Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy

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Abstract

Background: The prevalence of hypogonadism in HIV-infected patients is still a matter of debate as there is no standardized consensual diagnostic method. In addition, the etiology and endocrine/metabolic implications of hypogonadism in this population remain controversial. This study aims to determine the prevalence of testosterone deficiency in a single-site hospital and to evaluate its association with potential risk factors, lipodystrophy, metabolic syndrome, and cardiovascular risk.

Methods: This study analyzed 245 HIV-infected men on combined antiretroviral therapy. Patients with low total testosterone (TT) levels (<2.8 ng/mL) and/or low calculated free testosterone (FT) levels (<6.5 ng/dL) were considered testosterone deficient. According to their LH and FSH levels, patients were classified as having hypogonadotropic or hypergonadotropic dysfunction. Other clinical, anthropometric, and analytic parameters were also collected and analyzed.

Results: The prevalence of testosterone deficiency in our population was 29.4 %. Among them, 56.9 % had hypogonadotropic dysfunction and 43.1 % presented with hypergonadotropic dysfunction. Patients with testosterone deficiency were older (p < 0.001), had higher HbA1c levels (p = 0.016) and higher systolic blood pressure (p = 0.007). Patients with lower testosterone levels had higher prevalence of isolated central fat accumulation (p = 0.015) and had higher median cardiovascular risk at 10 years as measured by the Framingham Risk Score (p = 0.004) and 10-Year ASCVD risk (p = 0.002).

Conclusions: The prevalence of testosterone deficiency in this HIV population is high, with hypogonadotropic dysfunction being responsible for the majority of cases. Testosterone deficiency might predispose to, or be involved, in the pathogenesis of HIV-associated lipodystrophy. Patients with low testosterone levels have higher cardiovascular risk, highlighting the importance of early diagnosis of this condition.

Keywords: HIV infection, Hypogonadism, Lipodystrophy, Cardiovascular risk

Background

Several endocrine abnormalities, like hypogonadism, thyroid dysfunction, adrenal insufficiency, and diabetes were described as more prevalent in HIV patients in the pre-combined antiretroviral therapy (cART) era. They were mainly associated to HIV-related opportunistic infections and advanced multi-organ failure [1–3]. With the advent of highly active antiretroviral therapy in the 1990s, some of these metabolic diseases have waned but hypogonadism and diabetes remain frequent endocrinopathies in these patients [4].

Gonadal dysfunction leads to sexual impairment, bone and muscle mass loss, changes in body fat mass, fatigue, cognitive impairment, depressed mood and anemia, affecting the overall quality of life [1, 5, 6]. After assessing testosterone levels, additional tests are needed to determine whether hypogonadism is primary (hypergonadotropic), or secondary (hypogonadotropic) [1, 7]. According to previous
studies in this population, hypogonadotropic dysfunction is responsible for the majority of cases, while primary disease is seen less frequently (occasionally, patients may have a combination of both). [8]. Overall, the causes of testosterone deficiency among HIV-infected men remain controversial, and there is lack of studies concerning the etiology and metabolic and endocrine consequences of this condition [1]. Additionally, the prevalence of testosterone deficiency in the HIV population is not well defined, ranging from 16 to 54 %, as slightly different criteria are adopted in different studies [4, 6, 9].

Therefore, this study aims to determine the prevalence of testosterone deficiency in a population of HIV-infected men under cART, as well as the prevalence of hypo- and hypergonadotropic dysfunction. Additionally, it aims to assess the association between testosterone deficiency and potential risk factors, and to evaluate the relationship between lower testosterone levels, lipodystrophy, metabolic syndrome and cardiovascular risk.

**Methods**

**Subjects**

Two-hundred and forty five adult men with serologically documented HIV infection on cART were evaluated at the Endocrinology Outpatient Department of Centro Hospitalar São João (a tertiary center in Northern Portugal). Patients were consecutively referred from the Infectious Diseases Clinic between January/2008 to December/2014, and were enrolled in the first visit.

Patients with acute or severe illness, previous treatment with androgen-derived agents and concurrent endocrinopathy (e.g. uncontrolled hypothyroidism, adrenal insufficiency, hyperprolactinemia, known pituitary disease) were excluded.

**Clinical assessment**

For all patients, the following information was collected, using a standardized protocol: age, time since HIV diagnosis, risk factor for HIV transmission, type and duration of cART exposure, CD4+ count, plasmatic HIV RNA load, smoking history (current, past, or never) and alcohol consumption (yes or no). HIV stages were defined using the Centers for Disease Control and Prevention’s (CDC) classification into asymptomatic (A), symptomatic (B) and AIDS (C) [10].

Height was measured in the standing position, using a wall stadiometer (Holtain Limited Crymych, Dyfed®), and body weight was measured using the TANITA (Tanita®, model TBF 300) scale. Circumferences of neck, waist, hip, thigh and arm were measured, as previously described, and blood pressure (BP) was measured using the current recommendations [11, 12].

Clinical lipodystrophy was assessed by both patient and practitioner, and was defined as peripheral lipoatrophy, with or without central fat accumulation [12]. Abdominal prominence (central obesity) was defined by a waist circumference >102 cm, as defined by NCEP-ATP III modified criteria for metabolic syndrome [13]. All clinical assessments were performed by the same observer. Patients were classified into four different groups: (1) No lipodystrophy (patients without clinical lipoatrophy and without abdominal prominence); (2) Isolated central fat accumulation (patients without clinical lipoatrophy and with abdominal prominence); (3) Isolated lipoatrophy (patients with clinical lipoatrophy and without abdominal prominence), and; (4) Mixed forms of lipodystrophy (patients with clinical lipoatrophy and with abdominal prominence) [11].

**Laboratory analysis**

An early morning venous blood sample was taken after a 12-hour overnight fast. All samples were analyzed at the central laboratory of our hospital. Total testosterone (TT), sex hormone binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were determined using Cobas e411 (Roche Diagnostic). Glycosylated hemoglobin (HbA1c) was measured by Variant II Turbo (Bio-Rad). To evaluate lipid profile, we measured total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDLC) and triglycerides levels, using Olympus AU5400 (Beckman Coulter). The CD4+ cell count (×10⁶ cell/L) and plasma HIV RNA loads were assessed by flow cytometry and by a quantitative reverse transcriptase polymerase chain reaction (Roche Diagnostics), respectively.

**Criteria for the definition of gonadal status**

Testosterone deficiency was defined based on a serum total testosterone (TT) below 2.8 ng/mL and/or a calculated free testosterone levels (FT), according to Vermeulen formula, below 6.5 pg/mL [14].

According to the normal ranges for serum LH and FSH, as defined by our central laboratory (1.7–8.3 mU/mL and 1.5–12.4 mU/mL, respectively), patients were assigned as having hypogonadotropic (low or normal LH and/ or FSH) or hypergonadotropic dysfunction (high LH and/ or FSH). Patients were classified as having high sex hormone-binding globulin (SHBG) according to the threshold value of 48.4 nmol/L.

**Metabolic syndrome definition and cardiovascular risk scores**

We defined Metabolic Syndrome (MS) according to the modified NCEP-ATP III criteria, requiring the presence of three of the following risk factors: (1) elevated waist circumference (>102 cm); (2) elevated triglycerides (≥150 mg/dL or specific treatment); (3) reduced HDL-C levels (<40 mg/dL), (4) elevated blood pressure (>130/85 mmHg or treatment with anti-hypertensive drugs),
and; (5) elevated fasting glucose (≥100 mg/dL or use of glucose-lowering drugs) [13].

The cardiovascular disease (CVD) risk at 10 years was measured by the Framingham Risk Score (FRS), using a sex-specific algorithm that incorporates age, treated, and untreated systolic blood pressure, HDL-C, total cholesterol, glucose, and smoking status [15]. Based on the Adult Treatment Panel III (ATP III) guidelines, individuals were stratified into four risk categories: (1) Low risk (0–1 CVD risk factors); (2) moderate risk (≥2 CVD risk factors and a 10-year CVD risk <10 %); (3) moderately high risk (≥2 CVD risk factors and a 10-year CVD risk 10–20 %), and; (4) high risk (CHD or CHD equivalent or ≥2 CVD risk factors and a 10-year CVD risk >20 %) [16].

The 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated based on the American College of Cardiology (ACC)/American Heart Association’s (AHA) guidelines. For all patients, we used a sex, ethnic group and age-specific multivariable risk factor algorithm that incorporates total cholesterol, HDL-C, untreated systolic blood pressure, diabetes history, and smoking status [17].

Statistical analysis

Categorical variables were presented as absolute frequencies and percentages, and were analyzed using Chi-square or Fisher’s exact test. Continuous variables were presented as medians and interquartile ranges, and were analyzed using the Mann-Whitney U test. P values <0.05 were considered to be statistically significant. All statistical analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).

Results

A total of 245 HIV-infected males on cART were evaluated, and 29.4 % were found to have testosterone deficiency, with a median of TT and calculated FT of 2.6 ng/mL and 5.2 ng/dL, respectively. Among the patients with reduced TT, 50 % had high SHBG levels.

In the group of patients with testosterone deficiency, 56.9 % had hypogonadotropic and 43.1 % had hypergonadotropic dysfunction. When different clinical, anthropometric and analytic variables were analyzed regarding these two categories of testosterone deficiency, patients with elevated gonadotrophins presented a higher frequency of NRTI use (100 % vs. 86.7 %; p = 0.028) and lower CD4+ counts (336.0 vs. 449.0; p = 0.030). No other differences were found between the two groups of patients.

The baseline characteristics of our study population are shown in Table 1. Patients with testosterone deficiency were older than the remainder (median age of 51.5 versus
to avoid false negatives that would possible occur if only TT levels had been used. Accordingly, if only serum TT had been used, some patients with low testosterone levels would have been missed as 50 % of them had high SHBG levels [14, 21].

Regarding the categories of testosterone deficiency, our results shows that hypogonadotropic dysfunction was responsible for the majority of cases. This is in accordance with several studies that report a progressive change in the etiology of testosterone deficiency in HIV-infected patients. Publications in the pre-cART era reported higher prevalences of gonadal dysfunction caused by direct involvement by the virus with a reduction in the Leydig cell number [22]. Recent investigations, after the appearance of more effective therapy, showed a relatively higher preponderance of secondary dysfunction [6]. Several different mechanisms have been suggested to explain the effect on the hypothalamic-pituitary-gonadal (HPG) axis, including poor health status, undernutrition, frailty, anti-retroviral drugs, the virus per se, opportunistic infections and increased visceral adiposity [8].

Consistently with other studies, the presented data shows that the prevalence of testosterone deficiency increases with age, as it happens in the general population. However, there was no significant impact of the HIV transmission risk factor and sexual orientation on testosterone levels, confirming the findings of other groups [1]. With regards to the antiretroviral agents, our study did not find any difference between patients with low testosterone levels and the remaining ones among the five studied pharmacologic groups. In fact, previous studies show conflicting results in this area [1, 7, 18].

We have shown that 18.1 % of patients with testosterone deficiency presented visceral obesity (as measured by waist circumference >102 cm), contrasting to 7.5 % of eugonadal individuals. The lipodystrophy syndrome, which has a reported prevalence of 41 % in HIV-infected patients, is a well-known adverse effect of cART. It comprises fat redistribution abnormalities, insulin resistance and dyslipidemia [7, 23]. However, the impact of cART on the HPG axis is still not completely understood, and little is known about the influence of sex hormone levels on the development of lipodystrophy [23]. Testosterone is one of the major determinants of regional distribution of fat and body composition, favoring the accumulation of visceral fat. The underlying pathophysiological mechanisms include an increase in tissue sensitivity to glucocorticoids, reduction of adipokines, and a reduction of peroxisome proliferator-activated receptor (PPAR-γ) activity [24]. Testosterone role in insulin sensitivity in HIV-lipodystrophy has also been proposed since several studies have shown that low levels of serum testosterone correlate not only with central fat accumulation but also with higher insulin levels [7].
Table 2 Participants clinical characteristics according to the presence of testosterone deficiency

|                                | Testosterone deficiency (n = 72) | Without testosterone deficiency (n = 173) | p value |
|--------------------------------|----------------------------------|-----------------------------------------|---------|
| Weight [kg, median (IQR)]      | 76.3 (25.9)                      | 71.3 (16.2)                             | 0.857a  |
| Height [cm, median (IQR)]      | 171.0 (8.0)                      | 169.0 (7.5)                             | 0.204a  |
| BMI [kg/m², median (IQR)]      | 26.5 (16.8)                      | 25.2 (5.4)                              | 0.160a  |
| Underweight [n (%)]            | 5 (7.0)                          | 6 (3.6)                                 | 0.028b/0.155c |
| Normal weight [n (%)]          | 26 (36.3)                        | 78 (46.2)                               |         |
| Overweight [n (%)]             | 23 (32.4)                        | 67 (39.6)                               |         |
| Obesity [n (%)]                | 17 (23.9)                        | 18 (10.7)                               |         |
| Neck circumference [cm, median (IQR)] | 40.0 (4.8)                   | 39.0 (3.0)                              | 0.196a  |
| Upper-arm circumference [cm, median (IQR)] | 28.3 (3.8)                  | 28.0 (3.8)                              | 0.197a  |
| Abdominal circumference [cm, median (IQR)] | 98.0 (13.8)                | 93.0 (8.6)                              | 0.492a  |
| Waist circumference [cm, median (IQR)] | 99.5 (19.8)                  | 93.0 (13.5)                             | 0.030a  |
| Hip circumference [cm, median (IQR)] | 47.0 (6.0)                    | 47.5 (6.0)                              | 0.906a  |
| Metabolic syndrome [n (%)]     | 33 (45.8)                        | 69 (39.9)                               | 0.390b  |
| Blood pressure [n (%)]         | 30 (41.7)                        | 69 (40.1 %)                             | 0.822b  |
| Systolic blood pressure [median (IQR)] | 133.5 (40.0)                 | 130.0 (30.0)                            | 0.007b  |
| Diastolic blood pressure [median (IQR)] | 79.0 (25.0)                  | 80.0 (15.0)                             | 0.756a  |
| Smoothing history [n (%)]      |                                 |                                         |         |
| Current                        | 21 (30.4)                        | 72 (42.6)                               | 0.127b  |
| Former                         | 25 (36.2)                        | 42 (24.9)                               |         |
| Never                          | 23 (33.3)                        | 55 (32.5)                               |         |
| Alcohol consumption [n (%)]    | 41 (59.4)                        | 77 (45.6)                               | 0.052b  |
| Total cholesterol [mg/dL, median (IQR)] | 210.0 (69.0)               | 221.0 (70.5)                            | 0.668a  |
| LDL cholesterol [mg/dL, median (IQR)] | 129.0 (37.0)                | 129.0 (72.8)                            | 0.573a  |
| HDL cholesterol [mg/dL, median (IQR)] | 43.5 (13.3)                   | 42.5 (13.3)                             | 0.125a  |
| Triglycerides [mg/dL, median (IQR)] | 215.0 (215.3)                | 218.0 (162.0)                           | 0.631a  |
| HbA1c [% median (IQR)]         | 5.5 (1.7)                        | 5.3 (1.0)                               | 0.016a  |
| Total testosterone [ng/mL, median (IQR)] | 2.5 (2.6)                    | 5.9 (2.7)                               | <0.001a |
| Free testosterone [ng/dL, median (IQR)] | 5.2 (1.5)                    | 9.1 (3.6)                               | <0.001a |
| SHBG [nmol/L, median (IQR)]    | 35.2 (44.6)                      | 46.6 (29.6)                             | 0.083a  |
| LH [mIU/mL, median (IQR)]      | 5.0 (4.9)                        | 5.2 (3.2)                               | 0.001a  |
| FSH [mIU/mL, median (IQR)]     | 6.7 (7.1)                        | 5.1 (4.1)                               | <0.001a |
| FRS [median (IQR)]             | 13.0 (5.0)                       | 12.0 (6.0)                              | 0.004a  |
| 10-Year ASCVD risk [% median (IQR)] | 7.1 (6.5)                     | 6.8 (8.3)                               | 0.002a  |
| Lifetime ASCVD risk [n (%)]    |                                 |                                         |         |
| <40 %                          | 4 (10.0)                         | 11 (8.0)                                | 0.789b  |
| 40–50 %                        | 22 (55.0)                        | 84 (60.9)                               |         |
| >50 %                          | 14 (35.0)                        | 43 (31.2)                               |         |
| Lipodistrophry [n (%)]         | 39 (56.5)                        | 96 (58.5)                               | 0.776b  |
| Waist circumference [cm, median (IQR)] | 23 (31.9)                   | 30 (17.3)                               | 0.011b  |
| No lipodistrophry [n (%)]      | 20 (27.8)                        | 59 (34.3)                               | 0.321b  |
HIV-infected patients also present an increased cardiovascular risk when compared with the general population. The pathogenesis of CVD in these patients is complex, and several factors appear to be involved, including androgen dysfunction [7, 25]. Low testosterone levels are independently associated with cardiovascular risk and are independent predictors of mortality [19, 26]. Accordingly, in our study, HIV patients with lower testosterone levels had a significantly higher 10-year risk of coronary heart disease, as measured by the FRS and 10-Year ASCVD. We could hypothesize that men with testosterone deficiency, besides being older, are at additional CV risk due to the higher frequency of hyperglycemia, abdominal obesity and hypertension as described in our results. Regan et al. compared the proportion of HIV patients with high predicted 10-year CVD risk using the FRS versus the ASCVD risk prediction algorithm [27]. The authors reported that the ASCVD algorithm classified a larger proportion of HIV patients as high-risk, compared to the FRS. This is consistent with our results, since a higher percentage of individuals were classified as having a high-risk by the ASCVD algorithm, independently of their testosterone status. Nevertheless, no significant differences were found in the lifetime risk of cardiovascular disease. This discrepancy can possibly be explained by the fact that only patients aged between 20 and 59 years-old could be included in this score. Regardless, we should mention that both the FRS and ASCVD appear to underestimate the actual risk of events, as reported by Thompson-Paul et al. [28]. Therefore, risk assessment remains reliant on the use of traditional risk factors, despite their inherent limitations. To better estimate CVD risk, different models including additional HIV-specific risk factors, such as immunologic or virologic status, may need to be considered [25, 28].

The prevalence of testosterone deficiency in HIV-infected men is high, with hypogonadotropic dysfunction being responsible for the majority of cases. Patients with lower testosterone levels were older, had poorer glycemic control, higher systolic blood pressure and increased waist circumference. Our results corroborate the hypothesis that testosterone deficiency may predispose or might be involved in the pathogenesis of HIV-associated lipodystrophy. This has a significant clinical impact, since both conditions are common in this population and are associated with a negative impact on the quality of life and with poor adhesion to therapy. Additionally, this study suggests that patients with lower testosterone levels have higher cardiovascular risk scores, highlighting the importance of early diagnosis of this condition.

**Conclusions**

The prevalence of testosterone deficiency in HIV-infected men is high, with hypogonadotropic dysfunction being responsible for the majority of cases. Patients with lower testosterone levels were older, had poorer glycemic control, higher systolic blood pressure and increased waist circumference. Our results corroborate the hypothesis that testosterone deficiency may predispose or might be involved in the pathogenesis of HIV-associated lipodystrophy. This has a significant clinical impact, since both conditions are common in this population and are associated with a negative impact on the quality of life and with poor adhesion to therapy. Additionally, this study suggests that patients with lower testosterone levels have higher cardiovascular risk scores, highlighting the importance of early diagnosis of this condition.

**Abbreviations**

ACC: American college of cardiology; AHA: American heart association; AIDS: Acquired Immune Deficiency Syndrome; ASCVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; cART: Combined antiretroviral therapy; CDC: Centers for Disease Control and Prevention; FI: Fusion inhibitor; FRS: Framingham risk score; FSH: Follicle stimulating hormone; FRS: Framingham risk score; FSH: Follicle stimulating hormone; FT: Free testosterone; HbA1c: Glycosylated hemoglobin; HDL: High density lipoprotein; HIV: Human immunodeficiency virus; HPG: Hypothalamic-pituitary-gonadal; IDF: International diabetes federation; II: Integrase inhibitor; LDL: Low density lipoprotein; LH: Luteinizing hormone; MS: Metabolic syndrome; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; SHBG: Sex hormone binding globulin; TT: Total testosterone

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**Availability of data and materials**

The data that support the findings of this study are available on request from the corresponding author [ARG]. The data are not publicly available.
because they contain information that could compromise research participant privacy/consent.

Authors’ contributions
ARG conceived the study, participated in its design, in the acquisition of data and drafted the manuscript; AS and FF participated in the acquisition of data; BSP drafted the manuscript; All authors read and approved the final manuscript.

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

Consent for publication
Not applicable.

Ethics approval and consent to participate
All patients provided written informed consent and the study protocol was approved by the São João Hospital’s Ethics Committee for Health.

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