Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study

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Context: The prevalence of frailty increases, whereas testosterone decreases, as men age. Low testosterone may be a risk factor for development of this syndrome.

Objective: Our objective was to determine whether testosterone levels are associated with frailty.

Design: We conducted a prospective cohort study.

Setting and Participants: Between 2001 and 2004, frailty was assessed in 3616 community-dwelling men aged 70–88 yr. Frailty was reassessed in 1586 men aged 76–93 yr in 2008–2009.

Main Outcome Measures: Frailty was assessed with the FRAIL scale, comprising five domains: fatigue, difficulty climbing a flight of stairs, difficulty walking more than 100 m, more than five illnesses present, or weight loss greater than 5%. Testosterone, SHBG, and LH were assayed at baseline. Free testosterone was calculated using mass action equations.

Results: At baseline, 15.2% of men (n = 548) were frail (at least three deficits), increasing to 23.0% (n = 364) at follow-up. At baseline, each 1 SD decrease in total or free testosterone level was associated with increased odds of frailty [odds ratio (OR) = 1.23; 95% confidence interval (CI) = 1.11–1.38, and OR = 1.29; 95% CI = 1.15–1.44 for total and free testosterone, respectively]. Lower LH was associated with reduced odds of frailty (OR = 0.88; 95% CI = 0.81–0.95). Adjustments were made for age, body mass index, smoking, diabetes, social support, and other covariates. At follow-up, only lower free testosterone levels (OR = 1.22; 95% CI = 1.05–1.42) predicted frailty.

Conclusions: Lower free testosterone was independently associated with frailty at baseline and follow-up. Randomized trials should explore whether testosterone therapy can prevent the development of frailty. **(*J Clin Endocrinol Metab* 95: 3165–3172, 2010)**

Frailty becomes more prevalent with increasing age but is not an inevitable consequence of aging (1). Although many clinicians believe they can easily recognize the syndrome, it is not specified in the International Classification of Diseases, and there is no consensus as to its definition (2). Generally, frailty is defined as a decline in multiple organ systems leading to loss of function, diminished capacity to cope with stressors, and increased risk of death and disability (1–3). A key consequence of the syndrome is that even minor stressors are likely to result in adverse outcomes.

Frailty is typically operationalized in one of three ways. Some have postulated a phenotype-based approach in

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Abbreviations: BMI, Body mass index; CI, confidence interval; OR, odds ratio; W1, wave 1.

which an individual is considered frail if a given number of features are present. For example, Fried and colleagues (3) suggest an individual is frail if three or more of the following five criteria are met: unintentional weight loss, exhaustion, poor grip strength, slow walking speed, or low physical activity. Others have proposed a frailty index based on a count of accumulated deficits (4). Alternatively, clinicians can form a subjective opinion based on a clinical examination and history taking. The first approach is simple but uses a restrictive set of criteria that may not be relevant to every case. The second approach has good predictive ability but is time consuming and not practical in a clinical setting, whereas the final approach is not feasible in large-scale epidemiological studies (5). Recently, the International Academy of Nutrition, Health, and Aging proposed the FRAIL scale, incorporating elements from both of the first two approaches (6, 7).

The physiological pathways leading to frailty are complex, but there is evidence that testosterone may play an important role in aging men (8). Testosterone is the major circulating androgen in males and is mostly bound to SHBG and albumin, with approximately 2% unbound, or free (9). The free and albumin-bound portions are generally considered the more biologically active. Testosterone supports muscle function and growth (10), promotes erythropoiesis (11), maintains bone mineral density (12), and may stimulate appetite (13). Hypogonadal men typically present with muscle wasting, decreased bone mineral density, and loss of energy (14), reminiscent of the frailty syndrome. Androgen deprivation therapy for prostate cancer produces similar effects (15). In contrast, hemoglobin levels and grip strength have been shown to improve in hypogonadal men treated with testosterone (16), whereas androgen therapy in older men generally results in at least modest increases in muscle strength (17).

Two studies have explored the association between testosterone and frailty, reporting conflicting results. The first, a cross-sectional analysis, found an association between high SHBG levels and frailty but not with testosterone (18). The second, a prospective study, found a cross-sectional association between low free testosterone and frailty but was unable to demonstrate a longitudinal association (19). However, both studies may have lacked statistical power to detect small to moderate effects. We designed the present study to determine the association between testosterone and frailty (measured by the FRAIL scale) in a large cohort of community-dwelling men aged 70–88 yr at baseline. We hypothesized that men with lower testosterone levels would be more likely to be frail at baseline and after a follow-up period of 4–7 yr.

Subjects and Methods

Study population

The Health in Men Study is a longitudinal study of men who originally participated in a trial of screening for abdominal aortic aneurysm. A detailed description of the Health in Men Study is published elsewhere (20), but in summary, in 1995, 41,000 mostly Caucasian men aged 65 yr and older living in Perth, Western Australia, were randomly selected from the electoral roll (enrollment to vote being compulsory for Australian citizens). Of these, 2296 died before invitation, and 19,352 men were subsequently invited into each of the screening and control arms of the trial. Between 1996 and 1999 (wave 1, W1), 12,203 men in the screening arm attended a clinic and completed a questionnaire, providing a range of demographic and risk factor data. Approximately 5 yr later, 10,940 surviving men were invited to participate in a follow-up study. Between 2001 and 2004 (wave 2, W2), 4263 completed a second questionnaire and attended a clinic, whereas 1322 returned a questionnaire only. An early morning blood sample was obtained from 4249 clinic attendees. In 2008–2009 (wave 3, W3), 7445 surviving men were mailed a third questionnaire, of which 3274 responded. The Human Research Ethics Committee of the University of Western Australia provided ethical approval for the study, and all men gave written informed consent to participate. Research protocols complied with the Helsinki Declaration for research conducted with humans.

Cohort for assessment of frailty

Of the 4249 men who provided sera at W2, testosterone, SHBG, and LH could be assayed in 4150. Of these, we excluded men with prostate cancer or previous orchidectomy and those receiving GnRH analogs, antiandrogen therapy, or testosterone supplementation, leaving 3638 men. Of these, an additional 22 men with missing data for at least one frailty component were excluded, leaving 3616 men for analysis at W2. Of the 3274 men returning a questionnaire at W3, 1757 had provided sera at W2 and satisfied exclusion criteria as outlined above. After exclusion of 171 men with missing frailty data, 1586 men remained for analysis at W3.

Assessment of frailty

We assessed frailty at W2 and W3 with the FRAIL scale (6, 7). Five domains are assessed in this screening tool: fatigue, resistance (ability to climb a single flight of stairs), ambulation (ability to walk one block), illnesses (more than five), and loss of weight (more than 5%). Frailty increases with the progressive accumulation of deficits. Fatigue, resistance, and ambulation were assessed from responses to the SF-36 Health Survey (21). Participants scored positive for fatigue if they responded "all of the time," "most of the time," or "a good bit of the time" to the questions "did you feel worn out?" or "did you feel tired?" or answered "some of the time," "a little of the time," or "none of the time" to the question "did you have a lot of energy?" Deficits were recorded for resistance or ambulation if participants reported that they were "limited a lot" or "limited a little" in their ability to climb one flight of stairs, or walk 100 m, respectively. A deficit was recorded for illness if the participant reported more than five of the following: arthritis, diabetes, angina or myocardial infarction, hypertension, stroke, asthma, chronic bronchitis, emphysema, osteoporosis, colorectal cancer, skin cancer, de-

pression or an anxiety disorder, Alzheimer's disease or other dementia, or leg ulcers. Participants scored positive for weight loss if their weight decreased by more than 5% between W1 and W2 or W2 and W3.

Biochemical assessment

Blood samples were collected at W2 between 0800 and 1030 h to minimize circadian variation. Serum was prepared immediately after phlebotomy and stored at −80 C until assayed. Biochemical assays were performed in the Biochemistry Department, PathWest, Royal Perth Hospital, Western Australia. Serum total testosterone, SHBG, and LH were determined by chemiluminescent immunoassays on an Immulite 2000 analyzer (Diagnostic Products Corp. Biomediq, Doncaster, Australia). Between-day imprecision (coefficient of variation) for total testosterone was 11.2% at 7.2 nmol/liter and 8.9% at 18 nmol/liter; for SHBG, it was 6.7% at 5.2 nmol/liter and 6.2% at 81 nmol/liter; and for LH, it was 6.4% at 2.3 IU/liter and 5.8% at 19 IU/liter. The working ranges of the assays were 0.7–55 nmol/liter for testosterone, 2–180 nmol/liter for SHBG, and 0.1–200 IU/liter for LH. The normal range for these assays in men is 8–35 nmol/liter for testosterone, 10–70 nmol/liter for SHBG, and 1–8 IU/liter for LH. Free testosterone, the fraction not bound to SHBG or albumin, was estimated using mass action equations as described by Vermeulen and colleagues (22). The few men with undetectable results were assigned the lower limit of the working range. Serum glucose, low-density lipoprotein, high-density lipoprotein, total cholesterol, and triglycerides were assayed using a Roche Hitachi 917 analyser (Roche Diagnostic GmbH, Mannheim, Germany).

Validation of the FRAIL scale

The FRAIL scale has yet to be validated (6). We therefore tested its predictive value for death and disability, an approach consistent with previous studies (3, 5). Mortality records were obtained from the Western Australian Data Linkage System (23), which links together data from the state cancer registry, death registry, and hospital morbidity data system (which includes codes for multiple medical diagnoses and procedures for all admissions to private and public hospitals). Medical comorbidity, assessed by Charlson's weighted comorbidity index (24), was included as a covariate in the mortality and disability models as a risk factor, and also because it may confound the relationship between frailty and these endpoints. Hospital morbidity records from 1990 to W2 were used to build the index. Disability was assessed at W3 from responses to modified forms of the Katz Index of Independence in Activities of Daily Living (ADL) (25) and Lawton Instrumental Activities of Daily Living (IADL) scale (26). Participants were considered to have a disability if they were unable to perform at least one ADL or IADL.

Other items of interest

Height (in centimeters), weight (in kilograms), and blood pressure were measured in clinic attendees at W1 and W2. Height and weight were self-reported at W3. Questionnaire data at W1 and W2 and biochemical assessment at W2 were used to identify men with dyslipidemia. Men who had been diagnosed with the condition, reported use of lipid-lowering medication, or men with fasting low-density lipoprotein of 3.4 mmol/liter or higher, high-density lipoprotein less than 0.9 mmol/liter, triglycerides of 1.8 mmol/liter or higher, or total cholesterol of 5.5 mmol/liter or higher were considered to have dyslipidemia. Questionnaire and clinical data at W1 and W2 was used to identify men with hypertension. Men who had been diagnosed with the condition, reported use of antihypertensive medication, or had a measured blood pressure greater than or equal to 140/90 mm Hg were considered to have hypertension. Questionnaire data at W1, W2, and W3 and biochemical assessment at W2 were used to identify men with diabetes. Men who had been diagnosed with the condition, reported use of glucose-lowering medication, or had a fasting or nonfasting glucose of 7 mmol/liter or higher or 11.1 mmol/liter or higher, respectively, were considered to have diabetes. Men were asked about tobacco use at all three time points. Social support was assessed with the Adaptability, Partnership, Growth, Affection and Resolve (APGAR) scale (27) at W2.

Statistical analysis

The statistical package Stata, version 10.0, was used to analyze the data (StataCorp, College Station, TX). A Cox proportional hazards model was used to test the association between frailty and mortality. Adjustments were made for age, body mass index (BMI), hypertension, dyslipidemia, diabetes, Charlson's index, and smoking. Assessment of the Schoenfeld residuals confirmed the proportional hazards assumption. The association between frailty and disability was tested with binary logistic regression. Adjustments were made as per the survival model. Tests for trend in hormone levels across categories of the FRAIL scale were performed with Cuzik's test for trend. Associations between hormonal parameters and frailty at W2 and W3 were assessed with binary logistic regression models. Men with three or more deficits were considered frail. Hormonal parameters were entered into the models as Z-scores, placing them on a common, metric-free scale. Odds ratios (OR) reflect the effect of a 1 SD decrease in hormone level. Adjustments were made for age, BMI, smoking, diabetes, social support, and impairments in vision and hearing. All tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Sociodemographic, biochemical, and clinical characteristics of men with complete frailty and sex hormone data are shown in Table 1. At W2, 38.6% (n = 1398) had no components of the frailty syndrome, whereas 46.2% (n = 1670) had intermediate frailty (*i.e.* one to two deficits), and 15.2% (n = 548) were frail (*i.e.* at least three deficits). After a follow-up period of 5.3 ± 0.8 yr (W3), 30.6% (n = 486) met no frailty criteria, whereas 46.4% (n = 736) had intermediate frailty, and 23.0% (n = 364) were frail. Of the 548 frail men at baseline, 343 did not participate in the follow-up study, and 165 (30.1%) of these had died. Of the 205 frail men who did participate in the follow-up study, complete frailty data were available for 156. Of these, 74.4% (n = 116) remained frail, 23.7% (n = 37) had returned to an intermediate state, and 1.9% (n = 3) had no components of the frailty syndrome.

TABLE 1. Sociodemographic, biochemical, and clinical characteristics of the study population

Variable	Time point W2 (n = 3616)	Time point W3 (n = 1586)
n (%)		
FRAIL scale		
0	1398 (38.6)	486 (30.6)
1	1107 (30.6)	450 (28.4)
2	563 (15.6)	286 (18.0)
3	383 (10.6)	214 (13.5)
4	147 (4.1)	120 (7.6)
5	18 (0.5)	30 (1.9)
FRAIL scale components		
Fatigue	1521 (42.1)	635 (40.0)
Resistance	1053 (29.1)	631 (39.8)
Ambulation	628 (17.4)	348 (21.9)
Illness	153 (4.2)	169 (10.7)
Loss of weight	705 (19.5)	511 (32.2)
Overall frailty (≥3 deficits)	548 (15.2)	364 (23.0)
Diabetes mellitus	568 (15.7)	313 (19.7)
Smoking status[a]		
Never smoked	1208 (33.4)	580 (36.6)
Ex-smoker	2208 (61.1)	958 (60.5)
Current smoker	200 (5.5)	45 (2.9)
Mean ± SD		
Age (yr)	76.9 ± 3.6	81.5 ± 3.6
BMI (kg/m^2)	26.5 ± 3.6	25.7 ± 3.4
Total testosterone (nmol/liter)	15.4 ± 5.6	
Free testosterone (pmol/liter)	278 ± 96.5	
SHBG (nmol/liter)	42.4 ± 16.7	
LH (IU/liter)	5.8 ± 5.3	
Family APGAR	8.4 ± 2.4	
Friends APGAR	7.0 ± 3.0	

APGAR, Adaptability, Partnership, Growth, Affection, and Resolve scale.

[a] Smoking categories sum to 1583 at W3 due to missing data.

Validation of the FRAIL scale

Frailty at W2 predicted all-cause mortality in a graded manner, as shown in Fig. 1.

This association was tested with a multivariate Cox proportional hazards model, given in Table 2. Owing to the small number of men with all five frailty components, men with four or more deficits were collapsed into a single category. After adjustment, frailty at W2 continued to predict all-cause mortality.

The predictive utility of the FRAIL scale for disability was tested with a logistic regression model. After adjustment for age, BMI, medical comorbidity, and smoking status as per the mortality model, frailty (at least three deficits) at W2 was associated with increased odds of disability at W3 [OR = 3.95; 95% confidence interval (CI) = 2.73–5.72; $P < 0.001$].

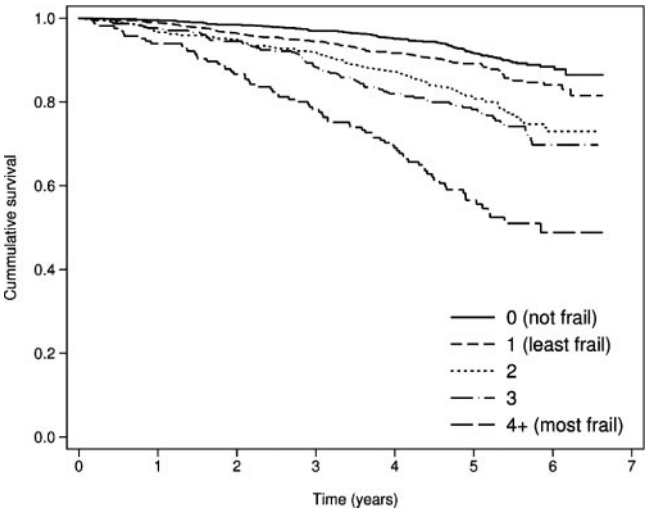

FIG. 1. Kaplan-Meier survival curves showing association between FRAIL scale at W2 and subsequent all-cause mortality.

Cross-sectional associations with frailty

As illustrated in Fig. 2, there was a trend for mean total testosterone ($z = -5.15$; $P < 0.001$) and free testosterone levels ($z = -7.83$; $P < 0.001$) to be lower, and LH levels to be higher ($z = 5.19$; $P < 0.001$) across increasing levels of frailty. SHBG levels were similar across the FRAIL scale ($z = 1.18$; $P = 0.237$).

Binary logistic regression was performed to determine factors associated with frailty at W2. In univariate analyses, each 1 SD decrease in total testosterone (OR = 1.32; 95% CI = 1.19–1.46) and free testosterone (OR = 1.47; 95% CI = 1.32–1.64) was associated with increased odds

TABLE 2. Cox proportional hazards model of variables at W2 and association with subsequent all-cause mortality

Variable	HR	95% CI	*P* value
FRAIL scale			
0	1		
1	1.38	1.07–1.78	0.013
2	2.00	1.53–2.63	<0.001
3	2.27	1.70–3.04	<0.001
≥4	3.97	2.89–5.45	<0.001
Age (yr)	1.10	1.07–1.12	<0.001
BMI (kg/m^2)	0.96	0.94–0.99	0.005
Hypertension[a]	0.92	0.75–1.13	0.418
Dyslipidemia[a]	0.87	0.72–1.05	0.140
Diabetes mellitus[a]	0.93	0.73–1.19	0.561
Charlson's index			
0	1		
1–2	1.33	1.09–1.64	0.006
3–4	1.71	1.30–2.26	<0.001
≥5	2.44	1.74–3.44	<0.001
Smoking status			
Never smoked	1		
Ex-smoker	1.13	0.92–1.38	0.251
Current-smoker	2.18	1.58–3.02	0.001

HR, Hazard ratio.

[a] Denotes diagnosis of or treatment for this condition.

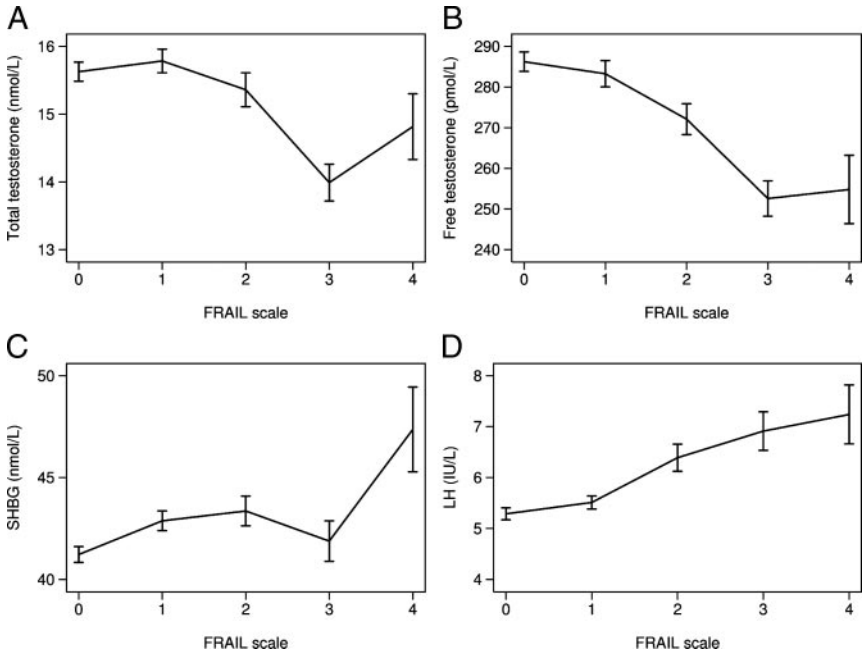

FIG. 2. Mean (±1 SEM) total testosterone (A), free testosterone (B), SHBG (C), and LH (D) measured at W2, stratified by FRAIL scale at W2. Higher scores indicate greater frailty. Men with four or more deficits were combined into a single category.

of frailty, whereas every 1 SD decrease in LH was associated with reduced odds of frailty (OR = 0.81; 95% CI = 0.75–0.87). Lower levels of SHBG were not associated with frailty (OR = 0.93; 95% CI = 0.85–1.01). After adjustment, total testosterone (OR = 1.23; 95% CI = 1.11–1.38), free testosterone (OR = 1.29; 95% CI = 1.15–1.44) and LH (OR = 0.88; 95% CI = 0.81–0.95) continued to be associated with frailty, as shown in Table 3.

Longitudinal associations with frailty

As illustrated in Fig. 3, there was a trend for mean total testosterone ($z = -3.79$; $P < 0.001$) and free testosterone levels ($z = -4.65$; $P < 0.001$) to be lower across increasing levels of frailty at W3, whereas LH levels were higher ($z = 2.41$; $P = 0.016$). No trend was observed for SHBG ($z = 0.13$; $P = 0.894$).

In univariate logistic regression analyses, lower levels of total testosterone (OR = 1.14; 95% CI = 1.01–1.29) and free testosterone (OR = 1.30; 95% CI = 1.13–1.51) were associated with increased odds of frailty at W3, whereas lower LH was associated with reduced odds of frailty (OR = 0.81; 95% CI = 0.71–0.92). SHBG was not associated with frailty (OR = 0.91; 95% CI = 0.80–1.03). After adjustment, only lower free testosterone (OR = 1.22; 95% CI = 1.05–1.42) predicted frailty at W3.

Individual components of the FRAIL scale

The association between free testosterone and individual components of the FRAIL scale at W3 was tested in a series of logistic regression models. After adjustment, lower free testosterone predicted the resistance (OR = 1.18; 95% CI = 1.05–1.33) and weight loss components (OR = 1.15; 95% CI = 1.01–1.30) but not fatigue (OR = 1.05, 95% CI = 0.94–1.16), ambulation (OR = 1.12; 95% CI = 0.98–1.29), or illness (OR = 1.05; 95% CI = 0.89–1.24).

Discussion

In this prospective cohort study of community-dwelling men aged 70 yr and older, lower total and free testosterone levels and higher LH levels were associated with frailty in cross-sectional analyses. Furthermore, lower free testosterone levels predicted frailty after a follow-up period of 4–7 yr. These associations remained after adjustment for age, BMI, smoking, diabetes, social support, and impairments in vision and hearing.

These findings are consistent with and extend previous research. This is the third study to explore the association between testosterone levels and frailty, and the first to find

TABLE 3. Eight separate multivariate binary logistic regression models exploring hormonal data measured at W2 and association with frailty (FRAIL scale ≥3) at W2 and W3

	Time point					
	W2 (2001–2004)			W3 (2008–2009)		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Total testosterone	1.23	1.11–1.38	<0.001	1.10	0.96–1.26	0.164
Free testosterone	1.29	1.15–1.44	<0.001	1.22	1.05–1.42	0.008
SHBG	0.94	0.86–1.03	0.229	0.91	0.79–1.05	0.193
LH	0.88	0.81–0.95	0.001	0.89	0.78–1.02	0.107

ORs indicate the effect of a 1 SD decrease in hormone level. Each model was adjusted for age, BMI, smoking, diabetes, social support, and impairments in vision and hearing.

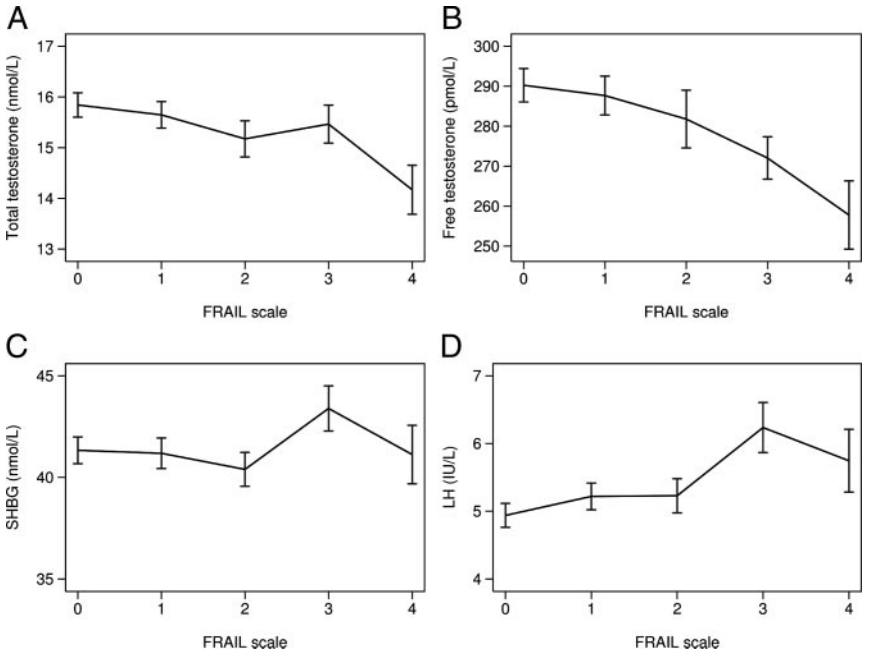

FIG. 3. Mean (±1 SEM) total testosterone (A), free testosterone (B), SHBG (C), and LH (D) measured at W2, stratified by FRAIL scale at W3. Higher scores indicate greater frailty. Men with four or more deficits were combined into a single category.

that free testosterone levels predict frailty in a longitudinal analysis. Mohr and colleagues (18) performed a cross-sectional analysis of 646 community-dwelling men aged 50–86 yr enrolled in the Massachusetts Male Aging Study. Frailty was operationalized using criteria proposed by Fried *et al.* (3). Free testosterone and SHBG were associated with frailty in univariate analyses, but only SHBG remained associated after adjustment. No associations were found for total testosterone. Cawthon and colleagues (19) described a longitudinal analysis of a subset of the Osteoporotic Fractures in Men study comprising 1469 community-dwelling men aged 65 yr and older at baseline. Frailty was operationalized with a modified version of the Fried criteria (3). In cross-sectional analyses, an association was found for total and free testosterone, but only free testosterone remained associated with frailty after adjustment for age, BMI, educational attainment, marital status, medical comorbidity, smoking, and self-rated health. Frailty was not associated with SHBG or estradiol. After a mean follow-up period of 4.1 yr, frailty was reassessed in 1245 men. A crude association was found with free testosterone but did not persist after adjustment; the authors suggested this was due to lack of power.

Several studies have explored the association between sex hormones and individual components of the frailty syndrome. Schaap and colleagues (28) reported results of a cross-sectional analysis of 623 men and 663 women aged 65–88 yr from the Longitudinal Ageing Study Amsterdam. Among men, total and free testosterone levels were positively associated with grip strength, whereas higher free testosterone levels were associated with better mobility (measured by a timed walking test, chair stand test, and tandem stand). In a cross-sectional analysis of 403 community-dwelling men aged 73–94 yr, LH was inversely associated with muscle strength and lean mass and positively associated with self-reported disability, independent of testosterone levels (29). In another subset of the Osteoporotic Fractures in Men study, physical performance and fall risk were assessed in 2587 community-dwelling men aged 65–99 yr (30). Men with higher free testosterone levels performed better in tests of muscle strength and mobility at baseline and were less likely to fall during a follow-up period of 4 yr.

These findings suggest that testosterone may be involved in the pathogenesis of frailty, and this has been investigated in several studies. Transdermal testosterone therapy decreased fat mass and increased lean body mass, muscle strength, and hemoglobin in 227 hypogonadal men aged 19–68 yr (31). Amory and colleagues (32) described a double-blind placebo-controlled trial of im testosterone comprising 25 men aged 58–86 yr awaiting knee replacement. Postoperative mobility was improved in the treatment arm (32). However, a double-blind, randomized, placebo-controlled trial of 207 men aged 60–80 yr with total testosterone levels below 13.7 nmol/liter failed to demonstrate improvement in bone mineral density and muscle strength in men treated with oral testosterone (33).

A role for testosterone in the development of frailty is suggested by its physiological effects. Anabolic actions include increased protein synthesis, inhibition of adipocyte production in favor of satellite cells necessary for muscle repair, inhibition of muscle protein breakdown, and enhanced amino acid reuse in muscle (34, 35). Erythropoiesis is promoted through stimulation of bone marrow and possibly a direct effect on erythropoietin (11). Testosterone may also stimulate appetite and food intake via actions on leptin and ghrelin. Leptin promotes satiety, whereas ghrelin induces hunger and stimulates GH release. Endogenous testosterone levels are positively associated with ghrelin (36) and correlate inversely with leptin (37). Testosterone therapy has been demonstrated to increase ghrelin (38) and decrease leptin (16), whereas androgen deprivation rapidly increases leptin levels (39).

Strengths of the study include its large sample size and recruitment of randomly selected community-dwelling

men. Circadian variation in hormone levels was minimized with early morning blood sampling, although circadian rhythmicity may be attenuated in older men. The size of the cohort and the substantial proportion of men participating in the follow-up study provided greater power to detect cross-sectional and longitudinal associations between hormonal parameters and frailty compared with previous studies. Limitations include reliance upon self-reported weight data at W3, assessment of frailty with different criteria from that used in other studies, and use of a single blood sample. Because clinical assessment was not performed at W3, we were forced to rely upon self-reported weight data, and it is possible that men may have under- or overestimated their weight. We were also unable to tell whether weight loss was unintentional at either time point, because this information was not collected. We could not use the Fried criteria (3) to assess frailty because measures such as grip strength and walking speed were not available. However, in the absence of a consensus definition of frailty, we believe the FRAIL scale to be a valid construct given its good predictive value for mortality and disability. Although the FRAIL scale is less comprehensive than some other constructs (3, 4) and may therefore define the risk of adverse outcomes less precisely, it is simple and easy to use and can be rapidly applied in the clinical setting. Unlike the Fried criteria (3), it does not require measurement of walking speed or grip strength, which are not always practical to measure. Although the FRAIL scale incorporates medical comorbidity, it is possible that we may not have fully accounted for this in the models. This could have introduced bias, given that chronic illness can lower testosterone levels. However, we did not find an association between free testosterone and the illness component at W3, suggesting this is unlikely. Finally, we did not measure hormone status at both time points or directly measure free testosterone through equilibrium dialysis. However, the method used to estimate free testosterone provides a reasonable approximation of actual levels (40).

In summary, this study shows that lower free testosterone levels are associated with an increased risk of becoming frail. Although other studies have found a cross-sectional association between sex hormones and frailty, this is the first to demonstrate a longitudinal association. These findings suggest that testosterone therapy could potentially treat or prevent the development of frailty. The association between free testosterone levels and the resistance and weight loss components of the FRAIL scale suggest that men with sarcopenia or impaired mobility may benefit most from therapy. Clinical trials of testosterone supplementation in which a frailty construct (such as the FRAIL scale) is an endpoint are warranted.

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