Testicular volume and clinical correlates of hypothalamic–pituitary–testicular function: a cross-sectional study in obese men

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The aim of this study was to determine whether testicular volume is correlated with clinical and biochemical markers of hypothalamic–pituitary–testicular (HPT) axis function. This was a cross-sectional substudy of a larger randomized controlled trial including obese men, body mass index (BMI) ≥30 kg m−2, with a total testosterone level <12 nmol l−1. Testicular volume was measured by orchidometer, testosterone by liquid chromatography/tandem mass spectrometry, and body composition by dual-energy X-ray absorptiometry. Men completed the Aging Males’ Symptoms (AMS) score, International Index of Erectile Function-5 (IIEF-5), physical function, and handgrip dynamometer testing. Eighty-nine men participated with a median (interquartile range [IQR]) age of 53.1 (47.6, 59.2) years, BMI of 37.0 (34.6, 40.5) kg m−2, and a total testosterone of 7.0 (6.1, 7.9) nmol l−1. Median testicular volume was 18 (IQR: 10, 20) ml. Testicular volume was negatively correlated with BMI (τ = −0.1952, P = 0.010) and total fat mass (τ = −0.2115, P = 0.005) independent of age and testosterone. When BMI, testosterone, sex hormone-binding globulin (SHBG), and luteinizing hormone (LH) were present in a multivariable model, only BMI (-0.38 ml change in testicular volume per 1 kg m−2 BMI; 95% CI: −0.74, −0.02; P = 0.04) and LH (-0.92 ml change in testicular volume per 1 IU l−1 LH; 95% CI: −1.75, −0.095; P = 0.03) remained independent significant predictors of testicular volume. Testicular volume was positively correlated with IIEF-5 (τ = 0.2092, P = 0.021), but not related to handgrip strength, physical function tests, or AMS. In obese men, testicular volume is inversely and independently associated with measures of adiposity, but not with most clinical or biochemical markers of HPT axis action. From a clinical perspective, this suggests that obesity might compromise the reliability of reduced testicular volume as a sign of androgen deficiency in men. Asian Journal of Andrology (2020) 22, 354–359; doi: 10.4103/aja.aja_96_19; published online: 17 September 2019

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INTRODUCTION

In men, circulating testosterone concentrations are commonly reported to be inversely correlated with age.1 However, much of the age-related decline may not be attributable to chronological aging in itself, but due to the development of comorbidities that accumulate with aging.2 Obesity and type 2 diabetes are associated with reductions in circulating testosterone, reductions in the testosterone carrier protein sex hormone-binding globulin (SHBG), and, particularly in men with morbid obesity (body mass index [BMI] >40 kg m−2), blunting of pituitary luteinizing hormone (LH) secretion.3 In contrast, the decline in testicular function considered purely related to aging is characterized by increased pituitary follicle-stimulating hormone (FSH) and LH in an attempt to maintain testicular androgen synthesis and spermatogenesis.

Testicular examination is an integral part of the clinical assessment of men presenting with suspected hypogonadism, and reduced testicular volume is generally accepted to be a specific physical sign of hypogonadism.3 However, although numerous studies have reported age- and comorbidity-related declines in circulating testosterone and in fertility,16–8 relatively few studies have examined the relationship between testicular volume and clinical features that are conventionally considered to reflect hypothalamic–pituitary–testicular (HPT) axis function. Such clinical features include standardized questionnaires quantifying psychological, somatovegetative, and sexual function;9,10 body composition; and physical performance. We therefore sought to determine, in obese men, the relationship of testicular volume with biochemical and clinical markers of HPT axis function. We hypothesized that testicular volume would be inversely correlated with such markers of HPT axis function. Specifically, we hypothesized that lower testicular volume would correlate with worse self-reported psychosomatic and sexual function, higher adiposity, and with lower muscle mass and performance.

PARTICIPANTS AND METHODS

This cross-sectional study included men being screened for participation in a previously described randomized controlled trial (RCT; ClinicalTrials.gov No. NCT01616732)11 to assess the effect of testosterone treatment on body composition in men undergoing a structured weight loss program. The RCT was conducted from April 2013 to November 2015 at an academic tertiary referral center.
(Austin Health, Melbourne, Australia). The trial protocol was approved by the Austin Health Ethics Committee (HREC 2012/0495), and each participant provided written informed consent. The full details of the RCT have been described previously. Briefly, inclusion criteria included BMI ≥30 kg m⁻², age of 18–70 years, and repeated testosterone concentrations ≤12 nmol l⁻¹. Exclusion criteria included pathological androgen deficiency due to pituitary or testicular disorders; testosterone treatment within the previous 12 months; and major medical comorbidities including symptomatic ischemic heart disease, cardiac failure above New York Heart (NYHA) class I, active cancer, uncontrolled blood pressure >160/100 mmHg, and chronic kidney disease with estimated Glomerular Filtration Rate (eGFR) <40 ml min⁻¹. Inclusion or exclusion to the RCT was not based on testicular volume. At baseline, prior to biochemical measurements and administration of study drug, all participants underwent a full clinical examination by a single observer (MNTF), including testicular examination by an ellipsoid orchidometer (Andrology Australia, Clayton, Victoria, Australia) consisting of 15 sequential beads estimating volumes from 1 ml to 35 ml (1, 2, 4, 6, 8, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, 30, and 35 ml) and measuring handgrip strength by a handheld medical dynamometer (Jamar 5030J1, Sammons Preston, Bolingbrook, IL, USA). Participants also completed the Aging Males’ Symptoms (AMS) scale and International Index of Erectile Function (IIEF-5), self-report instruments of symptoms of testosterone deficiency (AMS), and erectile function (IIEF-5). Higher AMS scores indicate worse symptoms and lower scores in the IIEF-5 indicate worse symptoms. Participants also underwent a battery of physical performance tests including a 15-m rapid walk test, a 3-m up-and-go test, and stair ascent and descent with a weighted vest.

Biochemical testing was conducted between 8–10 a.m. in the fasted state including total testosterone measured by liquid chromatography-tandem mass spectroscopy (LCMS/MS) batched tested from samples stored at −80°C, and free testosterone was calculated according to Vermeulen et al. Body composition was measured by dual-energy X-ray absorptiometry (DXA, version 13.60, DXA Prodigy; GE Lunar, Madison, WI, USA), and appendicular lean mass was corrected for height squared. All of the data in this substudy were collected prospectively during the RCT.

### Statistical analyses

Data were reported as median and interquartile range (IQR, 25th and 75th percentiles). Correlations were assessed using Kendall’s tau rank test. Multivariable analysis relied on a generalized linear regression model, after confirming model assumptions were met including acceptable variance inflation factors for collinearity. Statistical tests were considered exploratory and not adjusted for multiple testing. Two-sided P < 0.05 denoted statistical significance. Analyses were conducted using R version 3.5.1 for Mac.

### RESULTS

Of the 100 men randomized into the trial, testicular volume determination was available for 89 men. Median (IQR) testicular volume was 18 (10, 20) ml, and median (IQR) for age was 53.1 (47.6, 59.2) years, weight 116 (105, 129) kg, BMI 37.0 (34.6, 40.5) kg m⁻², total testosterone 7.0 (6.1, 7.9) nmol l⁻¹, calculated free testosterone 164 (142, 193) pmol l⁻¹, LH 4.2 (3.2, 5.4) IU l⁻¹, and FSH 4.8 (3.1, 7.7) IU l⁻¹. Other baseline characteristics are listed in Table 1. Kendall’s tau correlations are described in Table 2. Testicular volume was negatively correlated with BMI (τ = −0.1952, P = 0.01) and fat mass (τ = −0.2115, P = 0.005), but was unrelated to lean mass (τ = 0.0613, P = 0.42). Testicular volume was positively correlated with erectile function (IIEF-5) (τ = 0.2092, P = 0.02), but was not correlated with the AMS score, handgrip strength, or physical function tests (Table 2).

**Table 1: Baseline characteristics of study participants (n=89)**

| Variable                  | Value                        |
|---------------------------|------------------------------|
| Age (year), median (IQR)  | 53.1 (47.6; 59.2), 24–68     |
| Physical characteristics  |                              |
| Testicular volume (ml), median (IQR), range | 18 (10; 20), 2–30 |
| Weight (kg), median (IQR) | 116 (105; 129)               |
| BMI (kg m⁻²), median (IQR), range | 37.0 (34.6, 40.5), 31–57 |
| Waist circumference (cm), median (IQR) | 123 (117;132) |
| SBP (mmHg), median (IQR)  | 134 (121;142)                |
| DBP (mmHg), median (IQR)  | 80.0 (78.0;87.0)             |
| Handgrip (kg), median (IQR) | 44.0 (40.0,50.0)          |
| Fat mass (kg), median (IQR) | 44.1 (36.3, 50.8)          |
| Fat mass (%), median (IQR) | 37.9 (34.8,42.3)            |
| Lean mass (kg), median (IQR) | 66.5 (62.0, 71.7)   |
| ALM/height² (kg m⁻²), median (IQR) | 9.5 (9.0,10.3) |
| VAT area (mm²), median (IQR) | 23 299 (18 087, 30 262)    |
| Comorbidities and medications, n (%) |                             |
| Ischemic heart disease    | 11 (12.4)                    |
| Diabetes                  | 20 (22.5)                    |
| Metformin use             | 6 (6.7)                      |
| Statin use                | 26 (29.2)                    |
| Functional tests, median (IQR) |                             |
| Timed up and go (s)       | 6.3 (5.7; 7.1)               |
| Rapid walking (s)         | 8.3 (7.7; 9.1)               |
| Stair ascent (s)          | 11.9 (10.3; 12.9)            |
| Stair descent (s)         | 10.4 (9.2; 11.8)             |
| Steps per day             | 6445 (4761;7655)             |
| Questionnaires, median (IQR) |                             |
| Aging Males’ Symptoms score | 34 (27; 43)                |
| International Index of Erectile Function-5 | 22 (17; 24)  |
| Physical activity (% per day) | 14.2 (10.8; 17.5)           |
| Biochemical measurements  |                              |
| TT LCMS/MS (nmol l⁻¹), median (IQR), range | 7.0 (6.1, 7.9), 2.4–10.0 |
| cFT LCMS/MS (pmol l⁻¹), median (IQR) | 164 (142,193) |
| SHBG (nmol l⁻¹), median (IQR) | 23.0 (17.0; 29.0)          |
| LH (IU l⁻¹), median (IQR)  | 4.2 (3.2; 5.4)               |
| FSH (IU l⁻¹), median (IQR) | 4.8 (3.1; 7.7)               |
| Estradiol (pmol l⁻¹), median (IQR) | 116 (71.6; 155.7)          |
| Fasting glucose (mmol l⁻¹), median (IQR) | 5.8 (5.4; 6.3) |
| HOMA-IR, median (IQR)     | 3.3 (2.7;4.1)                |
| HbA1c (%), median (IQR)   | 6.0 (5.6;6.3)                |
| Total cholesterol (mmol l⁻¹), median (IQR) | 5.0 (4.3; 5.6)             |
| LDL-c (mmol l⁻¹), median (IQR) | 2.9 (2.2, 3.5)             |
| HDL-c (mmol l⁻¹), median (IQR) | 1.1 (1.0; 1.3)            |
| Triglycerides (mmol l⁻¹), median (IQR) | 1.8 (1.2; 2.5)           |
| Hematocrit, median (IQR)  | 0.43 (0.42; 0.45)            |
| Hemoglobin (g l⁻¹), median (IQR) | 150 (144; 155)           |
| PSA (µg l⁻¹), median (IQR) | 0.71 (0.51; 1.09)           |

BM1: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; ALM: appendicular lean mass; VAT: visceral abdominal tissue; SHBG: sex hormone-binding globulin; cFT: calculated free testosterone; FSH: luteinizing hormone; LCMS/MS: liquid chromatography-tandem mass spectroscopy; HbA1c: glycated hemoglobin; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; PSA: prostate-specific antigen; TT: total testosterone by LCMS/MS; HOMA-IR: homeostatic model assessment of insulin resistance.
Correlates of testicular volume

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Table 2: Correlates of testicular volume

|                          | Kendall’s rank correlation (τ) | P     |
|--------------------------|-------------------------------|-------|
| Age (year)               | 0.0972                        | 0.20  |
| Physical characteristics  |                               |       |
| Weight (kg)              | −0.1370                       | 0.07  |
| BMI (kg m⁻²)             | −0.1952                       | 0.01  |
| Handgrip (kg)            | 0.01645                       | 0.83  |
| Fat mass (kg)            | −0.2115                       | 0.005 |
| Lean mass (kg)           | 0.0613                        | 0.42  |
| Biochemical measurements |                               |       |
| Total testosterone       | 0.08203                       | 0.28  |
| Estradiol (LCMS/MS)      | −0.08174                      | 0.28  |
| cFT (LCMS/MS)            | 0.04002                       | 0.60  |
| LH                       | −0.1596                       | 0.04  |
| FSH                      | −0.09582                      | 0.21  |
| Functional tests         |                               |       |
| Timed up and go (s)      | 0.04153                       | 0.63  |
| Rapid walking (s)        | 0.03321                       | 0.70  |
| Stair ascent (s)         | 0.06109                       | 0.48  |
| Stair descent (s)        | 0.07372                       | 0.39  |
| Questionnaires           |                               |       |
| Aging Males Symptoms score | −0.02728                    | 0.72  |
| International Index of Erectile Function-5 | 0.2092 | 0.02 |

BMI: body mass index; DBP: diastolic blood pressure; LCMS/MS: liquid chromatography-tandem mass spectroscopy; cFT: calculated free testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone

Following a multivariable analysis, the inverse relationship between testicular volume and BMI remained significant after adjustment for both age and total testosterone (decrease of 0.40 ml per 1 kg m⁻² increase in BMI; 95% CI: −0.77, −0.034; P = 0.03). This was also true when replacing testosterone with estradiol (−0.41 ml per 1 kg m⁻²; 95% CI: −0.1, −0.01; P = 0.046). When BMI, testosterone, SHBG, and LH were present in a multivariable model, only BMI (−0.38 ml change in testicular volume per 1 kg m⁻² BMI; 95% CI: −0.74, −0.02; P = 0.04) and LH (−0.92 ml change in testicular volume per 1 IU l⁻¹ LH; 95% CI: −1.75, −0.095; P = 0.03) remained independent significant predictors of testicular volume, but not age (0.08; 95% CI: −0.36, 1.78; P = 0.20), testosterone (0.71; 95% CI: −0.36, 1.78; P = 0.20), or SHBG (−0.03; 95% CI: −0.25, 0.18; P = 0.78).

**DISCUSSION**

**Key findings**

In this cross-sectional study among obese men with serum testosterone ≤12 nmol l⁻¹, testicular volume was negatively correlated with markers of adiposity including BMI and fat mass, independently of age and circulating total testosterone concentrations. Testicular volume was positively correlated with erectile function, but not with the Aging Males’ Symptoms score or with physical function tests reflective of HPT axis function examined.

This study provides new insights into the relationship between testicular volume and biochemical as well as clinical features traditionally considered representative of HPT axis function. This is, to our knowledge, the only study which has assessed testicular volume across a broad range of such features. Moreover, it is the only study focusing on men with obesity, a group which constitutes a substantial proportion of community-dwelling men who are middle-aged and older found to have low testosterone concentrations in epidemiologic studies.

Possible mechanisms

A number of mechanisms may explain the inverse association of testicular volume with adiposity and circulating LH. Higher leptin levels in men with obesity may suppress the HPT axis by decreasing LH secretion via kisspeptin neurons. However, the lack of correlation of LH with BMI in our cohort suggests that other mechanisms, not directly tested here, such as proinflammatory cytokines and insulin resistance, previously reported to negatively affect HPT function in obese men, may play a role. While we did not measure sperm parameters, the bulk of testicular volume is devoted to spermatogenesis. Reductions in sperm production are well described in obese men, with possible mechanisms including direct effects of leptin, higher levels of reactive oxygen species, and elevated temperatures due to excess scrotal adipose tissue or ischemia.

Our finding that testicular volume was negatively correlated with BMI even after correction for circulating testosterone levels is consistent with such potential mechanisms not directly related to androgenic signaling. While testicular volume was positively correlated with erectile function, no correlation existed with self-reported constitutional symptoms or crude measures of physical function. This could possibly be due to a type 2 error, or due to the fact that other factors, rather than testicular volume, affect these parameters in this group of obese men.

**Comparisons to previous work**

We conducted MEDLINE and PubMed searches of English-language papers of human subjects using the terms “testicular size or volume” from inception to September 2018, and studies identified are summarized in Table 3. While we confirm some findings of these previous studies, we also note key differences and extend these correlations to obese men with lowered circulating testosterone.

In a study of nonobese men without known testicular pathology, older men (mean age 78 years) had 31% smaller testicular volume compared to young men (mean age 26 years), and the older men had higher gonadotropin concentrations. Unlike that in our study, testicular volume in the older men was positively correlated with (bioavailable) testosterone in that study, perhaps due to the wider range of testosterone concentrations in these men (mean: 20.6 nmol l⁻¹, standard deviation: 10.9) compared to our cohort where inclusion criteria restricted circulating concentrations to ≤12 nmol l⁻¹.

The negative correlations of testicular volume with markers of adiposity are in contrast to a number of studies in men not selected for obesity. As summarized in Table 3, cross-sectional studies were conducted mostly in young lean men, and testicular volume was generally (albeit weakly) positively correlated with body weight and or BMI. One potential explanation for the difference is that we exclusively focused on men who were obese and in whom obesity-driven hyperleptinemia and hypotestosteronemia-driven leptin resistance may have directly inhibited testicular function. Moreover, these previous studies in men without obesity (Table 3) did not report body composition, and the effects of adipose tissue on testicular volume were therefore not elucidated.

Notably, our study did not find an inverse relationship between age and testicular volume, as has been reported by others. In Handelsman’s large necropsy study of 1056 men, when corrected for illness which may affect testicular volume, aging was only correlated with decreased testicular volume from the 8th decade onward. Our study did not include men older than 70 years, and any effect of age on testicular volume may be surmounted by obesity blunting gonadotropin secretion, consistent with prior studies, indicating that obesity has a greater effect on testosterone concentrations than aging. Two other studies in relatively young men (mean age 33 years and 26 years) did not find a negative correlation between testicular volume and age, possibly due to relative younger age.

In men presenting with infertility, testicular volume was negatively associated with circulating LH and FSH concentrations and...
positively with testosterone in some of these studies.\textsuperscript{34,38} In contrast, in our cohort, men who were not selected for infertility and men with known prior testicular disorders were excluded. This may explain why we did not find an inverse correlation of FSH with testicular volume and only a weak negative correlation of LH with testicular volume. It is also possible that obesity, due to central gonadal axis suppression,\textsuperscript{39} may have prevented the otherwise expected compensatory rise in FSH in those men with smaller testes. Consistent with our findings, a prior study reported lower concentrations of inhibin B in obese compared to normal-weight young men, but no difference in FSH levels,\textsuperscript{40} despite the fact that inhibin B is a major negative regulator of FSH. We speculate that adiposity may override the stimulatory effects of lower inhibin B on FSH to cause lower levels of FSH in men with obesity.\textsuperscript{41} Similarly, the lower testosterone levels found in our cohort of men with obesity resulted in only a weak negative correlation of LH with testicular volume (a much higher LH might otherwise have been expected in men with smaller testes). Again, this may be due to the suppressive effects of obesity on pituitary LH secretion.\textsuperscript{3} The mechanisms by which obesity depresses FSH\textsuperscript{42} are not as well defined as those depressing LH.\textsuperscript{3}

In our cohort, testicular volume was not associated with indirect potential surrogate markers of HPT axis function such as lean mass,\textsuperscript{43} strength (handgrip), and speed (physical function testing). Moreover, there was no association with the Aging Males’ Symptoms score, but a positive correlation did exist with erectile function. Testicular volume was not correlated with circulating testosterone concentrations, consistent with the fact that the majority (70%–80%) of testicular mass devoted to spermatogenesis.\textsuperscript{16}

Strengths and limitations
The strengths of our study include the comprehensive testing regimen involving both biochemical parameters and clinical features attributed to HPT function. While a number of other groups have

| Study | Cohort | Age (year) | BMI (kg m\(^{-2}\)) | Testicular volume correlates |
|-------|--------|------------|----------------|-----------------------------|
| Mahmoud et al.\textsuperscript{21} 2003 | 42 healthy young Belgian men, 115 healthy older men | 26.5, 78.0 | NA | Age (–) FSH (–) BioT (+) and LH (–) in older men only |
| Bahk et al.\textsuperscript{18} 2010 | 1139 Korean military personnel | 23.5 | 22.5 | FSH (–) LH (–) Weight (+) Height (+) BMI (+) Testosterone (+) |
| Ku et al.\textsuperscript{23} 2002 | 2080 healthy Korean military conscripts | 20 | 21 | Weight (+) Height (+) BMI (+) |
| Wikramanayake et al.\textsuperscript{25} 1995 | 200 healthy Sinhalese medical students | 24 | 19.5 | Weight (+) Height (nil) |
| Aribarg et al.\textsuperscript{24} 1986 | 307 healthy Thai fathers | 26.4 | 20.8 | Weight (+) Height (+) FSH (–) LH (–) Testosterone (nil) |
| Handelsman and Staraj\textsuperscript{25} 1985 | 1056 unselected Australian male necropsies | 18–96 | NA | Weight (+) Height (+) Age (–) Illness (–) |
| Johnson et al.\textsuperscript{28} 1988 | 16 younger men and 18 older men at autopsy | 18, 63 | NA | Age (–) |
| Neaves et al.\textsuperscript{29} 2002 | 15 younger men and 15 older men at autopsy | 42, 58 | NA | Age (–) |
| Paniagua et al.\textsuperscript{30} 1988 | 25 young controls and 64 men with prostate cancer undergoing orchidectomy | 25–39, 51–90 | NA | Age (–) |
| Pasqualotto et al.\textsuperscript{32} 2005 | 889 Brazilian men seeking vasectomy | 33.2 | NA | Age (nil) |
| Spyropoulos et al.\textsuperscript{33} 2002 | 52 Greek men attending urology clinic | 25.9 | 25.7 | Age (nil) BMI (nil) |
| Stewart et al.\textsuperscript{34} 2009 | 225 infertile Australian men | 35 | 27 | FSH (–) LH (–) Testosterone (+) |
| Ehalia-Aleksejev and Punad\textsuperscript{35} 2017 | 2672 infertile Estonian men | 32.6 | 26.6 | BMI (+) Height (+) FSH (–) LH (–) Testosterone (nil) |
| Araiz et al.\textsuperscript{36} 1998 | 486 infertile Japanese men | NA | NA | FSH (–) LH (–) Testosterone (nil) |
| Bujan et al.\textsuperscript{37} 1989 | 174 infertile French men | NA | NA | FSH (–) LH (–) Testosterone (nil) |
| Ruiz-Olvera et al.\textsuperscript{38} 2018 | Spanish men with infertility or sexual dysfunction, TT ≤5 nmol l\(^{-1}\) or ≥12 nmol l\(^{-1}\) | 42.1, 45.9 | 28.5, 25.0 | Testosterone (+) |

\textsuperscript{1} Age: median, mean, \[8\text{.15} \pm \text{3.05} - 38\text{.16} \pm \text{3.04} \text{ or all subjects; } \text{2} \text{ BMI: mean} \[10\text{.49} \pm \text{3.05} - 31\text{.49} \pm \text{3.05} \text{ or median; } \text{3} \text{ NA: not available; BioT: bioavailable testosterone; (+): positive correlation; (–): negative correlation; (nil): no correlation with testicular volume; BMI: body mass index; FSH: sex hormone-binding globulin; LH: luteinizing hormone.}
correlated testicular volume with age and weight, to our knowledge, very few studies have correlated validated physical and symptom-based questionnaires with testicular volume. We also assayed total testosterone using a validated LCMS/MS platform.2,12

Limitations of the study, in addition to those discussed above, include the modest sample size. The cross-sectional design of the study precludes causal inferences. Given the exploratory approach, the findings are hypothesis generating and require confirmation in studies designed specifically to examine these endpoints. Orchidometry is not the reference standard method to estimate testis volume. Previous studies have reported that imaging methods such as ultrasound are more accurate, with orchidometry demonstrating a systematic 25% deviation from accurate testis volume by direct measurement.4,4,4 While testicular volume was measured prior to the availability of biochemical and clinical data, it was not blinded, and we cannot exclude the possibility that measurement was influenced by the degree of obesity in the man being examined. Free testosterone was calculated according to Vermeulen et al.13 which is less accurate than direct measurements using gold-standard methodology such as equilibrium dialysis.4,4 We focused on adult men aged 70 years and younger (median 53 years) with obesity and a low–normal testosterone concentration selected for participation in an RCT.11 Findings are not generalizable to other populations of adult men, including those older than 70 years, who were excluded from the RCT-based theoretical (but unproven) concerns regarding increased risks with testosterone treatment. While testicular volume was correlated with erectile function, the latter is a risk factor of cardiovascular disease, a potential confounder not addressed in the current analysis. However, our cohort had a relatively low rate of ischemic heart disease (12%), and median glycated hemoglobin (HbA1c) was 6.0%. We present our findings in the context of the published literature and selected manuscripts considered particularly relevant to our data, rather than performing a formal systematic review. Consequently, we have not attempted to meta-analyze the data.

Potential clinical implications

Making a clinical unequivocal diagnosis of androgen deficiency is not always straightforward, given the relative nonspecificity of many clinical symptoms and signs.1 For example, in the European Male Aging Study (EMAS), of 32 candidate symptoms commonly attributed to hypogonadism, only 3 sexual symptoms had a syndromic association with testosterone levels, whereas the other 29 did not.4 While testicular volume was not reported in EMAS, reduced testicular volume is considered a relatively specific sign of hypogonadism.5 While further studies are required, our findings raise the possibility that obesity might compromise the reliability of reduced testicular volume as a sign of androgen deficiency in men, a hypothesis that should be addressed in future studies. The findings, especially if confirmed by future studies, may also help inform a discussion about the significance of testicular volume in obese men who are concerned about gonadal size, including a potentially negative role of excess adiposity.

CONCLUSION

In men with obesity and a low–normal testosterone concentration, testicular volume is inversely correlated with markers of adiposity and LH while positively correlated with erectile function. There was no correlation of testicular volume with other markers of HPT axis function such as circulating sex steroids, androgen-deficiency like symptoms, or crude measures of physical function. Further studies should investigate the mechanisms underlying the relationship between testicular volume and obesity, particularly whether testicular volume increases following weight loss, in parallel to the reported increases in circulating testosterone and in measures of sexual function. Moreover, the reliability of reduced testicular volume as a sign of hypogonadism in obese men deserves further evaluation.

AUTHOR CONTRIBUTIONS

MNTF and MG designed the study. MNTF collected the data. RH and MNTF performed the statistical analysis. MNTF, RH, GW, and MG drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

MNTF has received research funding from Bayer Pharma. RH has nothing to disclose. GW has received research funding from Bayer, Lilly, Lawley Pharmaceuticals and Weight Watchers, and speaker honoraria from Bayer, Lilly and Besins Healthcare. MG has received research funding from Bayer, Novartis, Weight Watchers, Lilly and speaker’s honoraria from Besins Healthcare.

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