Testosterone, Sex Hormone–Binding Globulin, and Frailty in Older Men

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OBJECTIVES: To determine whether testosterone (T) levels are associated with frailty or its components.

DESIGN: Population-based cohort study conducted in three waves (T1: 1987–1989, T2: 1995–1997, T3: 2002–2004).

SETTING: Communities in the Boston, Massachusetts, area.

PARTICIPANTS: Six hundred forty-six men aged 50 to 86 at T_3 with complete data on frailty components and hormone measurements.

MEASUREMENTS: The frailty phenotype was defined as the presence of three or more of the following: weight loss, exhaustion, low physical activity, slowness, and weakness. Men were classified as frail (≥3 components), intermediate (1–2 components), and nonfrail (0 components). Whether total and free T or sex hormone–binding globulin (SHBG) levels were associated cross-sectionally with frailty and with degree of frailty was determined. Potential confounders such as age, chronic disease, lifestyle factors, diet, and physical activity were considered.

RESULTS: No association was observed between total or free T and the frailty phenotype after adjusting for confounders. Conversely, a significant association was observed between SHBG and frailty phenotype with an adjusted odds ratio of 1.25 (95% confidence interval = 1.06–1.46) per 10-nM increase in SHBG levels. Associations between hormones and degree of frailty were similar to those for overall frailty. Of frailty components, grip strength and physical activity, but not exhaustion, slow walking, or weight loss, were associated with total T levels, whereas SHBG was related to weight loss, exhaustion, and physical activity.

CONCLUSION: Total and free T levels were not associated with frailty phenotype, but SHBG was. Furthermore, T and SHBG levels were associated with some, but not all, components of frailty. Therefore, T trials in older men should focus on men experiencing decreases in strength. **J Am Geriatr Soc 55:548–555, 2007.**

Key words: frailty; testosterone; androgens; epidemiology

As human life expectancy has increased steadily on most continents, there has been more attention focused on aging-associated impairments.[1–4] With advancing age, humans experience significant loss of muscle mass and strength that contributes to risk of falls, fractures, and disability.[2,4–8] Functional decline and dependence in older individuals place a large burden on healthcare services and account for more than $62 billion in direct costs and incalculable loss of productivity and quality of life.[9,10] Anabolic therapies, such as androgens, thought to restore muscle mass, strength, and physical function, would be expected to improve clinical outcomes and quality of life and reduce healthcare costs.[11] However, several conceptual and regulatory obstacles have hindered their development. For instance, one significant problem in the design of these trials is that it is not known which measures of physical dysfunction are associated with low testosterone (T) levels and therefore should be used for subject selection.[11]

Several recent efforts to operationalize the concept of individuals at risk for disability are notable. One demonstrated that physical function, assessed according to performance on a short physical performance battery, is predictive of outcomes.[12–14] In a pioneering effort, another described a frailty phenotype characterized by the fulfillment of three or more of the following five criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.[15] The Cardiovascular Health Study (CHS) definition of frailty has been applied with similar results in the Women's Health and Aging Study.[16] For men and women participating in the CHS, frailty defined in this manner was predictive of the risk of incident and future disability, falls, hospitalization, and death.[15,17] Intermediate frailty, defined as the presence of one or two of the five criteria listed above, was also predictive of outcomes and of the risk of becoming frail.[15]

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Frailty is a complex syndrome that likely has a multifactorial pathophysiology; comorbid conditions, systemic inflammation, decreased physical activity, and nutritional and hormonal factors likely contribute to its pathogenesis.[18,19] Of these, hormonal factors, such as alterations in androgen levels and the growth hormone–insulin-like growth factor-1 axis, have received considerable attention, because they are amenable to therapeutic intervention and potentially remediable.[20–22] However, whether frailty phenotype, as defined previously,[15] is associated with circulating T levels is unknown.

To determine whether the frailty phenotype or one or more of its components are associated with circulating T or sex-hormone binding globulin (SHBG, a glycoprotein that binds to sex hormones, specifically T) levels, data from the Massachusetts Male Aging study (MMAS),[23] a prospective, community-based, observational study of aging in middle-aged and older men, were used.

METHODS

Design

The MMAS is a prospective, community-based, observational study of aging in middle-aged and older men, conducted in three waves (T_1: 1987–1989, T_2: 1995–1997, T_3: 2002–2004). The current report uses follow-up T_3 data only. The design has been described previously.[24] At baseline (T_1), men aged 40 to 70 from 11 cities and towns in the Boston, Massachusetts, metropolitan area were randomly selected from annual state census listings. To obtain a sample with approximately equal percentages in each age decade (40–49, 50–59, 60–70), age-stratified cluster sampling was used. Of those eligible, 1,709 (52%) participated at T_1. This response rate reflects, in part, the early-morning phlebotomy, extensive in-home interview, and absence of financial incentive. At T_2, 1,156 of 1,496 eligible men participated (conditional response rate 77%). At T_3, 853 of the 1,351 eligible (conditional response rate 63%) were re-interviewed. More-specific details about follow-up rates are provided elsewhere.[25]

Trained interviewer–phlebotomists visited the men in their homes, administered a standardized interview, and obtained physical measures and blood samples. Unless noted, data collection methods were the same for all waves. The New England Research Institutes' institutional review board approved all protocols, including informed consent procedures, and all participants gave written informed consent.

The primary aim of this analysis was to determine whether hormone levels are associated with frailty, using cross-sectional data from T_3.

Independent Variables

Hormones

The MMAS attempted to account for the fact that features of the research design (e.g., time of day of blood sampling, assay technique) and the type of sample (volunteers vs patients) affect T levels.[26] To control for diurnal variation in hormone levels, two nonfasting blood samples were collected within 4 hours of subjects' awakening.[27] The samples were drawn 30 minutes apart and pooled in equal aliquots at the time of assay to smooth episodic secretion.[28] Blood samples, transported in ice-cooled containers and centrifuged within 6 hours, were stored at -70°C until assayed.

All assays were performed at the Endocrine Laboratory, University of Massachusetts Medical School (Worcester, MA). Total T was determined using radioimmunoassay (Diagnostic Products Corp. Los Angeles, CA). The assay cross-reactivity with dihydrotestosterone was 2.8%. The intra- and interassay coefficients of variation (CVs) for total T were 3.5% and 8.3%, respectively. SHBG was measured using radioimmunoassay (Orion Diagnostica, Espoo, Finland), using chemiluminescent enzyme immunometric assay with Immulite (Diagnostic Products Corp.) at T_3. The intra- and interassay CVs for SHBG were 2.0% and 3.0%, respectively. Free T was calculated from total T and SHBG concentration using the mass action equations as previously described.[29] Calculation of free T concentrations according to this method closely approximates those obtained from equilibrium dialysis.[30] Hormone concentrations are reported in nmol/L using the International System of Units (SI) (conversion factor of 1/0.0347 for T levels to conventional units ng/dL).

Confounders

All measurements used well-validated instruments: depression (Center for Epidemiologic Studies Depression Scale),[31] alcohol,[32] physical activity,[33] height and weight,[34] and diet (Willet semiquantitative 1-year food-frequency questionnaire[35]). Chronic disease, including diabetes mellitus, high blood pressure, heart disease, cancer, arthritis, stroke, and Parkinson's disease, were ascertained according to self-report. An endocrinologist reviewed self-reported prescription medications and identified those that may affect hormone levels.[25]

Dependent Variable: Frailty

Two frailty measures were examined: overall frailty and degree of frailty, both based on the previous approach.[15] Overall frailty was defined as the presence of three or more of the following components: weight loss, exhaustion, low physical activity, slowness, and weakness. For degree of frailty, men were classified as frail (3 or more components), intermediate (1–2 components), and nonfrail (0 components).

The component definitions, as well as a comparison with the previous definition from the CHS, are presented in Table 1. Walking speed was measured using the 50-foot walking test of the Physical Performance Test.[36] The Jamar Hydraulic Hand Dynamometer (Sammons Preston, Bolingbrook, IL), an instrument that quantifies isometric grip force from 0 to 200 pounds, was used to measure grip strength. More details about the Physical Performance Test and grip strength test administration are provided elsewhere.[22]

All cutpoints, including stratification variables (height, body mass index (BMI)), were based on the MMAS rather than the CHS sample, because the studies are based on different populations (CHS: men and women aged 65–101 selected from Health Care Financing Administration (now called Centers for Medicare and Medicaid Services) Medicare eligibility lists; MMAS: population-based, random sample of men who aged 55–86 at T_3).

Because a large percentage of men were missing at least one component (28%), frailty status was inferred using available data, when possible. For overall frailty, those meeting at least three of the criteria regardless of missing

Table 1. Comparison of Cardiovascular Health Study (CHS) and Massachusetts Male Aging Study (MMAS) Frailty Component Definitions

Component	CHS Definition[15]	MMAS Definition*
Weight Loss		
Measure	**Single question (baseline), Change in weight between 2 consecutive years (follow-up).**	**Weight loss between T_2 and T_3. Base cutoff on 20th percentile of weight loss in men aged $\geq$60 at T_2 and who lost weight between T_2 and T_3.**
Definition	**''In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?'' = Yes (baseline) -OR- Unintentional weight loss of at least 5% of previous year's body weight (follow-up)**	**Weight loss $\geq$7 kg (15.4 pounds)**
Exhaustion		
Measure	**Modified 10-item** CES-D	**20-item** CES-D
Definition	''I felt that everything I did was an effort'' $\geq$3 days in the past week. -OR- ''I could not get 'going''' $\geq$3 days in the past week.	Same as CHS definition
Low Physical Activity		
Measure	**Short version of the Minnesota Leisure Time Activity questionnaire.** Use 20th percentile of as cutoff.	**Stanford Five-City questionnaire.** Base cutoff on 20th percentile of activity for **men aged $\geq$60 at T_3.**
Definition	Physical activity $<$ **383 kcal/wk**†	Physical activity $<$ **1.78 metabolic equivalents**†
Slowness		
Measure	**Standardized performance-based measure of physical function.** Stratify by **medium** height. For each height group, use stratum-specific, slowest 20th percentile as a cutoff.	**Physical Performance test 50-foot walk test.** Stratify by **median** height. For each height group, use stratum-specific, slowest 20th percentile of walking time. For both height and walking time, base cutoffs on **men aged $\geq$60 at T_3.**
Definition	Time to walk **15 feet** at usual pace: **height $\leq$173 cm: $\geq$7 seconds** **height $>$173 cm: $\geq$6 seconds**	Time to walk **50 feet.** **height $\leq$174 cm: $\geq$20 seconds** **height $>$174 cm: $\geq$19 seconds** **Any height: Unable to do the walk test (Exception: If the man could not walk because of special circumstances such as amputation, stroke, polio, blindness, back problems, not enough room in the home, this component was considered missing).**
Weakness		
Measure	Grip strength in dominant hand using a Jamar handheld dynamometer, average of **3 measures**, stratified according to BMI quartiles based on the **CHS** sample. Use stratum-specific 20th percentiles.	Grip strength in dominant hand using Jamar Hydraulic Hand dynamometer, **maximum of 2 measures.** Stratified according to BMI quartiles and 20th percentile of strength. Base BMI and strength cutoffs on **men aged $\geq$60 at T_3. Men who attempted but could not perform the test were coded as frail according to the weakness component. Note: Men who reported pain (e.g., arthritis, tendonitis) were not offered grip test, so they were considered to be missing this component.**
Definition	**BMI$\leq$24 = $\leq$29 kg** **BMI 24.1–26 = $\leq$30 kg** **BMI 26.1–28 = $\leq$30 kg** **BMI $\geq$28.0 = $\leq$32 kg**	**BMI$\leq$24.9 = $\leq$28 kg** **BMI 25.0–27.2 = $\leq$30 kg** **BMI 27.3–30.2 = $\leq$32 kg** **BMI $>$30.2 = $\leq$32 kg**

Note: Differences are **bolded.** Overall frailty definition for CHS and MMAS: men who satisfied three or more of the components were classified as frail; otherwise, they were considered nonfrail. Degree of frailty: participants were classified as frail ($\geq$3 components), intermediate (1–2 components), and nonfrail (0 components).

* All cutoffs including cutoffs for stratification variables are based on the MMAS sample.

† The 20th percentiles for the two questionnaires are substantially different because the Minnesota Leisure Time Activity questionnaire measures energy expenditure for leisure time activities only, whereas the Stanford Five-City questionnaire measures total expenditure (including sleep, light, moderate, hard, and very hard activities).

T2 = 1995–1997, T3 = 2002–2004; CES-D = Center for Epidemiologic Studies Depression Scale; BMI = body mass index.

data on the other two were classified as frail, because satisfying three components automatically made them frail. Similarly, those who did not satisfy at least three were classified as nonfrail. For degree of frailty, an analogous approach we used, although a status could not be assigned to men who had some missing and some unsatisfied components. For this reason, the degree of frailty outcome has slightly more missing data.

Analysis Sample

Of the 1,709 men in the original cohort, 795 participated at both T_2 and T_3. From this group, men who reported stroke (n = 56) or Parkinson's disease (n = 1), were taking levodopa-carbidopa (treatment for Parkinson's disease, n = 3) or donepezil (treatment for Alzheimer's disease, n = 7) at either time point, did not have enough data to determine overall frailty status (n = 67), or were missing hormone data at both time points (n = 15) were excluded, resulting in a sample of 646 men. As noted above, the sample size for the degree of frailty outcome was slightly smaller (n = 601) because of missing component data.

Statistical Analysis

Crude and age-specific prevalence were defined as the number of frailty cases divided by the total number of men. The Cochran-Armitage trend test was used to test for linear trend in prevalence across age groups. To test for differences in characteristics according to frailty status, the chi-square or Fisher exact test was used for categorical variables, and the *t* test (overall frailty outcome) or analysis of variance (degree of frailty outcome) for continuous characteristics. Because of their skewed distributions, BMI, total calories, and protein were log transformed before statistical tests were performed, although descriptive statistics were presented on the original scale.

Multiple logistic regression was used to model overall frailty as a function of hormones and confounding variables. The effect of three hormones was examined: total T, free T, and SHBG. Separate models were fit for each hormone. The following confounders were examined: age, chronic disease (diabetes mellitus, hypertension, heart disease, cancer, arthritis, and depression), lifestyle (drinking, physical activity), and diet (calories, protein intake). Smoking was not included because of the small number of frailty cases who smoked. Tests for interactions between the hormones and each confounder were conducted to determine whether the relationship between hormone and frailty differed according to level of the confounder. The analyses for the degree of frailty outcome were done in an analogous fashion using the proportional odds model. Age-adjusted mean total and free T and SHBG were compared in frail and nonfrail men according to each component.

RESULTS

The analysis sample of 646 men was predominantly white (98%) and married (73%) and had a high school education (94%). Mean age ± standard deviation 67.9 ± 8.0 (range 55–86. Approximately half the sample (48%) was overweight (25≤BMI<30), and 28% were obese (BMI ≥30).

Table 2 presents prevalence estimates of overall frailty, degree of frailty, and frailty components at T_3. For the 646 men studied, the prevalence of overall frailty was 7.7% (95% confidence interval (CI) = 5.8–10.1%). The percentage of men who were frail increased substantially with age, starting in those aged 60 to 69. This trend across age groups was statistically significant ($P<.001$, Cochran-Armitage trend test). The number of cases in their 50s and 60s was small (n = 4 and n = 3, respectively). Of the 601 men whose degree of frailty status could be determined, 49.1% had intermediate frailty at T_3 (95% CI = 45.0–53.2%). The prevalence of intermediate frailty increased with each successive age decade except for those in their 80s, of whom there were substantially fewer men (n = 50). The percentage of men who were intermediate or frail also increased

Table 2. Prevalence of Overall Frailty, Degree of Frailty, and Frailty Components at T_3

Frailty Variable	Cases n	Men n	Prevalence at T_3 %	95% Confidence Interval
Overall frailty*				
Crude	50	646	7.7	5.8–10.1
Age-specific				
50–59	4	136	2.9	0.8–7.4
60–69	3	240	1.3	0.3–3.6
70–79	24	218	11.0	7.2–15.9
80–86	19	52	36.5	23.6–51.0
Degree of frailty†‡				
Crude				
None	256	601	42.6	38.6–46.7
Intermediate	295	601	49.1	45.0–53.2
Frail	50	601	8.3	6.2–10.8
Age-specific				
50–59				
None	75	127	59.1	50.0–67.7
Intermediate	48	127	37.8	29.4–46.8
Frail	4	127	3.2	0.9–7.9
60–69				
None	104	220	47.3	40.5–54.1
Intermediate	113	220	51.4	44.6–58.1
Frail	3	220	1.4	0.3–3.9
70–79				
None	70	204	34.3	27.8–41.3
Intermediate	110	204	53.9	46.8–60.9
Frail	24	204	11.8	7.7–17.0
80–86				
None	7	50	14.0	5.8–26.7
Intermediate	24	50	48.0	33.7–62.6
Frail	19	50	38.0	24.7–52.8
Frailty component§				
Weight loss	55	631	8.7	6.6–11.2
Exhaustion	82	644	12.7	10.3–15.6
Low physical activity	109	618	17.6	14.7–20.9
Slowness	142	638	22.3	19.1–25.7
Weakness	139	603	23.1	19.8–26.6

* Men who satisfied three or more of the components were classified as frail; otherwise, they were considered nonfrail.
† Participants were classified as frail (≥3 components), intermediate (1–2 components), and nonfrail (0 components).
‡ Total number of men is lower for degree of frailty because of difficulties in classifying men with missing component data.
§ Total number of men differs by component because of item nonresponse.

with age decade (41%, 53%, 65%, and 86%, respectively). The prevalence of the frailty components ranged from 9% (weight loss) to 23% (weakness).

On average, men who were frail at T_3 had significantly lower free T and higher SHBG at T_3 than those who were not frail (Table 3). Total T did not differ by overall frailty status. The degree of frailty results was consistent with those for overall frailty and, except for total T, exhibited a dose–response effect. Mean free T decreased and SHBG increased with increasing degree of frailty.

Overall frailty was significantly associated with all of the other characteristics shown in Table 3 except for heart disease, cancer, and caloric intake. Frail men were older (76.2 ± 7.4 vs 67.2 ± 7.6). The prevalence of chronic disease was much higher in frail men than in nonfrail men. Thirty-three percent of the frail men were depressed at T_3, compared with 7% of the nonfrail men ($P < .001$). The results for degree of frailty were consistent with those for overall frailty. There was a dose–response relationship between many of the T_3 characteristics and degree of frailty. Mean age and the prevalence of chronic disease increased with increasing degree of frailty.

Table 4 presents crude and adjusted odds ratios (ORs) for overall frailty. There was no significant association between total T and frailty in crude ($P = .66$) or adjusted models ($P = .59$). Before adjustment, low free T was associated with a higher risk of frailty, although when confounding variables were controlled, the effect disappeared. A significant association was observed between SHBG and frailty. After adjustment for confounding, an increase of 10 nM in SHBG levels was associated with a 25% greater risk of frailty (OR = 1.25, 95% CI = 1.06–1.46). Similar results for T and SHBG predicting degree of frailty were observed (data not shown).

Whether total and free T and SHBG levels were associated with individual frailty components was evaluated (Table 5). There were no differences in total or free T levels according to weight loss or exhaustion. Mean total T levels were higher in men considered frail according to the physical activity criterion. Total and free T levels were lower in men considered frail according to slow walking or grip strength, although after adjusting for age, only the association between total T and grip strength remained statistically significant. SHBG was unrelated to walking speed or grip strength but was significantly higher in men considered frail according to the weight loss and physical activity components and significantly lower in men considered frail according to exhaustion.

DISCUSSION

To the authors' knowledge, this is the first study to examine the association between T levels and frailty. Cross-sectional analyses revealed no associations between total T and frailty phenotype, whereas the crude association between higher odds of frailty and lower free T did not hold after adjusting for confounders. In contrast, an increase of 10 nM in SHBG levels was associated with 25% greater odds of frailty ($P = .006$). Associations between hormones and degree of frailty were similar to those for overall frailty. Of frailty components, grip strength and physical activity, but not exhaustion, walking speed, or weight loss, were associated with total T levels. After adjustment for age, none of the components were associated with free T.

The prevalence of overall frailty in the MMAS at T_3 was 7.7% and intermediate frailty 49.1%; these prevalence rates are similar to those reported previously in the CHS[15] but lower than those reported in the Women's Health Initiative.[37] The average age of participants in the Women's Health Initiative was considerably higher than those of men in the current study.[37] The prevalence rates were low in men younger than 70 but increased substantially with age starting in the 70s.[15]

Two possible limitations arise in this work. First, the way the Stanford Five-City Questionnaire was administered may have artificially inflated the scores. The precise contribution of this component requires further investigation, although in this investigation, the physical activity measure was used to establish a 20% cutoff and no attempt was made to interpret actual values. Second, the definition of frailty used was necessarily an approximation of the previous definition. Given the debate still surrounding the operational definition, the MMAS data, gathered originally for other purposes, provided a unique opportunity to examine the relationship between hormone levels and frailty in older men.

In general, frail individuals were more likely to report comorbid conditions, such as diabetes mellitus, high blood pressure, arthritis, and depression. These data were consistent with previous studies that also found similar associations between comorbid conditions and the risk of frailty and dependency.[15,17,38–40] In longitudinal studies, the development of chronic illnesses increases the risk of incident,[41] prevalent,[40,42–44] and future physical dependency.[38] Chronic conditions are associated with greater risk of mobility limitations,[45] disability, institutionalization, and mortality.[15,42,46] It has been shown previously that occurrence of chronic disorders affects T levels in men.[47,26] A summary index based on the number of comorbid conditions provides a good measure of fitness and frailty and robustly predicts mortality.[48] Thus, chronic illness not only increases the risk of frailty, but also increases the likelihood of having low T levels.

Although no association was observed between frailty and total or free T after adjusting for confounders, some frailty components (grip strength and physical activity) were associated with total T levels, whereas others (exhaustion and weight loss) were not, and age confounded the association with walking speed. Several cross-sectional surveys have also reported an association between total and bioavailable T levels and measures of muscle strength[49,50] and self-reported and performance-based measures of physical function.[50,51] In clinical trials in healthy older men and men with chronic illnesses, T supplementation improves muscle strength[52–56] and self-reported physical function.[57] Some, but not all, T trials have reported improvements in performance-based measures of physical function.[11,57,58] A significant association was not found in the current study between total and free T levels and exhaustion or weight loss.

Although weight loss was associated with higher SHBG levels, the results regarding physical activity and SHBG were surprising, because obesity, which is associated with lower SHBG,[59] would be inversely related to physical activity and thus positively related to SHBG. However, the

Table 3. Descriptive Statistics for Wave 3 (T_3) Characteristics According to T_3 Frailty and Degree of Frailty

	T3 Frailty			T3 Degree of Frailty				
T_3 Characteristic	No (n = 596)	Yes (n = 50)	*P*-value*†	No (n = 256)	Intermediate (n = 295)	Frail (n = 50)	*P*-value†‡	All
Hormones, nM, mean ± SD								
Total testosterone	14.5 ± 5.7	14.3 ± 6.3	.82	15.2 ± 5.7	14.1 ± 5.5	14.3 ± 6.3	.12	14.5 ± 5.7
Free testosterone	0.25 ± 0.10	0.2 ± 0.08	<.001	0.26 ± 0.10	0.25 ± 0.10	0.2 ± 0.08	<.001	0.25 ± 0.10
Sex-hormone binding globulin	50.5 ± 19.7	64 ± 22.4	<.001	50.6 ± 19.8	51.1 ± 20.1	64 ± 22.4	<.001	51.5 ± 20.2
Age, mean ± SD	67.2 ± 7.6	76.2 ± 7.4	<.001	65.5 ± 7.1	68.6 ± 7.9	76.2 ± 7.4	<.001	67.9 ± 8.0
Chronic disease, n (%)§								
Diabetes mellitus	54 (9)	11 (22)	.004	15 (6)	36 (12)	11 (22)	<.001	65 (10)
High blood pressure	281 (47)	32 (64)	.02	112 (44)	143 (49)	32 (64)	.03	313 (48)
Heart disease	130 (22)	16 (32)	.1	52 (20)	69 (23)	16 (32)	.19	146 (23)
Cancer	144 (24)	18 (36)	.06	50 (20)	80 (27)	18 (36)	.02	132 (20)
Arthritis/rheumatism	246 (41)	29 (58)	.02	99 (39)	124 (42)	29 (58)	.04	275 (43)
Depression	42 (7)	16 (33)	<.001	6 (2)	34 (12)	16 (33)	<.001	58 (9)
Lifestyle								
Daily alcohol use, ounces, n (%)								
0	111 (19)	23 (46)	<.001	43 (17)	64 (22)	23 (46)	<.001	134 (21)
>0	485 (81)	27 (54)		213 (83)	231 (78)	27 (54)		512 (79)
Dietary intake, mean ± SD								
Calories, kcal/d	1,904 ± 678	1,786 ± 749	.17	1,860 ± 611	1,941 ± 734	1,786 ± 749	.29	1,896 ± 683
Protein, g/d	82 ± 30	71 ± 30	.04	79 ± 28	84 ± 31	71 ± 30	.01	81 ± 30

* Test of the null hypothesis that characteristic does not differ by frailty status; *t*-test for continuous variables, Fisher exact test for depression because of low expected cell counts, and chi-square test for the other categorical variables.

† All means and standard deviations (SDs) are reported on the original scale, but tests for total calories and protein were performed on the log scale.

‡ Test of the null hypothesis that characteristic does not differ by degree of frailty: analysis of variance F test for continuous variables and chi-square test for categorical variables.

§ Self-report.

Table 4. Frailty at Wave 3 (T_3)

T_3 Hormone*	OR†	(95% Confidence Interval)	*P*-value‡
Total T			
Crude	0.89	(0.51–1.54)	.66
Adjusted	1.18	(0.65–2.12)	.59
Free T			
Crude	0.59	(0.39–0.88)	.01
Adjusted	0.78	(0.50–1.22)	.27
SHBG			
Crude	1.31	(1.14–1.49)	<.001
Adjusted	1.25	(1.06–1.46)	.006

* Crude models contain a term for T_3 hormone and no other independent variables. Adjusted models are adjusted for age, diabetes mellitus, and depression; free testosterone (T) also adjusted for log caloric intake.
† Odds ratio (OR) for T_3 frailty expressed per 10 nM for total T, 0.1 nM for free T, and 10 nM for sex-hormone binding globulin (SHBG).
‡ *P*-value for test of null hypothesis that OR for hormone equals 1; Wald test.

opposite result was found; men who were less physically active had higher SHBG levels (Table 5). Although exercise has been associated with acute decreases in SHBG,[60] this is not sustained over time.[61] The higher SHBG in men with exhaustion could be related to underlying disease; the higher SHBG levels, exhaustion, and less physical activity could all result from chronic disease and systemic inflammation.[18] Further studies to determine the relationship between physical activity, exhaustion, frailty, and SHBG would clarify these findings. It is possible that not all the components of the frailty phenotype are pathophysiologically related and that the pathogenic factors that lead to exhaustion and weight loss are different from those that contribute to muscle strength and physical function and activity.

Table 5. Differences In Total Testosterone (T), Free T, and Sex-Binding Hormone Globulin (SHBG) According to Frailty Component

Frailty Component Hormone, nM	Frail According to Component					
	Unadjusted Mean			Age-Adjusted Mean		
	No	Yes	*P*-value*	No	Yes	*P*-value*
Weight loss						
Total T	14.5	15.3	.31	14.5	15.4	.26
Free T	0.249	0.244	.74	0.248	0.251	.85
SHBG	51.1	58.6	.01	51.2	57.1	.04
Exhaustion						
Total T	14.7	13.5	.08	14.7	13.5	.11
Free T	0.250	0.239	.36	0.249	0.244	.70
SHBG	52.1	47.8	.09	52.3	46.5	.02
Physical activity						
Total T	14.2	15.8	.01	14.2	16.1	.002
Free T	0.250	0.239	.29	0.247	0.255	.43
SHBG	49.4	61.7	<.001	50.1	58.7	<.001
Slow walking						
Total T	14.7	13.7	.076	14.7	13.9	.18
Free T	0.255	0.224	.002	0.251	0.239	.22
SHBG	50.5	54.9	.03	51.5	51.4	.99
Grip strength						
Total T	14.9	13.4	.008	14.9	13.6	.03
Free T	0.258	0.224	<.001	0.254	0.239	.13
SHBG	51.1	52.7	.42	52.2	49.0	.12

* Test of null hypothesis that mean hormone does not differ by frailty component.

These data have implications for the design of T trials in older men. The Institute of Medicine Expert Panel on the Future of Testosterone Research recommended short-term efficacy trials of T in older men with symptomatic physical dysfunction, cognitive dysfunction, sexual dysfunction, or loss of vitality.[62] A major concern in the design of these T trials for men with physical dysfunction has been the uncertainty about what domains of physical dysfunction are associated with T levels and should constitute the basis for subject selection in these trials. T therapy improves grip strength,[11,53] but it is not known whether T supplementation improves walking speed in older men with functional limitations. The observations in the current study that strength is associated with T levels suggest that T trials in older men should target men experiencing decreased strength rather than those reporting exhaustion and weight loss.

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REFERENCES

1. Spillman BC. Changes in elderly disability rates and the implications for health care utilization and cost. Milbank Q 2004;82:157–194.
2. Evans WJ, Campbell WW. Sarcopenia and age-related changes in body composition and functional capacity. J Nutr 1993;123:465–468.
3. Hughes VA, Frontera WR, Roubenoff R et al. Longitudinal changes in body composition in older men and women: Role of body weight change and physical activity. Am J Clin Nutr 2002;76:473–481.
4. Morley JE, Baumgartner RN, Roubenoff R et al. Sarcopenia. J Lab Clin Med 2001;137:231–243.
5. Baumgartner RN, Koehler KM, Gallagher D et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755–763.
6. Melton LJ 3rd, Khosla S, Riggs BL. Epidemiology of sarcopenia. Mayo Clin Proc 2000;75(Suppl):S10–S12; discussion S12–S13.
7. Roubenoff R, Hughes VA. Sarcopenia. Current concepts. J Gerontol A Biol Sci Med Sci 2000;55A:M716–M724.
8. Lexell J, Downham D, Sjostrom M. Distribution of different fibre types in human skeletal muscles. A statistical and computational study of the fibre type arrangement in m. vastus lateralis of young, healthy males. J Neurol Sci 1984;65:353–365.
9. Report to Congressional Requesters. SSA Disability: Other Programs May Provide Improving Return to Work Efforts (GA O-01–153). Washington, DC: U.S. General Accounting Office, 2000.

10. Americans with Disabilities: Household Economic Studies. Washington, DC: U.S. Department of Commerce, 2001.
11. Bhasin S, Calof OM, Storer TW et al. Drug insights: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab 2006;2:146–159.
12. Guralnik JM, Simonsick EM, Ferrucci L et al. A short physical performance battery assessing lower extremity function. Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94.
13. Guralnik JM, Ferrucci L, Simonsick EM et al. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–561.
14. Guralnik JM, Ferrucci L, Pieper CF et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55A:M221–M231.
15. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56A:M146–M156.
16. Bandeen-Roche K, Xue QL, Ferrucci L et al. Phenotype of frailty: Characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006;61:262–266.
17. Fried TR, Mor V. Frailty and hospitalization of long-term stay nursing home residents. J Am Geriatr Soc 1997;45:265–269.
18. Walston J, McBurnie MA, Newman A et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: Results from the Cardiovascular Health Study. Arch Intern Med 2002; 162:2333–2341.
19. Walston J, Fried LP. Frailty and the older man. Med Clin North Am 1999;83:1173–1194.
20. Villareal DT, Morley JE. Trophic factors in aging. Should older people receive hormonal replacement therapy? Drugs Aging 1994;4:492–509.
21. Morley JE, Kim MJ, Haren MT. Frailty and hormones. Rev Endocr Metab Disord 2005;6:101–108.
22. Morley JE, Kaiser FE, Sih R et al. Testosterone and frailty. Clin Geriatr Med 1997;13:685–695.
23. O'Donnell AB, Travison TG, Harris SS et al. Testosterone, dehydroepiandrosterone and physical performance in older men: Results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2006;91:425–431.
24. O'Donnell AB, Araujo AB, McKinlay JB. The health of normally aging men. The Massachusetts Male Aging Study (1987–2004). Exp Gerontol 2004; 39:975–984.
25. Mohr BA, Guay AT, O'Donnell AB et al. Normal, bound and nonbound testosterone levels in normally ageing men: Results from the Massachusetts Male Aging Study. Clin Endocrinol (Oxford) 2005;62:64–73.
26. Gray A, Berlin JA, McKinlay JB et al. An examination of research design effects on the association of testosterone and male aging: Results of a meta-analysis. J Clin Epidemiol 1991;44:671–684.
27. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983;56:1278–1281.
28. Brambilla DJ, McKinlay SM, McKinlay JB et al. Does collecting repeated blood samples from each subject improve the precision of estimated steroid hormone levels? J Clin Epidemiol 1996;49:345–350.
29. Södergard R, Backstrom T, Shanbhag V et al. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16:801–810.
30. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–3672.
31. Radloff LS. The CES-D Scale. A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
32. Khavari KA, Farber PD. A profile instrument for the quantification and assessment of alcohol consumption. The Khavari Alcohol Test. J Stud Alcohol 1978;39:1525–1539.
33. Sallis JF, Haskell WL, Wood PD et al. Physical activity assessment methodology in the Five-City Project. Am J Epidemiol 1985;121:91–106.
34. McKinlay S, Kipp D, Johnson P et al. A Field Approach for Obtaining Physiological Measures in Surveys of General Populations: Response Rates, Reliability and Costs. Proceedings of the Fourth Conference on Health Survey Research Methods (Publication no. PHS 84–3346). Washington, DC: U.S. Department of Health and Human Services, 1984.
35. Willett WC, Reynolds RD, Cottrell-Hoehner S et al. Validation of a semiquantitative food frequency questionnaire: Comparison with a 1-year diet record. J Am Diet Assoc 1987;87:43–47.
36. Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc 1990;38:1105–1112.
37. Woods NF, LaCroix AZ, Gray SL et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc 2005;53:1321–1330.
38. Wolff JL, Boult C, Boyd C et al. Newly reported conditions and onset of functional dependency. J Am Geriatr Soc 2005;53:851–855.
39. Dunlop D, Manheim L, Sohn M et al. Incidence of functional limitations in older adults: The impact of gender, race, and chronic conditions. Arch Phys Med Rehabil 2002;83:964–971.
40. Fried LP, Bandeen-Roche K, Kasper J et al. Association of comorbidity with disability in older women: The Women's Health and Aging Study. J Clin Epidemiol 1999;52:27–37.
41. Boult C, Kane R, Louis T et al. Chronic conditions that lead to functional limitations in the elderly. J Gerontol A Biol Sci Med Sci 1994;49A:M28–M36.
42. Fried LP, Guralnik JM. Disability in older adults. Evidence regarding significance, etiology, and risk. J Am Geriatr Soc 1997;45:92–100.
43. Freedman V, Martin L. Contributions of chronic conditions to aggregate changes in old age functioning. Am J Public Health 2000;90:1755–1760.
44. Guccione A, Felson D, Anderson J et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Public Health 1994;84:351–358.
45. Di Fazio I, Franzoni S, Frisoni GB et al. Predictive role of single diseases and their combination on recovery of balance and gait in disabled elderly patients. J Am Med Dir Assoc 2006;7:208–211.
46. Fried LP, Kronmal RA, Newman AB et al. Risk factors for 5-year mortality in older adults. The Cardiovascular Health Study. JAMA 1998;279:585–592.
47. Gray A, Feldman HA, McKinlay JB et al. Age, disease, and changing sex hormone levels in middle-aged men: Results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991;73:1016–1025.
48. Mitnitski A, Song X, Skoog I et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc 2005;53:2184–2189.
49. Roy TA, Blackman MR, Harman SM et al. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 2002;283:E284–E294.
50. Schaap LA, Pluijm SM, Smit JH et al. The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. Clin Endocrinol (Oxford) 2005;63:152–160.
51. van den Beld AW, de Jong FH, Grobbee DE et al. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 2000;85:3276–3282.
52. Bhasin S, Storer TW, Javanbakht M et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000;283:763–770.
53. Bhasin S, Woodhouse L, Casaburi R et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 2005;90:678–688.
54. Casaburi R, Bhasin S, Cosentino L et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:870–878.
55. Urban RJ, Bodenburg YH, Gilkison C et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 1995;269:E820–E826.
56. Ferrando AA, Sheffield-Moore M, Yeckel CW et al. Testosterone administration to older men improves muscle function. Molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 2002;282:E601–E607.
57. Snyder PJ, Peachey H, Hannoush P et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647–2653.
58. Page ST, Amory JK, Bowman FD et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90: 1502–1510.
59. Niskanen L, Laaksonen DE, Punnonen K et al. Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. Diabetes Obes Metab 2004;6:208–215.
60. Zmuda JM, Thompson PD, Winters SJ. Exercise increases serum testosterone and sex hormone-binding globulin levels in older men. Metabolism 1996;45:935–939.
61. Cooper CS, Taaffe DR, Guido D et al. Relationship of chronic endurance exercise to the somatotropic and sex hormone status of older men. Eur J Endocrinol 1998;138:517–523.
62. Liverman C, Glazer D. The IOM Report on the Future of Testosterone Research in Older Men. Washington, DC: The National Academies Press, 2004.