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Age-related testosterone decline in a Brazilian cohort of healthy military men

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ABSTRACT

Introduction: Androgen decline in the aging man has become a topic of increasing clinical relevance worldwide, as the reduction in testosterone levels has been reported to be accompanied by loss of muscle mass, accumulation of central adiposity, impaired mobility and increase risk of bone fractures. Although well-established in studies conducted in developed countries, progressive decline in serum testosterone levels with age has been poorly investigated in Brazil.
Aim: To determine the pattern of blood testosterone concentrations decline with age in a cohort of Brazilian healthy military men.
Materials and Methods: We retrospectively reviewed data on serum testosterone measurements of healthy individuals that had undergone a routine check-up at the Military Biology Institute. Blood samples were obtained early in the morning, and total testosterone concentration was determined using a commercial chemoluminescent immunoassay. Mean values were analyzed in five age groups: ≤ 40, 41 to 50, 51 to 60, 61 to 70, and > 70 years.
Main Outcome Measure: Mean total testosterone levels.
Results: 1,623 subjects were included in the analysis; mean age was 57 years (24 to 87), and mean testosterone level was 575.5 ng/dL (25.0 to 1308.0 ng/dL). The evaluation of age-related changes in total testosterone levels revealed a progressive reduction in serum levels of this hormone with increasing age. Testosterone levels below 300 ng/dL were reported in 321 participants, a prevalence of nearly 20% in the study population.
Conclusion: In agreement with other findings, a reduction of total testosterone levels with age was reported for healthy Brazilian men.

Key words: *testosterone; male; deficiency; epidemiological studies; cohort studies*
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INTRODUCTION

Over the last decades, an increase in life expectancy has been observed worldwide (1). In addition, population projections indicate that the world population will experience a marked increase in the proportion of individuals older than 65 years. According to the United Nations, the percentage of the world's population over 60 is expected to nearly double between 2005 and 2050 (2). In this context, projections for the Brazilian population estimate an increase in the number of men older than 60 years, from 9 million (representing 9% of the total country population) to 30 million (13%), between 2010 and 2020 (3). Despite the fact that males do not live as long as females, the health of aged men has been studied to a much lesser extent than that of postmenopausal women. Thus, growing attention is being devoted to health disorders in aging men.

Aging in men is associated with impaired mobility, accumulation of central adiposity, decreased lean body and muscle mass, strength, and bone mineral density, as well as increased body fat (4), abnormalities that are also present in non-elderly hypogonadal men. Unlike women, who experience a dramatic change in sex-hormone profile during menopause (5), age-related changes in reproductive hormones occur gradually throughout the years of life in men (6,7). As the alterations in hormonal status are subtle, the characterization of age-normal endocrine profile is particularly difficult in males.

It is well-established that after the fourth or fifth decade of life, men undergo a gradual shift in the levels of important sex hormones, with a rise in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex-hormone-binding globulin (SHBG), contrasting with a decline in testosterone and dehydroepiandrosterone (DHEA) (8-11). It has been estimated that from the age 19, circulating testosterone declines at an average rate of 1% per year of life, or 100 ng/dL (4,7,8).

Several age-related phenomena such as decrease in muscle strength and mass, decline in virility and sexual activity, and impairment of glucose metabolism have been associated with a reduction in testicular function in aging men (12). The extent to which declining testosterone levels may influence age-related deteriorations is not completely defined. In addition, androgen deficiency in the aging male (ADAM) is characterized by the presence of a group of signs and symptoms and a significant decline in the production of hormones, most importantly testosterone.

Age-related decline in testosterone levels has been demonstrated by several cross-sectional and longitudinal studies conducted in developed countries (4,11). However, data on the androgen profile of aging men are scarce for Brazil.

Aim

The aim of the present study was to investigate the age-related decline of total testosterone levels in healthy Brazilian men in military activity.

MATERIALS AND METHODS

Study design

In this retrospective study, data on testosterone levels of healthy military subjects were reviewed. Blood samples were collected from January 2009 to September 2009 at the Military Biology Institute ("Instituto de Biologia do Exército" - IBEX), located in Rio de Janeiro, Brazil, as part of a routine health check-up that was mandatory for military individuals in activity or retired at that time. The study was designed to collect demographic and laboratory parameters of healthy men, age 18 or older, in activity at the military service or retired. All individuals with available hormone measurements were included.

The patients were not on testosterone replacement therapy. They were not taking medications that affect testosterone level, such as clomid or HCG injections, nor were they taking antiandrogens such as cimitidine, Aldactone, etc. They had not undergone previous surgery e.g. orchiectomy, nor had they received chemotherapy or radiation on the testis. They did not have chronic liver disease or liver cell failure, nor did they suffer from morbid obesity, DM, or chronic illness.

Laboratory measurements and statistical analysis

Blood samples were obtained early in the morning, between 7:00 and 09:30 AM, and analyzed at the IBEX laboratory. Serum was immediately separated after blood collection and samples were stored at -80°C. Total testosterone level was measured using a commercial chemoluminescent immunoassay, with an analytical sensitivity of 300 to 1000 ng/dL. Data collected from each subject included age and mean total testosterone levels. Laboratory testosterone levels compatible with hypogonadism were defined as < 300 ng/dL, based on the guidelines for ADAM of the Brazilian Society of Urology.

Participants' total testosterone levels were used for analysis, and mean values were analyzed

regarding the age groups. For this purpose, subjects were divided in the following age groups: ≤ 40, 41 to 50, 51 to 60, 61 to 70, and > 70 years.

RESULTS

Sample characteristics

A total of 1623 healthy subjects were evaluated in the present study. Demographic and laboratory data of all individuals included in the analysis are summarized in Table-1. The mean age was 57 years, ranging from 24 to 87 years. Mean total testosterone level was 575.5 ng/dL, ranging from 25.0 to 1308.0 ng/dL. Concerning the distribution of participants according to different age groups, 13.6% were ≤ 40 years, whereas the majority of subjects were older than 50 years, as shown in Table-2.

Testosterone measurements according to age

In order to evaluate age-related changes in total testosterone levels, the concentration of this hormone was analyzed in the different age groups, as shown in Figure-1. In this regard, a progressive reduction in serum total testosterone levels was observed across age groups, with the mean testosterone value observed for younger men (821.1 ng/dL; age group ≤ 40 years) being almost twice as high as the levels found for individuals belonging to the older age group (436.6 ng/dL; age group > 70 years).

Figure-2 shows the distribution of participants according to the mean testosterone level groups. Although the study sample consisted of apparently healthy individuals, 0.8% of the subjects had testosterone levels ≤ 100 ng/dL, 3.6%

Table 1 *- Characteristics of the 1,623 participants included in the analysis.*

Characteristics	Value
Age (years)	
Mean	57.0
Range	24 to 87
Total testosterone levels (ng/dL)	
Mean	575.5
Range	25.0 to 1308.0

Table 2 *- Distribution of subjects according to age groups.*

Age group (years)	Number of subjects (%)
≤ 40	221 (13.6)
41 to 50	312 (19.2)
51 to 60	448 (27.6)
61 to 70	512 (31.6)
> 70	130 (8.0)
Total	**1623**

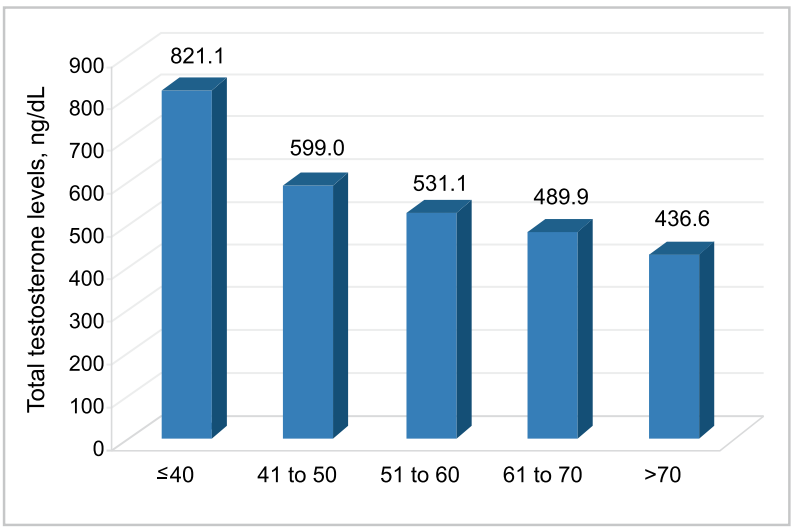

Figure 1 - *Age groups.*

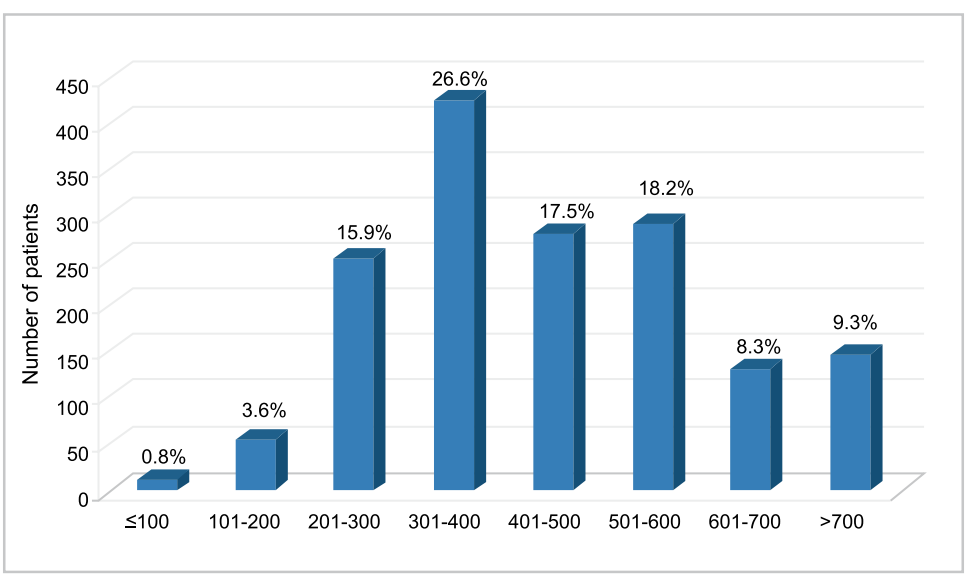

Figure 2 - *Testosterone level groups. (ng/ dL)*

had mean levels between 101 and 200 ng/dL, and 15.9% of participants had a mean concentration of this hormone in the range of 201 and 300 ng/dL. Testosterone levels below 300 ng/dL, compatible with hypogonadism, were reported for 321 participants, representing a prevalence of 19.8%.

DISCUSSION

In this study, the hormone profile of a cohort of healthy Brazilian men in military activity was investigated. We found, in agreement with the current literature, a decline in total testosterone levels associated with male aging.

Testosterone is largely bound to plasma proteins, with only 1-2% being free, 40-50% being bound to albumin, and the rest being strongly bound to SHBG (12). Plasma concentrations of this androgen show circadian variations with highest values in the morning, and serum free testosterone and albumin-bound testosterone represent the fractions readily available for biological action (13). As testosterone exerts a wide

role in male physiology, controlling gonadal function and altering libido, mood, aggressive behavior, liver function, muscle mass, bone formation, lipid metabolism, erythropoiesis, and immune system, its decline is of particular concern in the management of men's health (14).

In men, a progressive decline in testosterone levels with age has been suggested in several cross-sectional and longitudinal studies, with an average rate of decline of 1% to 2% per year after the age of 40. In addition, data indicate that a significant percentage (20%) of men over 60 years exhibit serum levels below the lower limits of young men. Moreover, at the age of 75 years, mean total serum testosterone level was found to be about two-thirds of the levels at age 25, whereas the mean values of free and bioavailable testosterone serum levels are only about half of those in young men, as demonstrated in different studies (4,8,15,16). In addition to changes in total testosterone, a decline in free and bioavailable testosterone has been demonstrated in cross-sectional studies.

Morley et al. demonstrated in a longitudinal study, conducted in older healthy men (61 to 87 years at entry), that testosterone levels decline with age, with an average rate of decrement of 110 ng/dL for every decade of life. In addition, LH and FSH were found to increase in older men (7). Longitudinal changes in androgen hormones have been also reported in more recent studies. In this regard, using longitudinal data from the Massachusetts Male Aging Study (MMAS), which included at baseline a large cohort of men aged 40 to 70 years. Feldman et al. reported a rate of decline in total testosterone with age of 0.8% per year, and a declining rate of 2.0% per year for both free and albumin-bound testosterone. Of note, in this study the rate of decline was similar in apparently healthy men and in those reporting obesity, chronic illness, alcoholism, prostate problems, or prescription medication (8). In another longitudinal study, Liu et al found that the decline in serum testosterone and increase in SHBG with age were comparable across two separate regional Australian populations (11). The influence of age in the testosterone levels was confirmed by Clapauch et al. in a study conducted in a cohort of 216 Brazilian men aged 52-84 years (17). In this study, a significant difference in the level of total testosterone was observed between patients < 60 years versus those aged 70 years or more. In addition to total testosterone, a significant difference in free testosterone levels was also observed between these two age groups (17).

In young patients, severe testosterone deficiency (170 to 230 ng/dL) is typified by a familiar array of symptoms, whereas in aging men, symptoms are non-specific and usually mimicked by other disorders. In older men, the testosterone level below which symptoms of androgen deficiency emerge remains unclear (18,19).

Adult hypogonadism can be caused by abnormalities of the hypothalamic-pituitary-testicular axis at the testicular level causing primary testicular failure, or by disturbances of the hypothalamus or pituitary resulting in secondary testicular impairment. Adult hypogonadism is manifested by infertility, alterations in behavior, low sexual desire, erectile dysfunction, depression, fatigue, loss of sense of well-being, and some secondary sexual characteristics (18,20). Obesity, severe systemic illness and medications are among the commonly acquired causes of adult-onset hypogonadism, and defects in both testicular and hypothalamic-pituitary function may underlie the age-associated reductions in testosterone levels demonstrated in cross-sectional and longitudinal studies. In our sample, testosterone levels compatible with hypogonadism (< 300 ng/dL) were observed in almost 20% of the participants. Although this concentration is not diagnostic of hypogonadism per se, it may indicate the need of preliminary screening for free or bioavailable testosterone levels below references values. Recently, Wu et al. found, in a systematic investigation of a large cohort of aging men from the general population, that late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone concentration lower than 11 nmol per liter (320 ng/dL) and a free testosterone level of less than 220 pmol per litre (64 pg/mL) (18).

Although an improvement in signs and symptoms of testosterone deficiency in younger adult men is supported by some studies, the treatment of testosterone deficiency in the older man is more controversial. Recently, an update of the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men was published,

recommending that the diagnosis of androgen deficiency should be restricted to men with consistent symptoms and signs and low serum testosterone levels (21). In this regard, the analysis of morning total testosterone levels is indicated as the initial diagnostic test, which should be confirmed in a repeated measure (21). In this guideline, testosterone therapy is recommended for men with symptomatic deficiency of androgens, aiming to maintain secondary sex characteristics and to improve sexual function, well being, and bone density, with the exception of patients with breast or prostate cancer, and other health conditions not mentioned here. Importantly, there is a recommendation against androgen deficiency screening in the general population. Regarding the elderly population, for older men with consistent low testosterone levels and clear clinical symptoms of androgen deficiency, testosterone therapy should be considered by clinicians on an individualized basis, considering the risks and benefits of this therapeutic approach (21). The effects of testosterone administration on body composition, bone density and muscle strength in middle-aged men were evaluated in a meta-analysis of randomized controlled trials. Testosterone treatment promoted reduction of body fat, increase in fat-free mass, with no change in body weight. In addition, testosterone also reduced total cholesterol, with no change in low density lipoprotein-cholesterol (22). Despite some good results, whether testosterone therapy is beneficial for aging men in preventing or delaying some aspects of ageing is still controversial, and more studies are needed (23,24).

CONCLUSIONS

In agreement with other studies we found that total testosterone levels decline with age in healthy Brazilian men. A high prevalence of testosterone levels below 300 ng/dL, compatible with laboratory hypogonadism, was found in this cohort.

CONFLICT OF INTEREST

None declared.

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