CLINICAL STUDY

The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study

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Abstract

Objective: Changes in adiposity affecting total testosterone (TT) and free testosterone (FT) levels have not been examined in a population-based survey. We aimed to determine whether changes in adiposity predict follow-up levels and rates of change in TT, FT and sex hormone-binding globulin (SHBG) in men.

Design: The Massachusetts Male Aging Study is a randomly sampled, population-based cohort interviewed at baseline (T₁, 1987–1989; n = 1709; aged 40–70 years) and followed-up approximately 9 years later (T₂, 1995–1997; n = 1156). Men were categorized as overweight (body mass index (BMI) ≥ 25 kg/m²) or having obesity (BMI ≥ 30 kg/m²), waist obesity (waist circumference ≥ 102 cm), or waist-to-hip ratio (WHR) obesity (WHR > 0.95). For each adiposity group, we constructed four categories to represent changes between T₁ and T₂: overweight (or obese, etc.) at neither wave, T₁ only, T₂ only, or both waves.

Results: After adjustment for confounding variables, men who were overweight at T₂ only, or at both waves, had significantly lower mean T₂ TT and SHBG levels than men in the neither group (P < 0.05). Mean FT did not differ between any overweight group and the neither group. Men who were obese at both times, had the highest mean BMI, the highest fraction of severely obese men, and significantly greater rate of decline in FT than the neither group.

Conclusions: In men who become overweight, the greater rate of decline in TT, but not FT, is related mostly to a lesser age-related increase in SHBG. Since weight gain is highly prevalent in older men, over-reliance on TT levels in the diagnosis of androgen deficiency could result in substantial misclassification.

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Introduction

Obesity is widely recognized as an important public health problem, whose prevalence has increased substantially in the recent decades. The relationship between obesity and testosterone levels is one of the longest running controversies in endocrinology. Cross-sectional surveys – most of them conducted in relatively small, convenience samples – have suggested that there is an inverse correlation between total testosterone (TT) levels and body mass index (BMI) (1–5). However, inferences from these studies are complicated by the finding that sex hormone-binding globulin (SHBG) levels are also inversely correlated with adiposity (1, 3, 6, 7). In fact, all measures of adiposity (BMI, waist-to-hip ratio (WHR), and waist circumference) are strongly negatively correlated with SHBG levels. Other studies have suggested that higher insulin levels associated with adiposity suppress SHBG levels (8–11). Since a significant fraction of circulating testosterone is bound to SHBG, lower serum SHBG concentrations would be expected to lower TT levels. In many studies, free or non-SHBG-bound testosterone levels were found to be normal (2, 12), consistent with the notion that lower TT levels were mostly due to the lower SHBG levels in obese men.

Other investigations that included small samples of selected men with severe obesity reported that obese men had low free testosterone (FT) levels (13). One hypothesis to explain the association between extreme adiposity and low FT levels (true androgen deficiency) suggests that high estrogen levels are the culprit. Some speculate that in extremely obese men, high estradiol levels, generated by aromatization of testosterone in the adipose tissue (14, 15), suppress gonadotropin-releasing hormone and luteinizing hormone levels.
thereby suppressing testicular testosterone production (13, 16, 17).

In addition, some uncommon genetic syndromes are characterized by extreme adiposity and hypogonadotropic hypogonadism (18, 19). These syndromes are relatively uncommon and can be ignored in evaluating the association of obesity and testosterone levels in general populations.

Therefore, the central issue is not whether the development of obesity is associated with low TT levels – this might be expected because obesity lowers SHBG levels – but rather whether the development of obesity in men lowers free or bioavailable testosterone levels. This issue has largely remained unresolved. Few large epidemiological surveys have examined whether changes in adiposity impact TT, FT, and bioavailable testosterone levels longitudinally, and none have examined the association between weight increases and age-related rates of decline in these hormones.

Using data from the Massachusetts Male Aging Study (MMAS), a prospective, community-based sample of older men, we investigated whether changes in adiposity over a 9-year period predict the follow-up TT, FT, and bioavailable testosterone levels. Since both adiposity and aging affect SHBG levels, which can influence TT levels, we also examined SHBG levels. In addition, we examined whether changes in adiposity affect the rates of change in these hormones.

**Methods**

**Design**

The MMAS is a prospective, community-based, observational study of aging in older men. This report uses data from the first two waves (T1, 1987–1989; T2, 1995–1997). The design has been described previously (20). At baseline (T1), men aged 40–70 years from 11 municipalities in the Boston, Massachusetts area were randomly selected from annual state census listings. Age-stratified cluster sampling was used to obtain approximately equal age strata (40–49, 50–59, 60–69 years). As reported elsewhere (21), 1709 of the eligible men (52%) participated at T1. This response rate reflects, in part, the early morning phlebotomy, extensive in-home interview, and absence of financial incentive. At T2, 1156 of the 1496 eligible men participated (conditional response rate of 77%).

Trained interviewers/phlebotomists administered a standardized, in-home interview, and obtained physical measures and blood samples. Unless noted, data collection methods were the same at both waves. The New England Research Institutes’ Institutional Review Board approved all protocols including written informed consent procedures.

**Independent variables**

**Adiposity** Height and weight, and waist and hip circumferences were measured using standard techniques (22). We defined overweight as BMI ≥ 25 kg/m². Obesity as BMI ≥ 30 kg/m², and waist obesity as waist circumference ≥ 102 cm (40 in.) (23–25). WHR obesity was defined as WHR > 0.95 (26). For each measure, we constructed four categories to represent the changes that occurred between T1 and T2: overweight (or obese, etc.) at neither wave, T1 only, T2 only, and both waves.

**Confounders** Validated instruments were used to evaluate alcohol intake (27) and physical activity (Stanford Five-City Physical Activity Questionnaire) (28). Smoking and chronic diseases (diabetes, hypertension, and heart disease) were ascertained by self-report. The interviewers obtained medication data by copying the name and use from the label. Pharmacoepidemiologists coded the medications using a system based on the American Hospital Formulary Service (29), and an endocrinologist identified prescription medications believed to decrease hormone levels (29), as previously described (21).

**Dependent variables**

**Hormones** Two non-fasting blood samples were collected within 4 h of the subject’s awakening to control for diurnal variations in hormone levels (30). Samples were drawn 30 min apart, pooled in equal aliquots to smooth episodic secretion (31), transported in ice-cooled containers, and centrifuged within 6 h. The samples were stored at −70 °C until assayed.

All the assays were performed at The Endocrine Laboratory, University of Massachusetts Medical School (Worcester, MA, USA) under Dr Christopher Longcope’s supervision. TT was determined by RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA). T1 TT was assayed in 1994 on sera stored since T1, and T2 TT shortly after collection. A structural equation model, equivalent to a Deming regression, showed negligible change due to assay drift or storage. The assay cross-reactivity with dihydrotestosterone was 2.8%. The T1 and T2 intra-assay coefficient of variation (CV) values for TT were 5.4 and 5.8%, and the inter-assay CV values were 8.0 and 9.0% respectively.

SHBG was measured by the same kit at T1 and T2 although distributors changed (T1: Farmos Diagnostica, Farmos Group Ltd, Oulunsalo, Finland and T2: Orion Diagnostica, Espoo, Finland). The intra-assay CV values...
of \( T_1 \) and \( T_2 \) SHBG were 8.0 and 4.5\%, and the intra-assay CV values were 10.9 and 7.9\% respectively.

The Södergard equation was used to calculate free and bioavailable testosterone, assuming a fixed albumin-bound concentration (32). The Södergard equation produces estimates of free and bioavailable testosterone, which closely approximate those obtained from equilibrium dialysis and ammonium sulfate precipitation respectively (33).

**Statistical analysis**

Out of the 1709 men recruited at \( T_1 \), 1156 participated at both waves. Men who were missing \( T_1 \) \((n=9)\) or \( T_2 \) hormones \((n=114)\) or \( T_1 \) \((n=0)\) or \( T_2 \) \((n=24)\) adiposity data, were excluded, resulting in an analysis sample of 1009 men. The sample sizes for each variable vary with item non-response.

A t-test was used to determine whether mean \( T_2 \) hormone levels differed by \( T_1 \) categorical confounders. Associations between \( T_2 \) and \( T_1 \) hormones and continuous confounders were assessed using Pearson correlation coefficients.

The key independent variable was change in adiposity between \( T_1 \) and \( T_2 \), defined using the four measures mentioned earlier: overweight, obesity, waist obesity, and WHR obesity. The dependent variables were \( T_2 \) TT, FT, bioavailable testosterone, and SHBG. The hormones were examined in two ways: (a) \( T_2 \) level (levels analysis) and (b) rate of change (change analysis). Rate of change was defined as \( T_2 - T_1 \) hormone divided by \( T_2 - T_1 \) age. For the analysis of levels, SHBG was log transformed to reduce the skew. Analysis of covariance (ANCOVA) was used to estimate the adjusted mean \( T_2 \) hormone or rate of change by the adiposity change categories. Each adiposity change variable was modeled using three dummy variables. Pairwise comparisons between the neither group (i.e. not overweight, obese, etc. at \( T_1 \) or \( T_2 \)) and the other adiposity change categories were adjusted for multiple comparisons using the Bonferroni procedure. Descriptive statistics were presented for free and bioavailable testosterone but model results for FT only. Since bioavailable testosterone is a multiple of FT, results from ANCOVA will produce identical conclusions.

All adjusted models included a term for \( T_1 \) hormone and years between interviews. Confounding by the following \( T_1 \) variables was examined: age, chronic illness (self-report of diabetes, heart disease and/or hypertension), prescription medications believed to decrease hormones, and lifestyle (smoking, alcohol intake and physical activity). Tests for interactions between each adiposity change variable and each independent variable were conducted to determine whether the relationship between hormone and adiposity change differed by the levels of these variables.

**Results**

**Baseline characteristics of participants**

At baseline (\( T_1 \)), the original cohort \((n=1709)\) was predominantly white (95\%), employed (78\%), and high school educated (89\%; data not shown). These demographics closely match the 1990 Massachusetts’ population. Men in the analysis sample were slightly younger at \( T_1 \) \((\text{mean (s.d.)})\), 53.8 (8.3) vs 55.2 (8.7); range for both 40–70 years), more likely to be employed (86\%), and have a high school education (91\%) than the original cohort.

At \( T_1 \), 33\% of men in the analysis sample reported diabetes, heart disease and/or hypertension (Table 1). Nine percent were on prescribed medications believed to lower hormone levels, and 22\% smoked cigarettes.

**Unadjusted follow-up hormone levels**

Mean TT levels declined from 18.0 to 15.7 nM, FT from 0.46 to 0.36 nM, and bioavailable testosterone from 8.8 to 6.8 nM from \( T_1 \) to \( T_2 \) (Table 1). Mean SHBG levels increased from 31.8 to 35.2 nM.

Men with chronic illness at \( T_1 \) had significantly lower \( T_2 \) TT, FT and bioavailable testosterone levels.

### Table 1 Characteristics of the analysis sample \((n=1009)\), Massachusetts Male Aging Study 1987–1997

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Analysis sample ((n=1009))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (s.d.)</td>
<td>53.8 (8.3)</td>
</tr>
<tr>
<td>Chronic disease(^a), n (%)</td>
<td>Diabetes 44 (4)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>90 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>255 (25)</td>
</tr>
<tr>
<td>Any(^c)</td>
<td>331 (33)</td>
</tr>
<tr>
<td>Medications affecting hormones(^d), n (%)</td>
<td>86 (9)</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Current cigarette smoking, n (%) 224 (22)</td>
</tr>
<tr>
<td>Alcohol ((\geq 1) drink/day)(^e), n (%)</td>
<td>492 (49)</td>
</tr>
<tr>
<td>Physical activity (kcal/day), mean (s.d.)</td>
<td>3102 (623)</td>
</tr>
<tr>
<td>Adiposity, mean (s.d.)</td>
<td>Body mass index (kg/m(^2)) 27.1 (4.0)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.9 (11.0)</td>
</tr>
<tr>
<td>Waist-to-hip ratio (cm)</td>
<td>0.94 (0.06)</td>
</tr>
<tr>
<td>( T_1 ) Hormones (nM), mean (s.d.)</td>
<td>Total testosterone 18.0 (6.1)</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>0.46 (0.18)</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>8.8 (3.4)</td>
</tr>
<tr>
<td>Sex hormone-binding globulin</td>
<td>31.8 (15.7)</td>
</tr>
<tr>
<td>( T_2 ) hormones (nM), mean (s.d.)</td>
<td>Total testosterone 15.7 (5.6)</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>0.36 (0.13)</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>6.8 (2.4)</td>
</tr>
<tr>
<td>Sex hormone-binding globulin</td>
<td>35.2 (16.7)</td>
</tr>
</tbody>
</table>

\(^a\)All characteristics were measured at baseline (\( T_1 \)) unless indicated (\( T_2 \), \( T_3 \), 1995–1997). \(^b\)Self-report of a diagnosis. \(^c\)Self-report of a diagnosis of diabetes, heart disease, and/or hypertension. \(^d\)Prescription medications believed to lower hormone levels. \(^e\)One drink is equivalent to 15 ml ethanol (10 oz beer, 4 oz wine, or 1.5 oz spirits).
than men without chronic illness (Table 2). Men on medications affecting hormones at baseline had lower free and bioavailable testosterone, and higher SHBG at follow-up. Baseline hormone and follow-up hormone levels were positively correlated ($P<0.0001$ for all). All the hormones were inversely correlated with adiposity. Age was negatively correlated with $T_2$ TT, FT, and bioavailable testosterone levels and positively correlated with SHBG levels. $T_1$ physical activity was inversely correlated with $T_2$ TT and SHBG levels; however, the correlations were small ($-0.15$ and $-0.16$ respectively). When controlling for BMI, the correlations became non-significant.

### Change in adiposity

The average time between $T_1$ and $T_2$ was 8.8 years (s.d. 0.72; range 7.1–10.4). During this period, 9% of men became overweight ($T_2$ only group), and 64% were overweight at both waves (Table 3). Nearly 26% were obese at $T_2$: 9% became obese and 17% were obese at both assessments. At $T_2$, 45% had waist obesity, and 54% had WHR obesity. As expected, the both group with obesity had the highest BMI at $T_2$ (34.5 compared with 25.6 kg/m² in the neither group) and the highest fraction of men with severe obesity (33.7 compared with 0% in the neither group).

For all adiposity change variables, the $T_1$ only group was small (range 3–11%). Many of these men had serious illness at follow-up. For example, among the 26 who were obese at $T_1$ only, 17 (65%) reported at least one of the following at $T_2$: cancer (lymphoma, prostate, kidney, or intestine), heart disease, diabetes, hypertension or HIV. In the $T_1$ only group, for the other adiposity measures, the follow-up prevalence of at least one of these illnesses was also high: overweight 55%, waist obesity 60%, and WHR obesity 49%.

### Adjusted follow-up hormone levels

Figure 1 displays adjusted mean (s.e.m.) $T_2$ hormone levels against adiposity change. The numbers above the means are Bonferroni adjusted $P$-values for the comparison between the respective adiposity change category and the neither group (referent group).

Men who became overweight between $T_1$ and $T_2$ ($P=0.0272$) or who were overweight at both waves ($P=0.0001$), had significantly lower $T_2$ mean TT than

<table>
<thead>
<tr>
<th>$T_2$ hormone</th>
<th>$TT$ (nM)</th>
<th>$FT$ (nM)</th>
<th>Bioavailable testosterone (nM)</th>
<th>SHBG (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r^1$</td>
<td>$P$-value $^b$</td>
<td>$r^1$</td>
<td>$P$-value $^b$</td>
<td>$r^1$</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.45</td>
<td>0.0001</td>
<td>0.30</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>0.15</td>
<td>0.0001</td>
<td>0.19</td>
<td>0.0001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.26</td>
<td>0.0001</td>
<td>0.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>0.0001</td>
<td>0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>Physical activity (kcal/day)</td>
<td>0.15</td>
<td>0.0001</td>
<td>0.04</td>
<td>0.2535</td>
</tr>
</tbody>
</table>

**Table 2** Association between baseline ($T_1$) health and lifestyle characteristics and follow-up ($T_2$) hormone levels ($n=1009$), Massachusetts Male Aging Study, 1987–1997.

TT, total testosterone; FT, free testosterone; SHBG, sex hormone-binding globulin; BMI, body mass index; WHR, waist-to-hip ratio.

$^a$N M may be converted to ng/dl by dividing by 0.0347. $^b$Test of the null hypothesis that mean $T_2$ hormone does not differ by levels of $T_1$ characteristic; $t$ test. For SHBG, log $T_2$ hormone was tested but untransformed means are presented. $^c$Self-report of a diagnosis of diabetes, heart disease, and/or hypertension. $^d$Prescription medications believed to lower hormone levels. $^e$One drink is equivalent to 15 ml ethanol (10 oz beer, 4 oz wine, or 1.5 oz spirits). $^f$Pearson correlation coefficient. For SHBG log SHBG was used. $^g$Test of the null hypothesis that correlation coefficient equals zero. $^h$Correlations in this row are between $T_1$ and $T_2$ TT, $T_1$ and $T_2$ FT, $T_1$ and $T_2$ bioavailable T, $T_1$, and $T_2$ log SHBG.
the men who were not overweight at either assessment (Fig. 1a). The results were similar for SHBG (T2 only, \( P = 0.0007 \); both, \( P = 0.0008 \)). However, FT levels were not significantly different between any of the overweight groups and the neither group.

For obesity change, the TT and SHBG results (Fig. 1b) were very similar to the overweight change except that men who were obese at both times did not have significantly lower SHBG than the neither group. FT levels in the ‘both’ group were significantly lower than in the ‘neither’ group (\( P = 0.0028 \)).

Compared to the neither group, having waist obesity at both waves resulted in lower mean T2 levels of all three hormones (Fig. 1c). In addition, the T2 only group with waist obesity had lower SHBG levels than the neither group (\( P = 0.0034 \)). For WHR obesity, the both group had lower mean T2 TT and SHBG (Fig. 1d). No significant differences were observed for FT.

For all comparisons, none of the means for the T1 only group were significantly different from those for the neither group.

Overall, 14% of the sample had TT < 300 ng/dl (10.4 nM) and 37% had FT levels less than the lower limit of the normal range at T2. Importantly, men who became obese at T2 had a higher prevalence of TT levels < 300 ng/dl than the group that was not obese at either time (18 vs 9% respectively). However, the prevalence of low FT levels was similar in both these groups (29 vs 34% respectively).

### Table 3

<table>
<thead>
<tr>
<th>Change in adiposity between baseline (T1) and follow-up (T2) ((n = 1009)), Massachusetts Male Aging Study, 1987–1997.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Change in adiposity</strong></td>
</tr>
<tr>
<td>between T1 and T2 ( n )</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
</tr>
<tr>
<td>Neither</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>Both T1 and T2</td>
</tr>
<tr>
<td><strong>Waist obesity</strong></td>
</tr>
<tr>
<td>Neither</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>Both T1 and T2</td>
</tr>
<tr>
<td><strong>WHR obesity</strong></td>
</tr>
<tr>
<td>Neither</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>T2 only</td>
</tr>
<tr>
<td>Both T1 and T2</td>
</tr>
</tbody>
</table>

BMI, body mass index; WHR, waist-to-hip ratio.

*Definitions: Overweight, BMI ≥ 25 kg/m²; obese, BMI ≥ 30 kg/m²; waist obesity, waist circumference ≥ 102 cm (40 in.); WHR obesity, waist-to-hip ratio ≥ 0.95.*

### Unadjusted rates of change in hormone levels

Figure 2 displays unadjusted mean hormone levels at \( T_1 \) and \( T_2 \) against adiposity change. Compared with the neither group, the \( T_2 \) only and both groups tended to have lower baseline and follow-up mean hormone levels. All changes occurred in the expected direction; TT and FT declined over time, and SHBG increased, except that SHBG decreased in the \( T_2 \) only group for overweight, obesity and waist obesity. For TT, the \( T_2 \) only group experienced the fastest declines for overweight and obesity categories, whereas for waist and WHR obesity, the both group decreased most rapidly.

### Adjusted rates of change in hormone levels

Table 4 presents the adjusted rates of change (or slopes) in hormone levels (nM/year) between \( T_1 \) and \( T_2 \) against adiposity change. For TT, the rate of decline for the both group was more than double the rate for the neither group for all adiposity measures. For example, TT decreased by 0.43 nM/year for men who were obese at both waves compared with 0.21 nM/year for those obese at neither wave (\( P = 0.0008 \)). For overweight and obesity, the \( T_2 \) only group also experienced significantly steeper declines than the neither group (\( P = 0.0386 \) and 0.0032 respectively).

For FT, the both group with obesity and waist obesity dropped significantly faster than the neither group (\( P = 0.0038 \) and 0.0046 respectively). No other rates were significantly different from the neither group.

Men who were overweight at both waves experienced a significantly smaller rate of increase in SHBG than in men who were overweight at neither wave: 0.25 vs 0.81 nM/year respectively (\( P = 0.0003 \)). Similarly, the rate of change in SHBG for men who had WHR obesity at both waves was significantly different from the neither group. However, in this case, the mean increase for the both group was indistinguishable from zero (mean (95% confidence interval), 0.08 (−0.098, 0.26)), indicating that while SHBG for the neither group increased, it stayed about the same for the both group.

The \( T_2 \) only group had significantly different rates of change in SHBG than the neither group for all measures except WHR obesity. SHBG in the neither group increased, but the rates of change for the \( T_2 \) only group were not different from zero.

### Discussion

Using data from the MMAS, a prospective, population-based survey, we found that \( T_2 \) TT levels were significantly lower in men who became overweight by \( T_2 \), or were overweight at both waves, compared with men who were not overweight at either wave. The same was true for obesity. However, \( T_2 \) FT levels did not differ between overweight and non-overweight men, or
Figure 1 Adjusted follow-up ($T_2$) mean (± s.e.m.) hormones in the four adiposity change groups (neither, $T_1$ only, $T_2$ only, both). BMI, body mass index; WHR, waist-to-hip ratio; TT, total testosterone; FT, free testosterone; SHBG, sex hormone-binding globulin.
Figure 2 Unadjusted baseline (T₁) and follow-up (T₂) mean hormones against adiposity change. BMI, body mass index; WHR, waist-to-hip ratio; TT, total testosterone; FT, free testosterone; SHBG, sex hormone-binding globulin. To convert nM to ng/dl, divide by 0.0347. Massachusetts Male Aging Study, n=1009, 1987–1997.
between those who became obese and who were not obese at either wave. Men who became overweight or obese are of particular interest because they provide insights into the effects of weight gain on changes in TT and FT. Compared with men who were not overweight or obese at either wave those who were overweight or obese experienced a greater rate of decline in TT levels and a lesser age-related increase in SHBG levels. However, their rate of decline in FT level was not significantly lower than men who were not obese or overweight at either time. Therefore, the larger rates of decline in TT levels in men who gained weight in the follow-up period than in men who did not can be attributed, in large part, to the differences in the rates of change in SHBG.

Lower SHBG levels in obese men have been attributed in part to the hyperinsulinemia associated with obesity (4, 34–37). Cross-sectional surveys have consistently demonstrated an inverse association between BMI and SHBG levels (34, 38). Obesity and weight gain are associated with higher insulin levels, which suppress hepatic SHBG production (39–41). In contrast, aging and chronic inflammatory conditions are associated with higher SHBG levels (5, 42–44). Thus, in obese, middle-aged and older men, the effects of adiposity are attenuated by those of age and illness. Not surprisingly, in our cohort, the rates of age-related increase in SHBG were lower in men who gained weight than in men who did not.

Unlike cross-sectional studies, the longitudinal design of the MMAS allowed us to evaluate the effects of changes in obesity on changes in hormones. In addition, we controlled for confounding by age, co-morbid conditions, and lifestyle. Our analysis demonstrates that both groups of obese men – those who were obese at both waves and those who became obese during the follow-up period – had greater rates of decline in TT levels and lower rates of increase in SHBG level than could be accounted for by aging alone.

The MMAS data on sex hormone levels are consistent with previous reports (43, 45–47). TT and SHBG levels correlated inversely with BMI, waist circumference, and WHR. Age correlated inversely with TT and FT levels and directly with SHBG levels. As expected the men with chronic illness also had lower TT, FT, and bioavailable testosterone levels than men who did not report a chronic illness. Smokers had higher TT, FT, and bioavailable testosterone levels, consistent with some previous reports (48, 49) but not with others (50, 51). Some of the inconsistencies across studies of androgens and smoking may be attributed to differences in the
population (healthy versus not), and some studies adjusted for confounding factors, while others did not.

Nine percent of the MMAS cohort became overweight between $T_1$ and $T_2$, and $64\%$ were overweight at both time points. Twenty-six percent either became obese by $T_2$ or were obese at both time points. Therefore, a significant proportion of middle-aged and older men were obese at $T_2$; furthermore, a substantial proportion gained weight and became obese. A small proportion of the cohort (3–11%) was overweight or obese and lost weight during the follow-up period, so that they were no longer overweight or obese at $T_2$. Most of these men developed serious health problems, such as cancer or heart disease. Their illness may have caused them to lose weight, or their physicians may have urged them to lose weight due to their illness.

The men who became obese at $T_2$ had a higher prevalence of TT levels $< 300$ ng/dl than the group that was not obese at either time (18 vs 9% respectively). However, the prevalence of low FT levels was similar in the two groups (29 vs 34% respectively). The clinical implication of these findings is that the evaluation of androgen deficiency in middle-aged and older men is complicated by the high prevalence of obesity and other confounding factors, such as chronic illness, lifestyle, and medications, all of which can affect TT levels through their effects on SHBG and/or hypothalamic–pituitary–testicular function. In any individual patient, the effects of obesity and weight gain on SHBG levels and TT levels are superimposed upon, and may not be easily distinguishable from, the effects of age and associated co-morbid conditions on testicular testosterone production rates. Therefore, in middle-aged and older obese men, the measurement of FT or bioavailable testosterone levels using a reliable assay system that is not affected by the prevalent SHBG concentrations is essential in making a correct diagnosis of androgen deficiency. Exclusive reliance on TT alone in the diagnostic work-up of androgen deficiency could result in misclassification and inappropriate treatment choices. Owing to the high prevalence of obesity and weight gain in the general population of middle-aged and older men, as indicated by this and other surveys, this misclassification of men being evaluated for possible androgen deficiency could have significant clinical consequences.

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