

Sleep pattern in transgender men on short-term cross-sex hormone therapy with testosterone

Padrão de sono em homens transexuais em terapia hormonal sexual de curto prazo com testosterona

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ABSTRACT

It is believed that hormone therapy with testosterone in transgender men may interfere in the sleep quality of these patients, since testosterone may induce worsening of obstructive sleep

apnea syndrome (OSAS) in hypogonadal cisgender men receiving testosterone replacement therapy. This study aims to evaluate the association between testosterone therapy and risk of sleep disorders, including OSAS, in transgender men. Eighteen transgender men in a regular and supervised use of testosterone (mean treatment time: 3 ± 1.6 years) were evaluated regarding the risk of sleep disorders through questionnaires already validated in the medical literature. Anthropometric, laboratory and clinical data were collected. According to the Epworth Sleepiness Scale (ESS), 50% of transgender men presented a risk of daytime sleepiness, while 22% and 23% of the participants were at high risk for OSAS according to the Berlin and updated STOP-Bang questionnaires, respectively. No significant association was found between risk of sleep disorders and testosterone type or therapy duration. However, there was a significant and negative correlation between androgen treatment time and ESS score. Regarding the clinical and laboratory profile of the patients, a high risk of sleep disorders was associated with lower levels of HDL cholesterol (HDL-c) and higher blood pressure values. Short-term treatment with testosterone in young transgender men is not associated with an increased risk of sleep disorders and may even improve daytime sleepiness in long-term. Blood pressure and HDL-c should be monitored in transgender men on androgen therapy as, when altered, they may indicate a higher risk of sleep disorders and OSAS.

Keywords: transgender persons, sleep disorders, testosterone, hormone.

RESUMO

Acredita-se que a terapia hormonal com testosterona em homens transgêneros possa interferir na qualidade do sono desses pacientes, uma vez que a testosterona pode induzir a piora da síndrome da apneia obstrutiva do sono (SAOS) em homens cisgêneros hipogonádicos que recebem terapia de reposição de testosterona. Este estudo tem como objetivo avaliar a associação entre a terapia com testosterona e o risco de distúrbios do sono, incluindo a SAOS, em homens transgêneros. Dezoito homens transgêneros em uso regular e supervisionado de testosterona (tempo médio de tratamento: $3 \pm 1,6$ anos) foram avaliados quanto ao risco de distúrbios do sono por meio de questionários já validados na literatura médica. Foram coletados dados antropométricos, laboratoriais e clínicos. De acordo com a Escala de Sonolência de Epworth (ESS), 50% dos homens transgêneros apresentaram risco de sonolência diurna, enquanto 22% e 23% dos participantes apresentaram alto risco de SAOS de acordo com os questionários de Berlim e STOP-Bang atualizado, respectivamente. Não foi encontrada nenhuma associação significativa entre o risco de distúrbios do sono e o tipo de testosterona ou a duração da terapia. No entanto, houve uma correlação significativa e negativa entre o tempo de tratamento com androgênios e a pontuação da ESS. Com relação ao perfil clínico e laboratorial dos pacientes, um alto risco de distúrbios do sono foi associado a níveis mais baixos de colesterol HDL (HDL-c) e valores mais altos de pressão arterial. O tratamento de curto prazo com testosterona em homens transgêneros jovens não está associado a um risco maior de distúrbios do sono e pode até melhorar a sonolência diurna em longo prazo. A pressão arterial e o HDL-c devem ser monitorados em homens transgêneros em terapia androgênica, pois, quando alterados, podem indicar um risco maior de distúrbios do sono e SAOS.

Palavras-chave: pessoas transgênero, distúrbios do sono, testosterona, hormônio.

1 INTRODUCTION

Gender-affirming hormone therapy (GAHT), carried out under medical supervision, is one of the means used by the transgender population to promote masculinization or feminization of the body, in order to adapt it to the gender identity. Transgender men (also called female-to-male individuals - FTM) are those who are born in the female biological sex, but who identify with the male gender, for whom testosterone therapy is indicated (1,2,3).

The main objectives of testosterone therapy are to induce the development of secondary male sexual characters and to soften female biological characteristics (4). Cross-sex hormone therapy with testosterone is similar to the treatment regimens prescribed for hypogonadal men (5,6). Due to the wide distribution of androgen receptors throughout the body, testosterone therapy has several desired and undesired physical and psychological effects (6).

In Brazil, the cross-sex hormone therapy with testosterone can be done with the following available medications: the injectable combination of propionates, isocaproate and testosterone decanoate (Durateston®), injectable testosterone cypionate (Deposteron®), injectable testosterone undecylate (Nebido®), as well as the testosterone gel 1% (Androgel®) and the 2% testosterone topical solution (Axeron®), with few systemic effects (7).

Robertson et al. described two cases with obstructive sleep apnea syndrome (OSAS) developed after initiating testosterone therapy in transgender men. (8). Such data arouses attention because it is a condition that, when left untreated, contraindicates hormone replacement with testosterone in cisgender hypogonadal men - since the therapy can worsen this condition (9).

OSAS is a chronic and underdiagnosed disorder defined as the occurrence of upper airway obstruction during sleep, characterized by repeated pauses in breathing that last from 10 to 40 seconds, despite efforts to maintain it, which can result in decreased blood oxygen saturation, daytime sleepiness and sleep fragmentation (10).

Burschtin and Wang affirm that there is an established association between the administration of high doses of testosterone to hypogonadal patients and the increase in sleep disorders, represented by changes in respiratory and polysomnographic parameters (9). Accordingly, Hoyos et al. evaluated the effect of testosterone therapy on obese patients (with and without hypogonadism) diagnosed with severe OSAS, and observed an increase in the rate of oxygen desaturation and in the percentage of hypoxia time during sleep (11).

Studies on this topic in transgender men groups are still scarce. Lerner, Robertson and Williams described a case of transgender men developing OSAS and they reaffirmed the importance of evaluating the effects of cross-sex hormone therapy on sleep disorders in this

particular group, since testosterone influences sleep and breathing in both genders, and the impact of high doses of testosterone, as in gender reassignment therapy, is inconsistently documented in the literature (12).

In order to better clarify the effects and risks of testosterone therapy in this specific transgender population, the present study aimed to evaluate, through validated questionnaires, the association between short-term cross-sex hormone therapy with testosterone and the risk of sleep disorders, including OSAS, in young transgender men.

2 MATERIALS AND METHODS

2.1 STUDY DESIGN AND PATIENT SELECTION

This is a cross-sectional analytical-descriptive study that evaluated transgender men individuals followed up at the Centro de Diabetes e Endocrinologia do Pará (CEDEPA) and at the Unidade de Referência Especializada em Doenças Infecciosas e Parasitárias Especiais (UREDIFE) in Belém - PA, from January 2018 to May 2019. The project was approved by the Human Research Ethics Committee of the Centro Universitário Metropolitano da Amazônia (CEP / UNIFAMAZ).

The inclusion criteria involved transgender men individuals under regular and supervised use of testosterone as hormone therapy for at least 1 year, in agreement and able to answer the research protocol, allowing their medical records to be used. The exclusion criteria were: transgender men individuals who were not on hormonal therapy with testosterone or who had insufficient clinical and laboratory data, as well as patients who did not completely answer the applied questionnaires.

The research protocol comprised the obtaining of the following groups of variables: 1) patient identification; 2) physical examination data; 3) results of complementary exams; 4) time of testosterone use, type and frequency of testosterone used; 5) use of other medications; and 6) presence of comorbidities, such as diabetes mellitus (DM), systemic arterial hypertension (SAH), dyslipidemia, lung diseases, among others. In addition, the application of the Epworth Sleepiness Scale (ESS), the Berlin questionnaire (BQ) and the updated STOP-Bang questionnaire (SB) were part of the protocol.

2.2 SLEEP SCALES

ESS, already validated for the Portuguese language for use in Brazil (ESS-BR), was idealized based on observations related to the nature and occurrence of daytime sleepiness. It is a self-administered questionnaire that assesses the probability of falling asleep in eight

situations involving daily activities. The global score ranges from 0 to 24, with scores above 10 suggesting the diagnosis of excessive daytime sleepiness (13).

The Berlin questionnaire is based on a series of self-administered questions, divided into three categories, which investigate snoring, daytime sleepiness and a previous history of systemic arterial hypertension (SAH), in addition to calculating the body mass index (BMI). The interpretation of the questionnaire recommends that the categories should be scored separately, adding 1 point to each positive answer in which the symptoms are frequent. Categories 1 and 2 will be considered positive when they get a total score greater than or equal to 2. Category 3 is considered positive if the patient has SAH or obesity ($BMI \geq 30 \text{ kg} / \text{m}^2$). Anyone with two or more positive categories is classified as “high risk” for OSAS. In 2011 this questionnaire was validated for the Portuguese language (14).

The STOP-Bang questionnaire (acronym for *Snoring, Tiredness, Observed apnea, highblood Pressure, Body mass index, Age, Neck circumference, and Gender*), validated for the Brazilian Portuguese language, proved to be adequate to identify OSAS and can be a tool effective for the diagnosis of this disorder, since it has high sensitivity and high negative predictive value. It is self-administered, consists of 8 yes/no questions, and the score achieved can classify the individual as low, moderate or high risk for OSAS (15).

The polysomnography exam, although considered as the gold standard exam to confirm the diagnosis of OSAS, is not used routinely in the investigation of sleep disorders, mainly in Brazilian public hospitals, due to its low availability, high cost and complex elaboration (need for qualified technicians and sleep laboratory for its realization). Because they are simple to use, scales and questionnaires related to sleep can be used for a presumptive diagnosis, with effective screening when OSAS is suspected (16).

2.3 STATISTICAL ANALYSIS

The descriptive analysis was presented as mean, standard deviation, minimum value, maximum value and percentage. The patients were divided into groups according to the results presented on the Epworth scale (greater and lesser possibility of sleep disorder) and on the Berlin and updated STOP-bang questionnaires (negative risk and high risk for OSAS; no patient was classified as intermediate risk). Additionally, the ESS score values were used as a continuous variable for correlation analysis. The data obtained were organized and transferred to the statistical software R 4.0.0 (R Development Core Team, Vienna, Austria).

Anthropometric, metabolic and hormonal variables, as well as variables related to testosterone treatment were compared between patients at high and low risk for sleep disorders.

To compare variables between groups, the Mann-Whitney non-parametric test was used. To perform correlation analyzes between the variables, Pearson or Spearman's correlation coefficient was used. The Chi-square test was applied to assess differences between frequencies. The level of significance used in the research was 5% ($p \leq 0.05$).

3 RESULTS

3.1 ANTHROPOMETRY, BLOOD PRESSURE AND HEMATOCRIT

Eighteen transgender men were included in the survey. The mean age of the group was 30 ± 2 years (range: 20-46 years) and the mean body mass index (BMI) was 26 ± 4 kg / m² (range: 16.7 - 33.9), 61% of the group were overweight and 89% had high values of Body Fat Percentage (PGC) considering the normal parameter for males (PGC > 20%). The mean waist-hip ratio was 0.88 ± 0.07 (range: 0.76 - 1.0) and the mean neck circumference was 36 ± 3 cm (range: 31 - 42 cm). The mean systolic and diastolic blood pressure were 121 ± 13 mmHg (range: 100 - 150) and 76 ± 12 mmHg (range: 60 - 110), respectively. Three individuals had blood pressure values $\geq 140 \times 90$ mmHg, but only two were receiving treatment for SAH. The mean hematocrit of the group was 48 ± 3 (range: 43.1 - 53.9).

3.2 HORMONAL TREATMENT WITH TESTOSTERONE

The parenteral testosterone treatment time, under medical supervision, was 3 ± 1.6 years (range: 1 - 8) and only 3 patients had ≥ 5 years of treatment duration. Testosterone cypionate was prescribed to 72% of patients, every 15 or 21 days, and the others received testosterone undecylate every 90 days. When asked about the use of other drugs, 47% claimed to use another class of drugs besides testosterone. Among the drugs cited, the antidepressant agents were the most class of drugs mentioned (25%), followed by vitamin D supplementation (11%) and others less frequent (captopril, losartan, levothyroxine, anti-inflammatories, fibrates). No individual received antidiabetic medication and only one individual was diagnosed with prediabetes (impaired fasting glucose).

The mean serum total testosterone levels were 563 ± 39 ng/dL (range: 146 - 1500). The hormonal and metabolic profile of transgender individuals is described in table 1.

3.3 SLEEP

According to the ESS, 50% of transgender men presented a risk of daytime sleepiness, while 22% and 23% of the participants were at high risk for OSAS according to the Berlin and updated STOP-Bang questionnaires, respectively. The duration of androgenic treatment, when

classified as above or below 3 years of androgenic treatment, was not associated with a higher risk of sleep disorders, as well as the type of testosterone used (tables 2 and 3). However, the ESS score correlation analysis showed negative statistical significance with the treatment time ($p = 0.046$; $R = -0.47$), but not with the serum testosterone level ($p = 0.9$; $R = -0.03$).

The hormonal and metabolic profile of the patients was analyzed for the risk of sleep disorders. There was a significant difference only for HDL levels, in which patients at low risk for sleep disorders by STOP-Bang had higher HDL-c levels when compared to patients at high risk (55 ± 11 versus 40 ± 7 , respectively, $p = 0.02$). The other variables were not statistically different between groups (Table 4).

Table 5 shows anthropometric and pressoric variables distributed according to the risk of sleep disorders. Systolic blood pressure showed a statistically significant difference between patients at high and low risk for sleep disorders according to the evaluation by the STOP-Bang (134 ± 10 versus 117 ± 9 , respectively, $p = 0.009$) and Berlin questionnaires (135 ± 11 versus 118 ± 9 , respectively, $p = 0.03$). Diastolic blood pressure, on the other hand, showed a statistically significant difference between the high and low risk groups only by assessing the STOP-Bang questionnaire (88 ± 12 versus 72 ± 7 , respectively, $p = 0.006$). The other parameters analyzed were not statistically different between the high and low risk groups for sleep disorders.

4 DISCUSSION

The demand for sex reassignment therapy, supervised by professionals, has grown recently and, accordingly, this area of medicine has shown itself to be a vast field, either due to the complexity of patients or to on the limited number of data based available evidence (17, 18).

In the present study, no significant association was found between risk of sleep disorders and testosterone type or therapy duration. However, there was a significant and negative correlation between androgen treatment time and ESS score, suggesting that the longer the testosterone treatment time, the lower the risk of daytime sleepiness in trans men, which may suggest a better quality of sleep in later stages of the androgenic treatment, possibly associated with a higher degree of satisfaction with the treatment due to their suitability to the male gender. Some effects of androgenic therapy in trans men, such as increased facial and body hair, increased muscle mass and redistribution of body fat, reach their maximum development around 4 to 5 years after the start of therapy, which may justify a greater sensation adequacy in that period (19).

This was the first study carried out in the Brazilian literature with the purpose of identifying the association of cross-sex hormone therapy with testosterone in transgender men and the risk for sleep disorders. In the literature review, only two case reports of transgender men diagnosed with OSAS using testosterone were found, and the authors reiterated the relevance of further investigation about the topic, given the scarcity of data in the medical literature (12, 18). Complementarily, Auer et al., in a cross-sectional study with 154 transgender individuals (72 of whom were transgender men), assessed the sleep quality of the participants and concluded that there was no significant role for hormonal therapy over it (20).

The effects of testosterone on the upper airways during sleep in cisgender men are unclear and the literature presents conflicting data. While some authors point to the association between testosterone deficiency and OSAS, others consider testosterone replacement as a cause or factor of worsening OSAS (21, 22). Su et al. found, in a systematic review and meta-analysis with 1823 men, that OSAS is inversely associated with male serum testosterone levels, independent of body mass index (BMI) and age. Also, that the severity of obstructive sleep apnea, measured by the Apnea-Hypopnea Index (AHI), is correlated with the reduction of levels serum testosterone (23).

In contrast, studies have shown that testosterone can induce obstructive sleep apnea through neuromuscular and central mechanisms. Its effects are reflected in increased airway collapse, ventilation and ventilatory response to hypoxemia and hypercapnia, leading to a reduction in the apnea threshold (24). Zhou et al. studied the change in the apnea threshold in 8 pre-menopausal women under the influence of transdermal testosterone, which revealed a change in the hypocapnic apnea threshold, with the consequent development of central apnea. This study argues that the respiratory disorder cannot be justified by the mechanisms of the upper airways, since the short duration of therapy would be insufficient to induce anatomical changes. In fact, there was no increase in upper airway resistance, nor in snoring or in limitation of inspiratory flow (25).

The young age of our study group and the short duration of androgen treatment may justify the non-significant results of the association between sleep disorders and aspects of androgenic therapy.

Regarding clinical and anthropometric variables, it was observed that high values of systolic blood pressure, for the QB, and of both blood pressures, systolic and diastolic, for the STOP-Bang questionnaire, were associated with a higher risk of OSAS. Such data are in line with the results of the review by Borel, which states that there is an association between high blood pressure values and OSAS, regardless of obesity and metabolic syndrome (26). Although

the presence of arterial hypertension is one of the criteria that scores in the Berlin and STOP-Bang questionnaires, only two trans men in our series have a previous diagnosis of arterial hypertension. It is likely, therefore, that the increase in blood pressure in the high-risk subgroup is already a consequence of sleep disorders in these individuals.

In respect of hormonal and metabolic laboratory measurements, lower levels of HDL-c were associated with a high risk of OSAS, according to the results of the STOP-Bang questionnaire, in agreement with the study by Bajpai et al., with 102 patients, who concluded that low levels of HDL-c are independent predictors of OSAS. The study observed a strong relationship between HDL levels and OSA severity, suggesting that the patients with a lower HDL level have a higher Apnea-Hypopnea Index (27,28). A reduction in HDL-c levels is frequently observed during testosterone therapy, however our study design does not allow us to infer a cause and effect relationship between testosterone therapy and low levels of HDL-c in the subgroup with sleep disorders.

Other limitations of our study are the small number of transgender individuals who met the inclusion criteria, the short follow-up time and the short-term androgenic treatment, since many cardiovascular and metabolic adverse effects are observed only after a long period of androgenic treatment in transgender men, and the absence of polysomnography, the gold standard test for the diagnosis of OSAS.

We conclude that short-term treatment with parenteral testosterone in young trans men is not associated with an increased risk of sleep disorders, and may even improve daytime sleepiness, but the mechanism is still unknown. Blood pressure and HDL cholesterol are parameters that must be monitored in trans men undergoing androgenic therapy since, when altered, they may indicate a greater risk of sleep disorders and OSAS.

Additional studies are still needed to better understand the role of cross-sex testosterone therapy in sleep disorders in transgender men.

Table 1. Hormonal and metabolic profile of transgender men receiving regular cross-sex hormone treatment with parenteral testosterone.

Variables	Mean	SD
Total testosterone (TT) (ng/dL)	563	± 39
Luteinizing Hormone (LH) (UI/L)	6,1	± 6,7
Follicle stimulating hormone (FSH) (UI/L)	9,9	± 15
Estradiol (pg/mL)	39	± 18
Total cholesterol (mg/dL)	181	± 28
HDL cholesterol (mg/dL)	51	± 13
LDL cholesterol (mg/dL)	116	± 39
Triglycerides (mg/dL)	109	± 58
Fasting glucose (mg/dL)	88	± 8
HOMA IR	1,3	± 0,9

SD: standard deviation
Source: Research collection.

Table 2. Association analysis of androgen treatment time in transgender men and the risk for sleep disorders, according to the different sleep scales.

Variable	Risk of sleep disorders					
	ESS		BQ		STOP-Bang	
Treatment time	≥ 10	< 10	High	Low	High	Low
≤ 3 years	89%	56%	75%	71%	80%	69%
≥ 4 years	11%	44%	25%	29%	80%	20%
<i>p</i> -value ^a	0,2		1,0		1,0	

^a Chi-square test
Source: Research collection.

Table 3. Association analysis of the type of testosterone administered in transgender men and the risk for sleep disorders, according to the different sleep scales.

Variable	Risk of sleep disorders					
	ESS		BQ		STOP-Bang	
Type	≥ 10	< 10	High	Low	High	Low
Testosterone cypionate	46%	54%	85%	15%	77%	23%
Testosterone undecylate	60%	40%	60%	40%	60%	40%
<i>p</i> -value ^a	0,6		0,26		0,47	

^a Chi-square test
Source: Research collection.

Table 4. Association analysis of hormonal and metabolic laboratory variables and the risk for sleep disorders, according to the different sleep scales.

Variable	<i>p-value</i> ^a		
	ESS (≥10 vs. < 10)	BQ (high risk vs. low risk)	STOP-Bang (high risk vs. low risk)
Hematocrit	0.6	0.6	0.4
Testosterone	0.4	0.2	0.1
LH	0.1	0.7	0.8
FSH	0.6	1	0.5
Estradiol	0.9	0.9	0.5
Total cholesterol	0.8	0.3	0.4
HDL-c	0.9	0.5	0.02
LDL-c	0.2	0.3	1
Triglycerides	0.3	0.3	0.8
Fasting blood glucose	0.08	0.3	1
Insulin	0.7	1	0.9
HOMA-IR	0.8	1	0.9

^a Mann-Whitney test
Source: Research collection.

Table 5. Association analysis of anthropometric and blood pressure variables and the risk for sleep disorders, according to the different sleep scales.

Variable	<i>p-value</i> ^a		
	ESS (≥10 vs. < 10)	BQ (high risk vs. low risk)	STOP-Bang (high risk vs. low risk)
Body mass index (BMI)	0.7	0.3	0.7
Waist circumference	0.5	0.2	0.4
Hip circumference	0.8	0.1	0.4
Neck circumference	0.6	0.7	0.6
Blood pressure			
Systolic	0.9	0.03	0.009
Diastolic	0.6	0.09	0.006
Body fat percentage (BFP)	0.7	0.2	0.8

^a Mann-Whitney test
Source: Research collection.

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