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The association between physiologic testosterone levels, lean mass, and fat mass in a nationally representative sample of men in the United States

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ABSTRACT

Testosterone deficiency leads to increased muscle loss with aging and increased fat mass. Supraphysiologic levels cause an increase in muscle mass and decrease in fat mass. The difference in lean and fat mass across physiologic levels of testosterone has been under examined in men.

Objective: Examine the association between physiologic testosterone levels with lean and fat mass.

Methods: Data from the 1999–2000 NHANES were used (n = 252 men; 18–85 yrs). Testosterone and SHBG values were obtained by a morning blood sample. Body composition was measured by DXA. Multivariable linear regression was used to compute unadjusted, minimally adjusted, and extended models of relative upper- and lower-body lean and fat mass.

Results: In the extended model, men with total testosterone levels in the highest 25% (4th quartile) had more lower-body lean mass (LBLM) (β = 22.1(%), 95%CI: 9.0, 35.3, p = 0.003) and upper-body lean mass (UBLM) (β = 5.6(%), 95%CI: 0.1, 11.2, p = 0.046), and less lower-body fat mass (LBFM) (β = −9.9(%), 95% CI: -17.7, −2.1, p = 0.016) and upper-body fat mass (UBFM) (β = −6.1(%), 95%CI: −10.1, −2.1, p = 0.005) than those in the 1st quartile. Men in the 3rd quartile had more LBLM (β = 14.2, 95%CI: 5.3, 23.1, p = 0.004), UBLM (β = 5.6, 95%CI: 2.0, 9.2, p = 0.004), and less LBFM (β = −9.7(%), 95%CI: −16.7, −2.7, p = 0.010) and UBFM (β = −4.7(%), 95%CI: −8.3, −1.2, p = 0.012) than those in the 1st quartile.

Conclusion: These findings suggest that, at physiologic levels, an association exists between higher levels of testosterone and favorable lean and fat measures.

1. Introduction

Testosterone is an androgen hormone produced, in men, primarily in the testes by the Leydig cells upon exposure to luteinizing hormone, and secondarily in the adrenal glands. It is carried in the blood as either free testosterone, or bound to albumin or sex hormone-binding globulin (SHBG). Both free testosterone and albumin-bound testosterone are bioavailable in the blood stream [16], whereas SHBG-bound testosterone is not available to the cells until it dissociates from this carrier protein. Under normal physiological conditions testosterone, among other actions, helps regulate muscle mass and strength [19]. Testosterone also contributes to the maintenance of lower levels of fat mass by its conversion to estradiol as shown by Finkelstein et al. in 2013. In that study, men were given an injection of goserelin acetate to suppress endogenous testosterone and estradiol, and subsequently given supplementary testosterone (placebo, 1.25 mg, 2.5 mg, 5.0 mg, or 10 mg); half of them were given anastrozole to suppress the conversion of testosterone to estradiol. Fat mass increased for both low and high testosterone groups, whereas the groups in which estradiol production was not blocked saw increases in fat mass only at the lowest levels (⩽2.5 mg) of testosterone supplementation [8].

Testosterone at supraphysiologic levels (e.g., >2000 ng·dl^{-1}) increases muscle size and strength independent of resistance exercise, as was found by Bhasin et al. in 1996. Following 10 weeks of weekly injections of testosterone enanthate, total testosterone levels increased from a baseline of 502 ng·dl^{-1} to 2828 ng·dl^{-1}, squatting strength increased 19%, and cross-sectional area of the

Abbreviations: UBLM, upper-body lean mass; UBFM, upper-body fat mass; LBLM, lower-body lean mass; LBFM, lower-body fat mass; SHBG, sex hormone-binding globulin; DXA, dual energy X-ray absorptiometry.

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quadriceps muscles increased in men performing no resistance exercise [3]. Low total testosterone is associated with increased fat mass [28], an increased loss of lean mass during aging [14], and in patients undergoing hemodialysis a decrease in muscle mass [12]. Low free testosterone is associated with a loss of muscle mass [33] in older (>60 years old) individuals. Total testosterone levels of 240–950 ng·dl^{-1} are considered normal for adult men according to the Mayo Clinic [34].

With age comes a gradual decline in testosterone production on the order of 1–2% per year, which in some men can lead to sexual dysfunction [10]. Lower testosterone levels are associated with a greater per year age-related decline in muscle mass in men, and this decline is greater in men with Type 2 diabetes [23]. Primary and secondary hypogonadism and other factors such as opioid and anabolic steroid use [2] can lead to low endogenous total testosterone. Concomitant to the age related decrease in total testosterone, there is an age related increase in SHBG [29], which can further reduce circulating levels of bioavailable testosterone. In men presenting with total testosterone levels $\leqslant$300 ng·dl^{-1}, testosterone replacement therapy (TRT) can be prescribed although there are controversies surrounding its use [27] given potential complications such as increased blood pressure, gynecomastia, and prostate cancer [21].

Although low levels of total testosterone and free testosterone are associated with increased fat mass and decreased lean body mass, and high levels are associated with increased muscle size and strength, whether or not a dose-response relationship exists between total testosterone and lean body mass within the normal physiologic range is unknown. Improving our understanding of this is important in order to determine if there are beneficial lean and fat mass adaptations due to circulating levels of testosterone that are on the high side of what is considered normal. Observing a potential dose-response relationship between normal range testosterone and lean/fat mass may identify individuals (e.g., those in the "low" normal range) who may be vulnerable to unfavorable levels of lean and fat mass, and who otherwise would not have been considered susceptible due to current diagnostic criteria. Therefore, the purpose of this study was to examine the potential dose-response of total testosterone within the normal physiologic range and lean body mass as well as fat mass in a nationally representative sample of U.S. men selected from the 1999–2000 National Health and Nutrition Examination Survey (NHANES).

2. Subjects and methods

2.1. Participants

Data was obtained from the 1999–2000 National Health and Nutrition Examination Survey (NHANES), which is an ongoing survey conducted by the United States Centers for Disease Control and Prevention. NHANES uses a complex, stratified, multistage, clustered probability design to select a representative sample of non-institutionalized United States civilians based on gender, race/ethnicity, and age. Survey protocols were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Board of the National Center for Health Statistics at the United States Centers for Disease Control and Prevention. All data used in the present investigation are publicly accessible via the CDC's website (http://www.csc.gov/nchs/nhanes/).

2.2. Testosterone

Testosterone values were selected for men completing the morning laboratory examination in order to better represent total testosterone levels due to diurnal variation in these hormones. A total of 4883 men participated in the 1999–2000 survey. There were 4562 men who participated in the laboratory examination, of whom 452 participated in the morning session from which testosterone values were measured via electrochemiluminescence immunoassay according to methods outlined in detail previously [18]. Coefficient of variation (CV) for testosterone measurement was 4.8%. Men who were younger than 18, had missing lean mass, fat mass or covariate data, or who fell outside of the normal ranges of testosterone (240–950 ng·dl^{-1}) were excluded, leaving 252 for final analysis, which constituted a weighted sample of 10,926,929 American adult men. Free and bioavailable testosterone were calculated using computer software according to methods set forth previously [30]. Participants were stratified by levels of total testosterone and free testosterone (in quartiles) for analysis (Table 1).

2.3. Body composition

Whole body Dual-Energy X-ray Absorptiometry (DXA) scans were completed on a Hologic QDR-4500A fan-beam densitometer with Hologic software version 8.26:a3*. Measures of upper and lower-body lean (excluding bone mineral content) and fat mass were included in the analysis, with full details described elsewhere [35,15].

2.4. Analysis

All statistical tests were performed using Stata (version 12.0), with all analyses accounting for the complex survey design

Table 1
Subject characteristics.

	Proportion	95%CI
Race/Ethnicity (%)		
Mexican American	7.13	2.57–11.69
Other Hispanic	8.32	1.23–15.42
Non-Hispanic White	70.69	59.59–81.79
Non-Hispanic Black	9.69	5.00–14.38
Other	4.15	−0.43 to 8.75
Diabetic status (%)		
Diabetic	5.69	1.22–10.15
	Median	IQR
Anthropometrics		
Age (yr)	42	26–60
Body mass (kg)	79.9	70.9–91.7
Laboratory Markers		
CRP (mg·dl^{-1})	0.17	0.06 – 0.345
Total T (ng·dl^{-1})	519	400–630
Free T (ng·dl^{-1})	10.6	7.6–13.2
Body Composition (kg)		
Upper body lean mass	7.2	6.2–8.1
Lower body lean mass	18.2	15.9–20.6
Upper body fat mass	2.6	1.8 – 3.3
Lower body fat mass	6.6	5.2–8.7
Dietary Measures (g)		
Daily Protein Intake	89.7	63.0–117.9
Quartile Total T Values (ng·dl^{-1})		
Q1	348	305–374
Q2	464	439–492
Q3	589	549–609
Q4	717	660–798
Quartile Free T Values (ng·dl^{-1})		
Q1	5.8	5.0–6.8
Q2	9.2	8.2–10.1
Q3	11.5	11.0–12.3
Q4	15.0	14.0–17.2

CRP: C-Reactive protein; T: Testosterone; Q1–Q4: 1st–4th quartiles.