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Biochemical Changes, Body Composition and Cardiovascular Aspects at the Ergometric Test of a 52-year-old Transgender Man Over the First Year of Testosterone Therapy: A Case Report and Review of the Literature

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Abstract

Introduction: Testosterone (T) therapy is able to promote biochemical, body composition and Cardiovascular (CV) alterations in Transgender Men (TM). However, existing data concern TM between 18 and 50 years old.

Objective: To describe the first year of usage of T in a 52-year-old TM: Hormonal and biochemical changes, body composition and CV aspects during exercise.

Methods: Medical record review was accessed as well as laboratorial and image exams performed during the first year of T use.

Results: TM, 52-years-old, no previous usage of T, initiated testosterone undecanoate 1000 mg. A second dose was given 6 weeks after the first one and then every 12 weeks. By the third month of treatment, the highest level of T was noted (586 ng/dL). After 7 months of treatment, hemoglobin and hematocrit reached their highest levels, 16.3 g/dL and 47.1% respectively, and dropped to 15.5 g/dL and 43.6% by the twelfth month. LDLc increased 31% by the seventh month and returned to baseline by the twelfth month. Bone density increased 3.1% in lumbar spine (L1-L4) and 2.7% in femoral neck. The Muscle Mass (MM) increased 10.9% in one year. Pretreatment Ergometric Test (ET) showed increase in Systolic Blood Pressure (SBP) of 38.4% (130 to 180 mmHg) during exertion and decrease of >100% in the sixth minute of passive recovery. Heart Rate (HR) increased 73 bpm during ET and returned to baseline at the third minute of rest (reduction of 72 bpm). One year post treatment results showed that SBP increased 61.5% (130 to 210 mmHg) and decreased >100% after six minutes of rest. HR increased 67 bpm during exertion and decreased by 75 bpm at the third minute of rest.

Discussion: A meta-analysis covering studies lasting 6 to 12 months with TM using testosterone undecanoate 1000 mg every 12 weeks showed that the increase of Hb and HT ranges from 4.9% to 12.5% and 4.4% to 17.6%, respectively, which is much lower than the averages presented in our case (23 and 27%, respectively). Progressive increase of LDLc up to 18.7% is described in the literature. The lowest drop in fat mass is described in young TM. Young cis women and men present an increase in SBP during ET around 34.0% and 39.8%, respectively, and in the third minute of recovery a drop around 20.6% and 23.4%. HR drops from 60.5 to 64.53 bpm in the third minute of rest and higher recoveries are associated with better parasympathetic reactivation and lower mortality.

Conclusion: TM over 50 years old seems to present higher increase of Hb/HT and decrease of HDLc when compared to younger TM. The lowest HR increase and highest variation of SBP during ET after 1 year of T might be a consequence of enlarged cardiac chambers, increased systolic volume and peripheral vascular resistance.

Keywords: Transgender • Transgender man • Testosterone

Introduction

Gender dysphoria is defined as the unceasing desire to live and be accepted as a member of the opposite sex; it often coexists with the desire to make the body consonant with the gender of identification. Transgender individuals suffer from gender dysphoria due to the inconsistency between their gender identity and the sex designated at birth; differently from cisgender individuals who have a gender identity equal to the biological gender. In the United States, the transgender individuals add up to approximately 0.6% of the total population, a number similar to the 0.46% found in the European population, and 75% of those presumably are under some form of hormone therapy. The Trans sexualizing process concerns both social elements, such as name and pronouns compatible with the individual's gender identity, and medical procedures, such as the use of androgen hormones and/or surgery. Hormone therapy, also called Cross-Sex Hormone Therapy (CSHT), and gender reaffirming surgery are the medical procedures of sex reassignment treatment [1-10].

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Regarding gender-affirming Hormonal Therapy (CSHT), for transgender men (Female to Male-F to M) those who have female sex as their native sex, but identify with male sex. The basis of treatment is the use of androgen hormones. CSHT is based on the reduction of endogenous sex hormones by replacement for exogenous sex hormones, according to the individual's gender identity. It consequently reduces individual's gender of birth secondary sexual characteristics and promotes the development of gender characteristics of identity, according to the principles of hormone replacement in hypogonadal individuals [11-30]. Therefore, transgender men undergo treatment with androgen hormones in order to induce virilisation. Injectable testosterone esters administered in doses of 100 to 250 mg every 7 to 21 days are the most prescribed drugs in Brazil. However, the literature suggests that long-acting testosterone undecanoate 1000 mg should be preferably used because it maintains more acceptable testosterone levels by administration each 12 weeks. The goal is to achieve testosterone levels within the expected reference value for cisgender men (total testosterone between 320 to 1000 ng/dL) as well as foreseen for hypogonadal men on hormone replacement. These levels are capable of developing secondary sexual characteristics of the male sex, such as increased musculature, appearance of hair in androgen-dependent regions, increased sexual desire, increased voice, altered fat pattern, and even acne or male pattern baldness in those genetically predisposed individuals.

It is believed that sex difference in cardiovascular pathologies is related to differences in sex steroids of women and men and their interactions with receptors on cardiovascular system and muscle cells. Estrogenic receptors demonstrate, both *in vivo* and *in vitro*, an anti-inflammatory, anti-atherosclerotic, and vasodilatory effect, which indicates less cardiovascular risk. In women and men with lower number of these receptors, increased cardiovascular risk was associated. Although gender transition has been associated with improved mental health and other areas of functioning, the long-term effects of CSHT are still uncertain. Most studies suggest that hormone therapy does not represent high risk of side effects, but others highlight increase in LDL and liver proteins, decrease in HDL and intensification of erythropoiesis as main consequences of this practice [28]. Most of these existing data concern TM between 18 and 50 years old. However, there is still not a large amount of evidence regarding transgender men or individuals with early hormonal therapy at an advanced age. Furthermore, there is also insufficient evidence to clearly elucidate the short and long-term cardiovascular effects. The present study, based on the case report of a transgender patient who started CSHT at 51 years of age, intends to contribute to the still incipient evidence regarding changes and consequences induced by this treatment.

Objective

To describe the first year of Testosterone therapy in a 52-year-old Trangender Man-hormonal and biochemical changes, body composition and cardiovascular aspects during exercise

Case Presentation

A 52-year-old premenopausal Transgender Man (TM), without previous Testosterone (T) use, started testosterone undecanoate 1000 mg. A second dose was given 6 weeks after the first one and then every 12 weeks. Lab exams were collected on the day before the next shot of T. By the third month of treatment, the highest level of T (586 ng/dL) was noted. Initial Hemoglobin (Hb) was 13.0 g/dL and Hematocrit (Ht) 37.1% (Table 1). After 7 months of treatment, they reached their highest levels, 16.3 g/dL (23%) and 47.1% (27%) respectively and dropped to 15.5 g/dL and 43.6% by the twelfth month. LDL-cholesterol (LDLc) increased from 106 to 139 mg/dL (31%) by the seventh month, and returned to baseline by the twelfth month. HDL-cholesterol (HDLc) dropped from 73 to 60 (17%) by the seventh month and increased to 64 around the twelfth month. Bone density increased 3.1% in lumbar spine (L1-L4) and 2.7% in femoral neck (Table 2). Densitometry was done with a GE Lunar DPX NT densitometer both in pre and post treatment. Body weight, Muscle Mass (MM) and fat mass were assessed by bioelectrical impedance analysis (In Body 120 analyzer) every 3 months. The total muscle mass increased 10.9% in one year and the total fat mass decreased 31.1% at the same period. Body weight remained the same (Figure 1). The exercise test was performed using the Ellestad protocol on a treadmill and electrocardiographic recording system in 13 simultaneous leads both in pre and post treatment. Pre-treatment Ergometric Test (ET) showed increase in Systolic Blood Pressure (SBP) of 38.4% (130 to 180 mmHg) during exertion and decrease of >100% in the sixth minute of passive recovery. Heart Rate (HR) increased 73 bpm during ET and returned to baseline at the third minute of rest (reduction of 72 bpm). The same ET was performed one year after T use. Post treatment results showed that SBP increased 61.5% (130 to 210 mmHg) and decreased >100% after six minutes of rest. HR increased 67 bpm during exertion and decreased by 75 bpm at the third minute of rest (Figure 2).

Table 1. Biochemical changes during first year of testosterone use in 52-year-old transgender man.

Variables	Initial	1st Month	3th Month	6th Month	9th Month	12th Month
Total Testosterone (ng/dL)	31	194	586	583	511	373
Estradiol (ng/dL)	27.5	3.1	2.9	2.3	3.4	2.7
FSH (UI/L)	14.5	14.6	62.6	12.5	11.7	25.7
LH (UI/L)	28	6.9	52.2	16.6	8.8	23.3
Hemoglobin (g/dL)	13	14.2	15.8	16.3	16.1	15.5
Hematocrit (%)	37.1	40.6	45.8	47.1	45.7	43.6
Total Cholesterol (mg/dL)	194	-	201	216	201	188
LDLc (mg/dL)	106	-	116	139	116	106
HDLc (mg/dL)	73	-	69	60	68	64
Triglyceride (mg/dL)	67	-	70	80	74	85

ng/dL: Nanograms per deciliter of blood; UI/L: International units per liter; g/dL: Grams per deciliter of blood; mg/dL: Milligrams per deciliter of blood; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; LDLc: Low-Density Lipoprotein Cholesterol; HDLc: High-Density Lipoprotein Cholesterol.

Table 2. Bone density changes during first year of testosterone use in 52-year-old transgender man.

Variables	Initial	12th Month
BMD (g/cm^2) Lumbar Spine L1-L4	1.448	1.494
T-Score Lumbar Spine L1-L4	+2.2	+2.6
BMD Right Femoral Neck	1.024	1.029
T-Score Right Femoral Neck	-0.1	-0.1
BMD Total Femur	1.032	1.06
T-Score Total Femur	+0.2	+2.2

BMD: Bone Mineral Density; g/cm^2: Gram per square centimeter

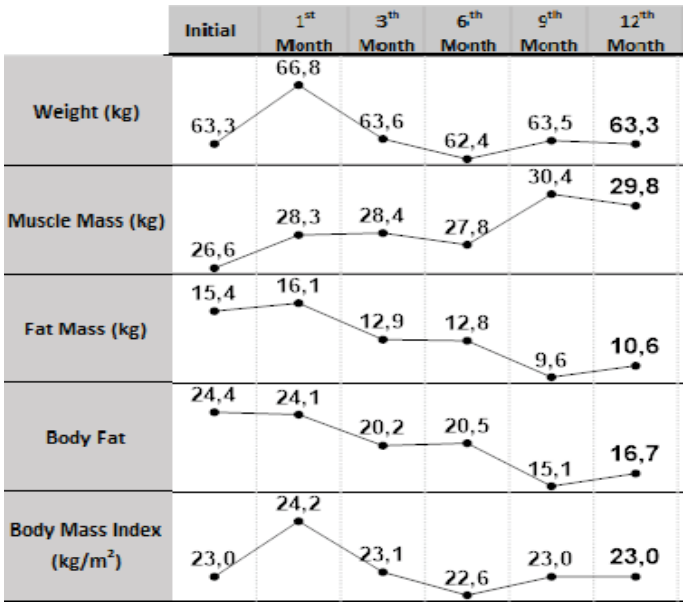
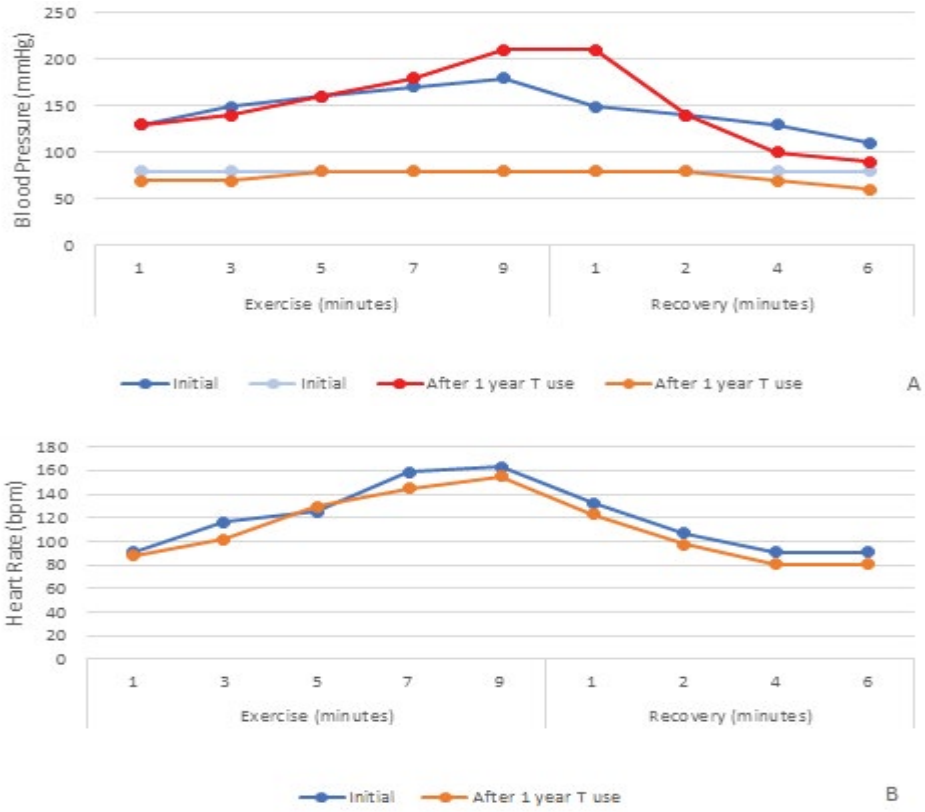


Figure 1. Changes in body composition over 1 year of testosterone use in 52-year-old transgender man.



Note: mmHg: Milimetre of Mercury; bpm: Beats per minute; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; T: Testosterone

Figure 2. Blood Pressure (A) and Heart rate (B) at the Ergometric test before and after 1 year of T use

Discussion

Erythropoiesis is one of the many physiological processes stimulated by androgens. Bachmanet et al. [24] suggest that androgens act indirectly to stimulate erythropoietin and directly to stimulate bone marrow erythropoiesis. Systematic reviews covering studies lasting 6 to 12 months, with TM using testosterone undecanoate 1000 mg every 12 weeks, show that the increase of hemoglobin during hormone therapy ranges from 4.9% to 12.5% while the increase in hematocrit ranges from 4.4% to 17.6%, which is much lower than the averages presented in our case (23 and 27%, respectively).

Lipid profile

Men are at an increased risk of Cardiovascular Disease (CVD) compared to premenopausal women, and it has been postulated that testosterone contributes to this high risk. Exogenous administration of testosterone may decrease serum HDL-cholesterol (HDLc) concentrations [31-40]. Since low HDLc correlates with increased risk of CVD, this decrease may contribute to the alleged cardiovascular adverse effects of testosterone [41-43]. Previous

studies with young TM undergoing hormone therapy showed a progressive fall in HDLc over 3, 6, 12 and 24 months of observation (-6.5, -8.1 and -8.5 mg/dL, respectively). A retrospective study of 97 HT using testosterone undecanoate 1000 mg every 3 months or testosterone gel 50 mg/5 g daily showed an average reduction of 7 mg/dl when evaluated for 24 months. A major fall was presented in our case (-13 mg/dL in the seventh month and -9 mg/dL in the twelfth month), compared to the initial value. Concerning LDLc behavior in testosterone undecanoate users, contradictory results are found in the literature, ranging from drops of 15.8% to increases of 18.7%, in a 1-year period [44-50]. In the present case, LDLc increased 31% at the seventh month of T use and returned to baseline by the twelfth month.

Blood pressure

Some studies have shown an increase in systolic and diastolic blood pressure due to hormone therapy (Emi YAM, et al. [19]). After 2 years of testosterone use, there was a variation ranging from 3.2 mmHg to 13.4 mmHg in Systolic Blood Pressure (SBP). Comparison of 63 TM without testosterone to 48 TM using testosterone presented in a cohort study found that both SBP and Diastolic Blood Pressure (DBP) were higher in the treatment group [19].

Body composition

Cis women's Bone Mineral Density (BMD) decreases around 2% in lumbar spine, 1.4% in total hip and MM shows reduction of 1lb 5.2oz during the first year of climacteric. An increase in muscle volume is expected due to the effect of testosterone administration, as steroid hormones act on regional fat deposition. Systematic reviews demonstrate that in TM on hormonal therapy there is an increase in Body Mass Index (BMI) ranging from 1.3% to 11.4%, as well as an increase in lean mass and a reduction in fat mass [51]. In the present case, bone density increased 3.1% in lumbar spine (L1-L4) and 2.7% in femoral neck. Muscle Mass (MM) increased 10.9% in one year and the drop of total fat mass was twice as high (31%) as that observed in the literature.

A recent Swedish study of 12 TM (average age of 25 ± 5-years-old) showed no significant difference in total body mass, but a significant decrease (15%) in total adipose tissue and increase in total lean tissue (13%). Strength also increased in 12 months [52,53]. Meta-analysis covering 10 studies and 354 TM reported an average gain of 3.9 kg of lean body mass during the course of 12 months of testosterone use. In a Belgium prospective study 23 TM (27 ± 9 years old) started CSHT using testosterone undecanoate 1000 mg. They had never used any kind of testosterone before. During the first year, lean body mass increased 10.4% and total body fat mass decreased 9.7%, but BMI remained unchanged. They also evaluated bone parameters and observed that markers of bone formation noticeably increased during the first year of treatment, especially P1NP. High levels of resorption markers in TM are contradictory in the literature [26]. Some studies even reported a higher BMD at cortical sites. Bone augmentation may be a consequence of indirect effects of testosterone on bone, such as increased bone stress due to increased muscle fiber as well as aromatization of testosterone into estrogen.

Cardiovascular implications

It is known that cardiovascular system is directly impacted by androgens and estrogens, due to their receptors located in endothelium, smooth muscle of the vessels and myocardial cells [36]. There is diverging information among *in vivo* and *in vitro* studies that indicate that testosterone can act both as a vasodilator and vasoconstrictor in the arteries of the heart [8]. Some studies have found that TM treated with Intramuscular testosterone showed an antithrombotic pattern with drop in activated protein C resistance (2.0 to 1.3) and increase in protein S antigen (105-118%). Increase in endothelin after 4 months of testosterone use by TM has also been reported. However, many previous studies show no higher risk of myocardial infarction or stroke in TM using various formulations of testosterone for short or long periods. It is necessary to emphasize that the age of the evaluated population ranged from 20 to 40 years, with little or no participation of individuals over 50-years-old [29].

Heart rate and blood pressure responses to ergometric test

In non-hypertensive subjects, SBP increases as the workload increases and peaks at maximal exercise. After rising to a maximum, it decreases to about normal levels by 6 minutes of recovery, then stays lower than pre-exercise values for several hours [22]. In this case, pretreatment SBP increased (130 to 180 mmHg) and decreased (>100% after 6 minutes) accordingly. The same pattern could be observed in post treatment values (increasing from 130 to 210 mmHg and decreasing >100% after 6 minutes). However, the peak SBP was considerably higher after one year T use. Regarding the effects of testosterone treatment on resting blood pressure in TM, mild, clinically irrelevant, or no changes were found in most previous studies [50-53]. Given the lack of studies about older TM, we can only speculate about resting blood pressure increases as well as at exercise. In a double-blind, randomized, placebo-controlled crossover design studies [9], ten female patients with adrenal failure were treated for 6 months with a daily morning dose of DHEA (50 mg) or placebo. The treatment normalized androgen status to levels seen in healthy women, but had no effect on echocardiographic parameters of myocardial dimensions or systolic and diastolic function, 24-h blood pressure and heart rate, cardiac output and maximal oxygen consumption during exercise cycle testing. However, all participants had evidence of concentric left ventricular remodeling by echocardiography.

Anabolic Androgenic Steroids (AAS) can often cause concentric left ventricular myocardial hypertrophy whose extent seems to be dose-related. It has been shown that AAS exert a long-standing hypertrophic effect on the myocardium [22]. Pathologic left ventricular myocardial hypertrophy, developing under AAS intake is often associated with a reduction of the ejection fraction of the left ventricle, as well as a restricted diastolic function of the affected heart chamber, probably caused by increasing myocardial fibrosis. Even though these results were shown in cis gender (males and females), it is intuitively possible to consider that high doses of strong steroids and long treatments could induce pronounced changes. As in the present case T use lasted longer than 6 months it could be enough to induce such changes. Unfortunately, we did not collect any echocardiographic data. The heart rate increases linearly with workload and VO_2 and reaches a peak that is age related [20]. It is expected to decrease at least 12 bpm within 2 minutes of passive recovery [10]. In this case, similar responses were observed during both pretreatment ET (73 bpm increase, returning to baseline in 3 minutes) and post treatment ET (67 bpm increase and 75 bpm decrease in 3 minutes of rest). After T use, a lower HR peak value was achieved during exertion. The same happened during recovery, reaching a HR value even lower that the rest value. Traditionally, the heart rate achieved with peak exercise is expressed as a percentage of the maximal predicted HR for age; however, there is so much individual variation in maximal heart rate that this expression has little use. The standard deviation from most studies of estimated peak heart rates for age is 10 to 15 beats per minute [23]. In this sense, it is not likely that age have influenced these different values.

Conclusion

TM over 50-years-old seems to present higher increase of Hb/HT and decrease of HDLc when compared to younger TM. The lower HR increase and higher variation of SBP during ergometric test after 1 year of T use might be a consequence of possible enlarged cardiac chambers, increased systolic volume and peripheral vascular resistance (não sei se ficou bom, ainda fiquei incomodado com o trecho). According to the literature, it is possible to conclude that hormonal therapy in transgender men can cause changes in lipids, possible increase in systemic blood pressure and endothelial or vascular changes. However, despite the few studies that hinder the quality of evidence in the present study, there is a consensus regarding the safety of using testosterone in TM in short term. Thus, vascular and endothelial changes described do not present an obstacle for hormonal therapy with testosterone, since there are no serious clinical implications. It is clear that more studies focusing on hormone therapy in transgender men are necessary, especially including patients of different ages. It will bring more consistent information and enlighten physicians and patients.

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