic effect of estrogen deficiency and androgen administration. Nevertheless, it is important to stress that, in fact, LDL values in our studied group of 23 patients increased as early as at 12 months, though never exceeding the cut-off for major cardiovascular risk (optimal < 130, moderate risk 130–159, and high risk > 160). On the other hand, HDL values in both FtM groups decreased, this suggesting reduced cardiovascular risk (cut-off HDL: optimal > 39 mg/dl for men and > 45 mg/dl for women, moderate risk 35–39 mg/dl for men and 40–45 mg/dl for women, high risk < 35 mg/dl for men and < 40 mg/dl for women). Finally, HCT results were within normal limits for females before hormone therapy. On the other hand, values increased significantly after surgery, but none of our patients exceeded the value of 47%, which represents the cut-off for thromboembolic risk in women (cut-off of HCT in men 42–52% and of HCT in women 35–47%). We therefore note that atherosclerotic risk indicators (BMI, LDL, HDL, and HCT) tend to reach higher values than those at the beginning of therapy but were still within normal limits in a follow-up study of only 2 years after ovariectomy. Subsequently, however, the increase of atherosclerotic risk indicators could expose transgender men to an augmented risk of cardiovascular and cerebrovascular disease, although there are conflicting opinions concerning this issue in the literature [19–21]. Based on our experience, albeit on a limited sample of patients, we support the view that FtM people who have undergone androgen treatment should be submitted to continuous multidisciplinary follow-up in order to reassess hormonal status and lipid profile. They should also be informed about the risks of alterations of lipid markers [22] while adopting, in any case, a low-calorie diet and a healthy lifestyle, reducing tobacco use, and increasing physical activity. Unfortunately, since the centers dedicated to the transgender population in Italy are limited, the patient often has to travel some distance to reach the nearest referral center, this resulting in reduction of patient compliance with the follow-up plan and with self-management of therapy, leading to possible harmful consequences for the patient.

Limitations of the study

The limitations of the study are mainly related to the discontinuity of patients' adherence to follow-up given that since ours is the only referral center in the region, for many it was not easily accessible. This affected the sample number by limiting the overall number of participants. However, the numbers reported need to be contextualized within what is considered a "niche" area.

Conclusions

In this study, we obtained statistically significant data on hormonal and metabolic indicators in FtM transgender subjects who underwent SRS. We are able to confirm that LH proved to be a valid marker of cross-sex hormonal therapy since its reduction under the value of 10 mi/ml corresponded to an optimal endocrine, metabolic, and hemato-chemical degree of androgenization. Moreover, during personalized follow-up, we analyzed lipid profile [23] as an indicator of correct hormonal dosage, and this was shown to be useful in preventing thromboembolic events and endocrinological and metabolic imbalance [24, 25]. We believe that lipid profile should be examined before the initiation of androgen treatment. However, close attention should be paid to early detection of subjects who have a constitutional predisposition to hypercholesterolemia. Moreover, great care must also be taken as to recommendations concerning lifestyle and proper nutrition, although this is more difficult to achieve among young people [26]. In addition, in operated FtM subjects, androgens used as long-term treatment, in particular when associated with estrogen deficiency due to ovariectomy, may induce metabolic changes related to long-term atherosclerotic risk [27, 28]. These risks can be limited by strict monitoring of lipid profile [29], regular BMI and HCT evaluation, avoidance of self-management of therapy, and adherence to a healthy lifestyle, without alcohol, smoking, or excessive daily calorie intake [30]. Institutions should be encouraged to set up more specialized centers and to enable of minor regional hospital wards with specialists dedicated to the care of transgender people undergoing long-term hormone treatment.

Availability of data and materials The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions LMS made substantial contributions to drafting the work and substantively revising it, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

MD (corresponding author) made substantial contributions to the conception of the work, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which she was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

ML made substantial contributions to the design of the work, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

CC made substantial contributions to the design of the work, approved the submitted version, and agreed both to be personally accountable for

the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

TC made substantial contributions to drafting the work and substantively revising it, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

CL made substantial contributions to revising the work, especially for the statistical reformulation required by the reviewers.

GL made substantial contributions to drafting the work and substantively revising it, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

ED made substantial contributions to the acquisition and analysis of the data, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which he was not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethical approval and consent to participate There was no formal approval of the Ethics Committee, but the procedures were carried out in accordance with the Declaration of Helsinki, as revised in 2013. Informed consent was obtained from the patients through distribution of a dedicated form explaining the study design.

Consent for publication Written informed consent for the anonymous publication of information relating to the disease is regularly obtained from all individual participants included in the study during the medical interview with the patient prior to the surgical or chemotherapy treatment.

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