ORIGINAL ARTICLE

# Effects of aging and the body mass index on male sex hormones: a cross-sectional study in 701 Brazilian men

## Efeitos do envelhecimento e do índice de massa corporal sobre os hormônios sexuais masculinos: um estudo transversal em 701 homens brasileiros

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### ABSTRACT

**Background:** Some studies indicated that body mass index (BMI) is inversely proportional to serum testosterone concentrations in men. **Purposes:** This study aimed to analyze the effects of aging and obesity on total testosterone (TT), free testosterone (FT), bioavailable testosterone (BT), luteinizing hormone (LH), and sex hormone-binding globulin (SHBG) levels. **Methods:** A cross-sectional study was performed to assess the clinical and laboratory profiles of 701 patients treated at a private urology clinic in Ponta Grossa, Brazil, from January 2016 to December 2018. **Results:** Patients' age ranged from 16 to 88 years (mean, 56.9 ± 13.62 years). Age did not significantly influence serum TT concentrations, except compared to patients aged >70 years. However, changes were observed in FT and BT ($p < 0.05$). The mean SHBG increased with age ($p < 0.05$). A tendency toward LH elevation was observed in older patients, but it was not statistically significant. An inverse proportional relationship between TT, FT, and BT and the testosterone deficiency rate (TT < 300 ng/dL) was observed within BMI groups ($p < 0.05$). The testosterone deficiency rate was 21.5% in individuals with normal BMI, 29% in overweight individuals, and 37% in obese individuals. **Conclusions:** Aging affected the testosterone concentrations in men and became increasingly evident using FT and BT instead of TT. SHBG increased with age. Obesity was associated with a decrease in TT, FT, and BT but also increased the rate of hypogonadism.


**Keywords:** Male aging, Sex hormone binding globulin, Pituitary luteinizing hormone, Hypogonadism.


### RESUMO

**Fundamentos:** Alguns estudos indicam que o índice de massa corporal (IMC) é inversamente proporcional à concentração de testosterona sérica em homens. **Objetivos:** O objetivo deste estudo é analisar o efeito do envelhecimento e da obesidade na testosterona biodisponível total e livre, bem como nos níveis de hormônio luteinizante e globulina ligadora de hormônio sexual. **Métodos**: Foi realizado um estudo transversal abordando o perfil clínico e laboratorial de 701 pacientes atendidos em uma clínica privada de urologia em Ponta Grossa, Brasil, de janeiro de 2016 a dezembro de 2018. **Resultados**: A idade dos pacientes variou de 16 a 88 anos (média de 56,9 ± 13,62 anos). A idade não influenciou significativamente as concentrações séricas de testosterona total, exceto quando comparada a pacientes com mais de 70 anos. No entanto, foi observada diferença na testosterona livre e biodisponível ($p < 0,05$). A média de globulina de ligação aos hormônios sexuais aumentou com a idade ($p < 0,05$). Embora uma tendência à elevação da luteinização tenha sido observada em pacientes mais idosos, ela não foi significativa. Relação inversa entre testosterona total, livre e biodisponível e taxa de deficiência de testosterona (testosterona total <300 ng / dL) foi observada dentro dos grupos de índice de massa corporal ($p < 0,05$). A taxa de deficiência de testosterona em indivíduos com índice de massa corporal normal foi de 21,5%, indivíduos com sobrepeso foi de 29% e em indivíduos com obesidade foi de 37%. **Conclusões:** O envelhecimento afetou a concentração de testosterona em homens, mais evidente ao avaliar testosterona livre e biodisponível em vez de testosterona total. A globulina de ligação aos hormônios sexuais aumentou com a idade. A obesidade foi associada à redução da testosterona total, livre e biodisponível e ao aumento da taxa de hipogonadismo.


**Palavras-chave:** Envelhecimento masculino, Globulina ligadora de hormônios sexuais, Hormônio luteinizante, Hipogonadismo.

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## ABBREVIATIONS LIST

BMI: body mass index
BT: bioavailable testosterone
FT: free testosterone
GnRH: gonadotropin releasing hormone
LH: luteinizing hormone
SHBG: sex hormone binding globulin
TT: total testosterone

## INTRODUCTION

As men grow older, testosterone production decreases, and serum concentrations drop (1,2). The circulating testosterone is between 95% and 97% binding to plasmatic proteins; most of it is connected to sex hormone-binding globulin (SHBG) and the rest to albumin. Only 2% to 5% of total testosterone (TT) remains free (3). The SHBG protein binds to high-affinity testosterone and does not provide disassociation and action on target tissues. In contrast, albumin binds to low-affinity testosterone and simplifies dissociation. Hence, the testosterone bound to albumin and free testosterone (FT) is those available to androgen action and referred to as bioavailable testosterone (BT) (1,3).

Testosterone secretion is stimulated by the hypothalamus by releasing the gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to produce luteinizing hormone (LH), hence stimulating testosterone production in the testicles (4). According to scientific literature, the average serum concentration in TT for younger adults is 650 ng/dL (2), considering a reliable gap ranging from 300 to 900 ng/dL. Patients older than 40 display an annual 1% decrease in these levels. Aging also brings an increase in the testosterone rate binding to SHBG and a decrease in FT (5). The decline in testosterone seen in aging men has clinical implications beyond the laboratory test of serum testosterone fractions (4). By decreasing the testosterone levels, men's health may be affected in areas such as loss of libido, depression, bone and muscle weakness, muscle mass reduction, erectile and ejaculatory dysfunction, and abdominal fat accumulation (2).

Some studies have indicated that body mass index (BMI) is inversely proportional to serum testosterone concentrations in men (6). Adipose tissue converts testosterone to estradiol. By increasing body fat, there is an increase in the testosterone release to a certain limit. After that, there is a reduction due to the adipokine and proinflammatory cytokine action, and insulin resistance increases (6). Few studies have investigated the relationship between obesity and serum testosterone concentrations, and it is controversial whether testosterone replacement therapy is beneficial to these patients (7). Low testosterone concentrations are associated with senility and overlap with various comorbidities (8); however, whether the comorbidities are related to the decrease in male hormone levels or are inherent to aging is unknown (9).

Therefore, this study aimed to evaluate the influence of age and BMI on serum androgen levels (TT, FT, BT, LH, and SHBG) in a Brazilian male population presenting to a primary medical care practice for routine evaluation.

## METHODS

### Study design and population

This study had a descriptive cross-sectional drawing and was approved in May 2018 by the research ethics committee under number CAAE 90036218.0.0000.0093. Patients' records that had been assisted at the private urology clinic in Ponta Grossa (Paraná State, Brazil) were analyzed from January 2016 to December 2018.

All patients with complete necessary data for the study were included. Patients who were replacing testosterone, patients with any neoplasia or severe disease, patients who were submitted to orchiectomy for any reason, and individuals evaluated for infertility with alterations on laboratory tests were excluded from this study. All other patients with complete data requested for the study, such as age, TT, albumin, SHBG, LH, weight, and height, were included in the sample group. These data were evaluated for their influence on age and BMI on the total free BT index as well as the age versus SHBG and age

versus LH. According to the American Urological Association (1), patients with hypogonadism with TT < 300 ng/dL were considered. FT and BT were calculated using the Free & Bioavailable Testosterone Calculator (10).

## Laboratory measurements

Albumin was measured by a colorimetric assay (Labquest–Labtest Diagnostic, MG, Brazil). TT and SHBG levels were determined by the electrochemiluminescence immunoassay method (Elecsys 2010; Roche Diagnostics, Indianapolis, IN, USA). FT and BT values were calculated from TT, SHBG, and albumin using a valid method (10). The normal ranges for the examinations considered in the study were as follows: albumin (3.5–5.5 g/dL), TT (280–800 ng/dL), FT (2.62–16.7 ng/dL), BT (131–682 ng/dL), and SHBG (13–71 nmol/L). All assays were performed in the same laboratory.

## Statistical analysis

Data were collected in frequency and contingency tables. To compare nominal data, Fisher's or chi-square test was used. To compare numerical data, the unpaired t-test and Mann–Whitney test were used. Data distribution was evaluated by the Shapiro–Wilks test, and the adopted significance was 5%.

# RESULTS

## Sample description

The characteristics of the studied sample are in **Table 1**. We studied 701 patients whose mean age was 56.9 ± 13.62 years old. For comparison purposes, the sample was divided into subsets according to the age range: 16 to 40, 41 to 50, 51 to 60, 61 to 70, and >70 years.

**Table 1**
Clinical and laboratory profile of men studied (n=701)

| Clinical data | Mean or frequence (%) |
|---|---|
| Age (years ± SD) | 56.9 ± 13.62 |
| Total Testosterone (ng/dL ± SD) | 398.5 ± 160.11 |
| Bioavailable Testosterone (ng/dL ± SD) | 177.5 ± 71.03 |
| Free Testosterone (ng/dL ± SD) | 7.3 ± 291 |
| SHBG(ng/dL ± SD) | 40.1 ± 21.61 |
| LH(ng/dL ± SD) | 6.0 ± 52 |
| Albumin (mg/dL ± SD) | 4.4 ± 0.78 |
| Height (cm ± SD) | 173 ± 6.5 |
| Weight (kg ± SD) | 85.2 ± 14.82 |
| BMI ($Kg/m^2$ ± SD) | 28.3 ± 4.3 |
| Normal weight (BMI = 16-24.9) | 22.3% |
| Overweight (BMI = 25-29.9) | 44.1% |
| Obesity grade I (BMI = 30-34.9) | 23.2% |
| Obesity grade II (BMI = 35-39.9) | 9.2% |
| Obesity grade III (BMI >=40) | 1.1% |
| Hypertension | 34.5% |
| Diabetes | 16.7% |
| Smoking (current) | 16.7% |
| Alcoholism (current) | 9.0% |

## Age and testosterone serum concentration

**Figure 1** displays the relationship between age and BMI over the average TT, FT, and BT. There was no significant difference (p = 0.56) in the total TT concentrations regarding the age range (**Figure 1A**), except for patients 51 to 60 years old who had the lowest TT values (371 ± 140.5 ng/dL), showing a statistical difference (p = 0.015) compared to patients 16 to 40 years old. Regarding

FT (**Figure 1B)** and BT (**Figure 1C**), there was a significant decrease (p < 0.0001) according to age. The average FT was 9.6 ± 3.56 ng/dL among the youngest individuals and 7.32 ± 2.91 ng/dL among the oldest individuals. The average BT was 236.8 ± 89.24 ng/dL among patients 16 to 40 years old and 177.8 ± 71.06 ng/dL among patients >70 years old (p < 0.0001).

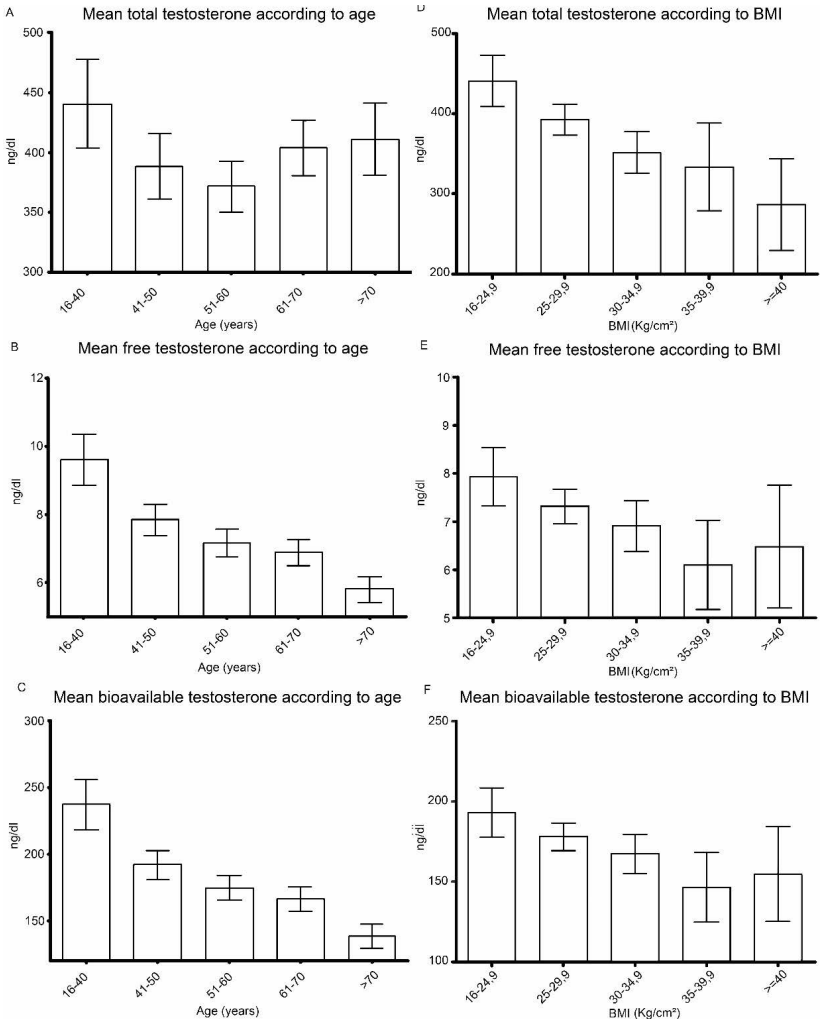


**Figure 1:** Relation between age and means of total testosterone (A), free testosterone (B), bioavailable testosterone (C). Relation between BMI and means of total testosterone (D), free testosterone (E) and bioavailable testosterone (F) in the sample studied.

Note: **Figure 1-A:** p = 0.16 comparing age and TT serum levels; except for the patients ranging from 51 to 60 years old who had the lowest values on TT (p = 0.015) when compared to 16-40 years old group.

**Figure 1-B and 1-C:** p<0.0001 comparing FT and BT serum levels according to the aging.

**Figure 1-D, 1-E and 1-F:** p<0.0001 comparing TT, FT and BD serum levels according to the BMI.

## BMI and testosterone serum concentration

Such analysis was achieved in 542 patients divided into five groups according to the BMI parameters established by the World Health Organization (11). Data are available in **Table 2**. BMI was correlated to the laboratory parameters of TT, FT, and BT (**Figure 1D–F**). A significant (p < 0.0001 in all parameters) decrease in TT, FT, and BT associated with an increase in BMI was observed. Additionally, a significant association was observed (p < 0.001) between hypogonadism presence (testosterone < 300 ng/dL) and BMI increase (**Figure 2C**).

**Table 2**

BMI and total, free and bioavailable testosterone in studied sample

| | BMI category | | | | |
|---|---|---|---|---|---|
| | Normal (n=121) | Overweight (n= 239) | Obesity I (n=126) | Obesity II (n=50) | Obesity III (n=6) |
| Total testosterone (ng/dL) (mean ± SD) | 440.5 ± 178.67 | 392.3 ±152.66 | 351.1 ± 146.21 | 333.4 ± 191.39 | 286.9 ± 162.15 |
| Free testosterone (ng/dL) (mean ± SD) | 7.9 ± 3.37 | 7.3 ±2.82 | 6.9 ± 2.99 | 6.1 ± 3.26 | 6.4 ± 1.21 |
| Bioavailable testosterone (ng/dL) (mean ± SD) | 193.0 ± 86.14 | 177.9 ± 68.96 | 167.2 ± 70.02 | 146.2 ± 76.39 | 154.6 ± 28.26 |

All the comparison between BMI normal *vs* obesity $p < 0.001$

## Age and SHBG and LH serum concentrations

The average SHBG was 40.1 ± 21.62 nmol/L. **Figure 2A** demonstrates how SHBG concentrations increased significantly with age ($p < 0.0001$). In relation to LH, there was no significant difference among the age ranges (**Figure 2B**). The average LH was 4.74 nmol/L, and there was no significant association between BMI and SHBG and LH serum concentrations.

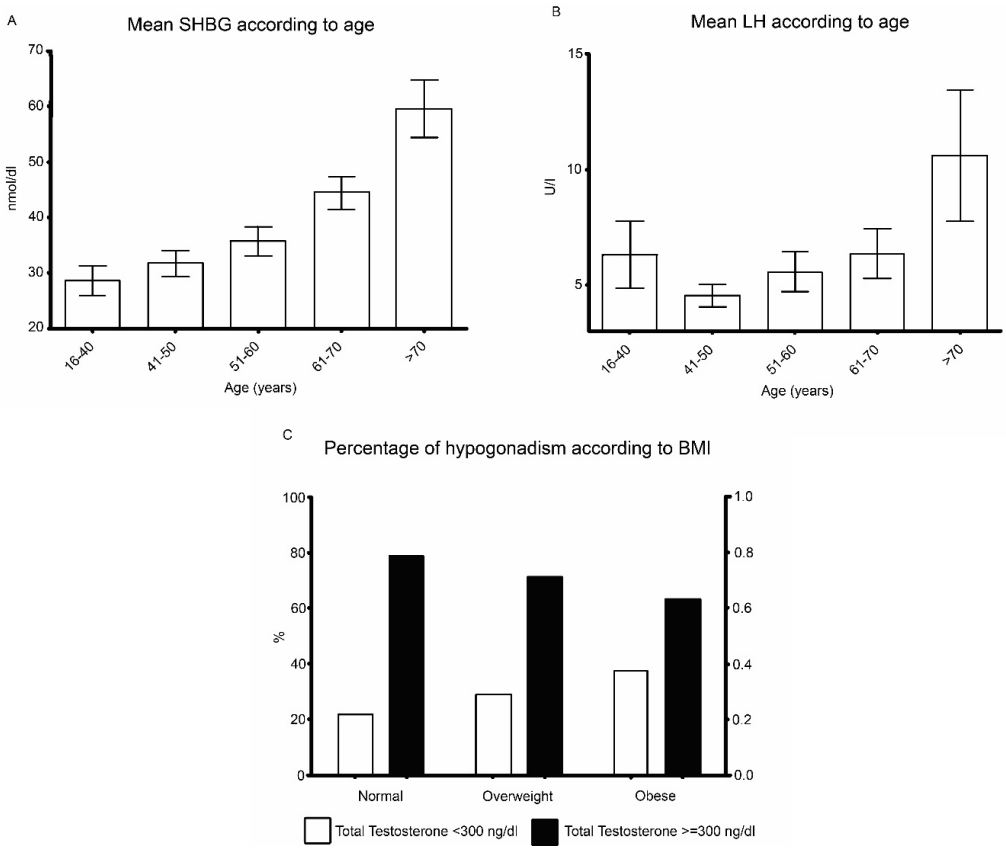


**Figure 2:** Relation between age and mean of SHBG (A) and LH (B). Relation between the percentage of patients with hypogonadism within BMI groups (C) in the sample studied.

Note: **Figure 2-A**: $p < 0.0001$ comparing SBHG serum levels according to the aging.

**Figure 2-B**: $p < 0.0001$ comparing LH serum levels according to the aging.

**Figure 2.C**: $p < 0.0001$ comparing presence of hypogonadism in according to BMI.

## DISCUSSION

TT measurement is highly useful in clinical practice to identify hypogonadism. However, analyzing only TT may not be enough, considering there is no significant decrease in TT with aging but with FT and BT, confirming previous data (5,12-16). It is important to consider a wider evaluation correlated to the clinical condition, age, and BMI for diagnosis and hypogonadism treatment.

Several dissertations have shown that TT concentrations do not decrease with aging (5,12-16). Fabbri *et al.* (12) only observed such findings in men >70 years, as also observed in this study. Deutschbein *et al.* (13) reported that using only TT to diagnose hypogonadism may not be enough to detect it, and FT and BT should be considered. Equally, Liu *et al.* (14), in a cross-sectional study, including 608 Chinese men >45 years old, also concluded that FT was more reliable in diagnosing hypogonadism than TT due to its more significant relationship with age. Mehta *et al.* (15) compared TT and FT to age and found a significant reduction in FT according to age. Fabbri *et al.* (12) studied 708 American men and women ages 30 to 96 years old for a decade and observed that BT decreased linearly with aging from both genders. Thus, as presented in this study, requesting FT and BT to diagnose hypogonadism is recommended.

As for SHBG, as observed in this study, there was a significant increase in the referred protein when aging, as demonstrated by other studies (16,17). Fabbri *et al.* (12) did not find a significant increase in SHBG compared to aging, and SHBG increase may decrease testosterone availability. Thus, it has to be considered, especially when TT values are on the limit (12).

This study observed no increase in LH with aging, and there was no significant difference among the age ranges, different from other studies (4,18,19). Golan *et al.* (4) stated that there is a reduction in pulsatility and a widening in GnRH and, consequently, a reduction in LH secretion. In contrast, others (18,19) described a positive relation between LH and age.

There was a significant relationship between obesity and decreased TT, FT, and BT levels (19-22). Wu *et al*. (20) described that TT, FT, and BT had a significant inverse correlation to BMI. Dhindsa *et al.* (21) noted that, in the United States, FT concentrations have declined due to BMI increase, besides noticing an SHBG increase in obese patients. Samipoor *et al.* (18) demonstrated the connection between hypogonadism and BMI increase. Pizarra (23) associated TT and BT low levels in men with a higher risk of obesity, type 2 diabetes, and metabolic syndrome. In contrast, a BMI increase may also lead to a serum testosterone decrease, as demonstrated in a study on European men (24). According to these authors, interventions to reduce BMI may increase serum testosterone in men. They realized that a BMI reduction from 30 to 25 g/cm$^2$ would result in an increase of 13% in serum testosterone (24). Ahima (25) verified that visceral fat tissues are associated with increased adipokines and cytokines (tumor necrosis factor-α and interleukin-6 and -8), causing an inflammatory condition that is local, generalized, and of low grade. Pelusi and Pasquali (26) found that these cytokines and adipokines may influence testosterone levels, directly interfering with the hypothalamus-pituitary-gonad axis control system. Other authors also observed that weight loss might contribute to an increase in FT levels (5,19,27). A meta-analysis about the effects of body weight loss on hormone levels implied a significant increase in TT and FT after weight loss (27).

The hypothalamus axis control system in elderly men suffers interference from a healthy lifestyle that may mitigate or revert the apparent decline in testosterone due to aging (19). Despite the myths, testosterone replacement may help reduce obesity (7,28).

Based on these data, it is crucial that, for Brazilian men's health, tools to avoid obesity collaborate to maintain adequate TT concentrations, indispensable for better life quality in every phase of adult life.

In conclusion, these findings indicate that aging is associated with decreased FT and BT levels. SHBG increases dramatically with aging, and there was no association between LH concentration and age. Regarding obesity, BMI increase leads to a significant reduction in TT, TL, and TB concentrations.

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**Statement of Ethics**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.This study was approved by the Committee of Ethics in Research (under protocol CAAE 90036218.0.0000.0093.

**Conflicts of interest/Competing interests**

None

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**Disclosure**

None

**Authors' contributions**

ALBS, ICLA, LFK, RJS and BPS conceived and carried out the study; RJS, BPS and RN organized and analyzed data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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