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ORIGINAL ARTICLE

Low testosterone is associated with frailty, muscle wasting and physical dysfunction among men receiving hemodialysis: a longitudinal analysis

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ABSTRACT

Background. Despite the high prevalence of frailty among patients receiving hemodialysis, few preventable or treatable contributing causes have been identified. Hypogonadism is also common in this population and low serum testosterone concentrations share several clinical phenotypes with frailty. We hypothesized that low serum testosterone concentrations would be associated with frailty and several of its individual components.

Methods. We used data from 440 men from A Cohort Study To Investigate the Value of Exercise in ESRD/Analysis Designed to Investigate the Paradox of Obesity and Survival in ESRD, a longitudinal study that recruited participants from 14 dialysis centers in Atlanta, GA and the San Francisco, CA Bay Area from 2009 to 2011. We assessed frailty using the Fried Frailty Phenotype. We examined the association between free testosterone (as a continuous and dichotomous variable) and frailty, individual frailty components, sarcopenia, lower extremity function and muscle mass estimation by creatinine and body impedance spectroscopy over 12 months using generalized estimating equations.

Results. The mean age was 56.1 ± 14.2 years and 27% were white. A 50% lower concentration of free testosterone was associated with 1.40-fold higher odds of being frail [95% confidence interval (CI) 1.05–1.53] and 1.40-fold higher odds of becoming frail over 12 months (95% CI 1.07–1.73). This association was mainly due to an association with two components of frailty: grip strength and gait speed. In addition, 50% lower free testosterone concentration was associated with a 1.55-fold higher odds of having sarcopenia (95% CI 1.09–2.02) and 1.72-fold higher odds for developing sarcopenia (95% CI 1.13–2.33) as well as with lower muscle mass and a decrease in muscle mass over 12 months as estimated by serum creatinine and by bioelectrical impedance spectroscopy.

Conclusion. Serum free testosterone concentration was associated with frailty, physical function, sarcopenia and muscle mass as well as with changes in these outcomes over 12 months. Testosterone replacement may be a feasible therapeutic target toward prevention of frailty, although clinical trials are needed to test this possibility.

Keywords: frailty, hemodialysis, muscle strength, testosterone, United States Renal Data System

INTRODUCTION

Frailty is a clinical syndrome characterized by decreased strength, endurance and physiological function. The prevalence of frailty among patients on dialysis of all ages appears to be 4- to 6-fold higher than that of the community-dwelling elderly population using the Fried Frailty Phenotype [1, 2]. Moreover, frailty is associated with higher mortality and hospitalization rates in end-stage renal disease (ESRD) [1, 3].

Causes of frailty are likely multifactorial, including advanced age and the cumulative effects of chronic disease. However, recent data support that frailty is a dynamic process that can improve and worsen over time [4]. It is therefore important to identify factors that may predict or even modify a patient's risk of becoming frail. These factors, if preventable or remediable, could allow clinicians to disrupt a spiral of deconditioning, inactivity and fatigue that leads to further deconditioning and frailty.

Testosterone is an anabolic steroid hormone that is important in the maintenance of muscle and bone mass. The prevalence of low serum testosterone increases with age and with chronic illness [5]. There are high rates of testosterone deficiency among patients treated with dialysis [6]. Recently

Carrero *et al.* [7] reported a prevalence of testosterone deficiency [defined by total testosterone concentration <288 ng/dL (10 nmol/L)] of 44% in a population of Swedish men with ESRD, which is considerably higher than estimates of 5.6–9.5% in otherwise healthy men of similar age [8, 9]. Clinical manifestations of low testosterone include sexual dysfunction, fatigue, increase in body fat, loss of muscle mass and decrease in physical performance. Many of these manifestations are similar to components of frailty (such as fatigue), or underlying factors that may lead to frailty, and are important outcomes in their own right (e.g. loss of muscle mass, poor physical performance, sarcopenia). It would be logical to consider that low testosterone concentration might be related to frailty or its development or with related changes in muscle mass and function (e.g. physical performance, sarcopnenia) in the dialysis population.

We aimed to examine the association between serum testosterone concentration and frailty in a longitudinal cohort of patients on dialysis. In addition, we explored the association between testosterone concentration and muscle mass [as estimated by creatinine concentration as well as by whole-body bioelectrical impedance spectroscopy (BIS)] and several measures of muscle function over 12 months. We hypothesized that testosterone would be associated with frailty and with the trajectory of frailty and its components over time.

MATERIALS AND METHODS

Study participants

A Cohort Study To Investigate the Value of Exercise in ESRD/Analysis Designed to Investigate the Paradox of Obesity and Survival in ESRD (ACTIVE/ADIPOSE) recruited 771 participants from 14 dialysis centers in Atlanta, GA and the San Francisco, CA Bay Area from 2009 to 2011. Participants were then followed annually with frailty assessment for 2 years through 2013 [10]. Participants were ≥18 years of age, English or Spanish speaking and on hemodialysis (HD) for at least 3 months. The study was approved by the University of California, San Francisco and Emory University Institutional Review Boards. Of 456 men in the cohort, 3 men were excluded due to not having at least one frailty assessment, 9 men were excluded due to not having at least one serum testosterone value and 3 men were excluded due to missing both testosterone values and frailty assessments. Men with at least one concomitant frailty assessment and serum testosterone value [$n = 440$ (96%)] were included in the analysis.

Laboratory values

Serum testosterone and sex hormone, binding globulin (SHBG) were measured at baseline and 12 months. Blood was collected prior to a midweek dialysis session. The serum was separated, frozen at −80° C, transferred to the University of California, Davis and stored in liquid nitrogen at −196°C until analysis. Testosterone was measured by enzyme-linked immunosorbent assay (ELISA) (DRG International, Springfield, NJ, USA). The interassay coefficient of variation (COV) was 4.73–9.94% and the intra-assay COV was 3.28–4.16%. SHBG was measured by ELISA (DRG International). Interassay COV was 3.7–5.23% and the intra-assay COV was 3.33%. Albumin was assayed by bromocresol green (Polymedco, Cortlandt Manor, NY, USA). Free testosterone was calculated from serum total testosterone, albumin and SHBG concentration using a method that has a correlation coefficient of 0.987 with free testosterone by equilibrium dialysis [11]. Baseline serum creatinine was recorded from the most recent monthly laboratory results prior to study enrollment and also recorded at 12 months.

Physical function and frailty

We assessed frailty using the Fried Frailty Phenotype [2, 12] at baseline and 12 months. Grip strength was assessed using a dynamometer (Jamar, Lafayette Instrument, Lafayette, IN, USA). Participants performed three trials with each hand and the average of the strongest hand was used in the analysis. Gait speed was assessed as participants walked a 15-foot course at a normal pace. The faster of the two trials was recorded. We used thresholds for grip strength and gait speed established in the Cardiovascular Health Study [12]. The weight loss criterion was fulfilled by asking participants if they had lost ≥10 pounds in the previous year unintentionally. The exhaustion component was based on questions about endurance and energy using the Center for Epidemiologic Studies Depression Scale [13]. Low physical activity was determined using the modified Minnesota Leisure Time Physical Activity Questionnaire, with questions about the frequency and duration of participation in activities over a 2-week time frame [14]. Participants meeting three or more of these five criteria were determined to be frail.

Short Physical Performance Battery (SPPB) scores were also calculated for participants using three components: gait speed, timed repeated chair stand and timed balance test. Gait speed was assessed over 15 ft, as above. The repeated chair stand was assessed by asking participants to stand from a chair and sit five times as quickly as possible. Balance testing was first assessed with side-by-side standing where the participant stood for up to 10 s with feet together. Those able to complete this were then assessed during semitandem standing with one heel of one foot touching the big toe of the other foot for 10 s and then asked to perform full tandem standing, placing the heel of one foot in front of and touching the toes of the other foot for 10 s. The SPPB score was tallied on a scale from 0 to 12 [15].

Sarcopenia

Sarcopenia was determined based on meeting criteria for muscle weakness (assessed by grip strength) and low muscle mass. Men with <26 kg grip strength met the criteria for muscle weakness [16]. Estimation of total-body muscle mass (TBMM) was by whole-body BIS. BIS was performed prior to a midweek dialysis session using a device that scans 256 frequencies between 4 and 1000 kHz (SFB7, ImpediMed, San Diego, CA, USA). Patients were placed in the supine position at least 10 min prior to measurement. Electrodes were placed on the wrist and ankle on the side opposite to the dialysis access and 10 measurements were performed. Total body water was estimated using resistance extrapolated to infinite frequency and extracellular water was estimated from resistance extrapolated

to zero frequency. TBMM was then estimated using the equation $2.074 + 1.064 \times$ BIS-derived intracellular water. This equation gives a value of $R^2 = 0.783$ compared with muscle mass determined from whole-body magnetic resonance imaging validated in a cohort of patients on HD [17]. Low muscle mass was defined as $\geq$2 standard deviation (SD) below the mean of young adults as obtained from the National Health and Nutrition Examination Survey 2003–04 [18]. TBMM was indexed to body mass index (BMI) and the mean 2 SD value for men was 0.97 m^2 for TBMM/BMI.

Clinical evaluation

Study personnel measured height using a stadiometer and weight was recorded as the mean postdialysis weight from the previous three dialysis sessions. Baseline comorbidities were ascertained from the Medical Evidence Report (Centers for Medicare & Medicaid Services Form 2728) data from the US Renal Data System and through chart review.

Statistical analysis

Characteristics of participants were described using mean (SD) or median (25–75th percentiles), as appropriate. Characteristics of participants were also stratified by high or low free testosterone concentration.

To study the association between serum testosterone and frailty over time, we employed generalized estimating equation (GEE) models using time-varying log-transformed serum free testosterone concentration as the predictor and time-varying binary outcomes of frailty and each component of frailty and sarcopenia as outcomes [19]. The coefficients from the GEE models were then back-transformed and reported as the odds ratio (OR) of outcome per 50% difference in testosterone concentration. We also studied the association between free testosterone and the change in frailty over 12 months. For this analysis, the GEE model also included log-transformed free testosterone, time and the change in free testosterone between baseline and 12 months. Including a variable for time describes the change over time in the outcome (frailty) variables in the GEE model. Inclusion of time interactions with baseline predictors allows analysis of whether baseline predictors are associated with change over time and inclusion of a time-varying predictor (testosterone) allows analysis of whether the change in testosterone is associated with the change in outcome (frailty). We adjusted for possible confounders including age, history of coronary artery disease (CAD), history of congestive heart failure (CHF), history of diabetes mellitus (DM), albumin and BMI. We further adjusted for the time of the HD session (before noon, noon to 6 p.m. or after 6 p.m.) to account for diurnal variations in testosterone concentration. For variables assessed at baseline only (history of CAD, history of CHF, history of DM, age), we also included the variable at baseline and a multiplicative interaction term between the predictor variable and time in the model. Using the above GEE model, we also examined the association between free testosterone concentration and sarcopenia as a binary outcome.

In a second modeling strategy, we further explored the association between serum free testosterone concentrations and the time-varying continuous outcomes of grip strength, gait speed and SPPB score as well as the association between testosterone and change in grip strength, gait speed and SPPB score over 12 months. We examined the association between serum free testosterone concentration and two surrogate measures of muscle mass: serum creatinine and BIS-derived TBMM indexed to BMI. We also examined the association between testosterone and the change in muscle mass over 12 months.

In addition, as a threshold would be of more practical use in clinical settings than a continuous association, we examined the association of 'low' serum free testosterone concentration as a binary variable with frailty and components of frailty among men in similar GEE models. Using unbiased nonparametric smoothing models (cubic splines and locally weighted scatterplot smoothing curves), we identified deflection points and a range of values that would be appropriate as a cut point [20]. A cut point <147 pmol/L, the median level among men in the cohort, was selected.

Finally, we performed sensitivity analyses using serum total testosterone and bioavailable testosterone rather than serum free testosterone. We performed sensitivity analyses comparing results including versus excluding participants who were prescribed testosterone replacement ($n = 4$) and sensitivity analyses including hemoglobin concentration as a covariate. We used Stata version 14.2 (StataCorp, College Station, TX, USA) for all statistical analysis.

RESULTS

Participants and baseline measures

Of 456 men in the ACTIVE/ADIPOSE cohort, 3 were excluded due to not having at least one frailty assessment, 9 were excluded due to not having at least one serum testosterone value and 3 were excluded due to missing both testosterone values and frailty assessments. A total of 440 men (96%) were included in the analyses. The mean age of included men was 56.1 ± 14.2 years; 27% were white and 60% were black (Table 1). Compared with men with higher testosterone concentration ($\geq$147 pmol/L), men with lower testosterone tended to be older ($P < 0.001$) and were more likely to have diabetes ($P = 0.01$). There were no statistically significant differences in the prevalence of CAD or CHF between men with low versus higher testosterone. Four participants were being prescribed testosterone replacement therapy at the time of the study. The median (25–75th percentile) for serum total testosterone among men was 267 ng/dL (210–394) and for serum free testosterone was 147 pmol/L (109–197).

Association between free testosterone (continuous) and frailty among men

Among men, having a 50% lower free testosterone concentration was associated with 1.40-fold higher odds of being frail (95% CI 1.12–1.69; Table2). Considering frailty components, a 50% lower free testosterone concentration was associated with higher odds of having weak grip strength [OR 1.29 (95% CI 1.05–1.53)] and higher odds of having a slow walk time [OR 1.44 (95% CI 1.12–1.76)]. Serum free testosterone

Table 1. Baseline characteristics

Characteristics	Included cohort ($n = 440$)	Men ($n = 440$)	
		Low (<147 pmol/L)	High (≥147 pmol/L)
Demographics			
Age, years, mean ± SD	56.1 ± 14.2	60.7± 13.1	51.5 ± 13.7
BMI, kg/m^2, mean ± SD	28.2 ± 6.5	28.2 ± 6.7	28.2 ± 6.2
Race, %			
White	26.8	27.9	25.8
Black	59.6	58.9	60.2
Other	13.6	13.2	14.0
Ethnicity, %			
Hispanic	13.9	9.1	18.6
Dialysis vintage	2.7 (1.2–5.3)	2.5 (1.1–5.2)	3.0 (1.5–5.4)
Comorbidities, %			
History of CAD	11.8	13.7	10.0
History of DM	41.1	47.0	35.3
History of CHF	20.9	24.7	17.2
Physical function measures			
Grip strength, kg, mean ± SD	31.1 ± 10.3	28.9 ± 10.1	33.2 ± 10.1
Gait speed, m/s, mean ± SD	0.99 ± 0.27	0.94 ± 0.27	1.03 ± 0.26
SPPB score, median (25th–75th percentile)	10 (7–11)	9 (5–11)	10 (8–12)
Frailty measures			
Frail, %	28.9	34.3	23.5
Sarcopenia measures			
Sarcopenic, %	17.1	24.4	10.8
Laboratory measures			
Total testosterone, ng/dL, median (25th–75th percentile)	266.9 (208.4–382.0)	221.7 (164.4–285.3)	351.0 (258.2–504.2)
Free testosterone, pmol/L, median (25th–75th percentile)	147 (109–197)	109 (71.6–127)	197 (169–260)
Bioavailable testosterone, nmol/L, median (25th–75th percentile)	3.25 (2.36–4.44)	2.37 (1.54–2.81)	4.41 (3.77–5.8)
SHBG, nmol/L, median (25th–75th percentile)	51.6 (33.8–73.6)	60.3 (42.3–84.9)	42.5 (27.7–64.8)
Albumin, mean ± SD	4.01 ± 0.38	3.94 ± 0.42	4.07 ± 0.34
Hemoglobin, mean ± SD	11.6 ± 1.38	11.4 ± 0.06	11.7 ± 0.09

A total of 440 include those that have at least one concomitant testosterone value and frailty assessment; 3 men were missing frailty assessment, 9 men were missing testosterone measurements, and 3 men were missing both testosterone measurements and frailty assessments.

Table 2. Association between free testosterone and frailty and its components[a]

Frailty and Components	Frailty by Fried phenotype			
	Frailty		Change in frailty over 12 months	
	OR, per 50% lower free testosterone (95% CI)	P-value	OR, per 50% lower free testosterone (95% CI)	P-value
Frailty	1.30 (1.03–1.58)	0.01	1.37 (1.06–1.68)	0.007
Exhaustion	0.97 (0.79–1.16)	0.77	0.98 (0.77–1.19)	0.86
Grip strength	1.33 (1.06–1.60)	0.006	1.36 (1.05–1.66)	0.008
Physical activity	1.05 (0.85–1.25)	0.59	1.00 (0.80–1.21)	0.94
Walk time	1.38 (1.06–1.70)	0.006	1.34 (1.01–1.68)	0.03
Weight loss	0.94 (0.74–1.14)	0.57	0.90 (0.68–1.12)	0.42

	SPPB			
	SPPB score		Change in SPPB score over 12 months	
	Score difference, per 50% lower free testosterone (95% CI)	P-value	Score change, per 50% lower free testosterone (95% CI)	P-value
	−0.44 (−0.67 to −0.22)	<0.001	−0.24 (−0.45 to −0.05)	0.016

	Sarcopenia			
	Sarcopenia		Change in sarcopenia over 12 months	
	OR, per 50% lower free testosterone (95% CI)	P-value	OR, per 50% lower free testosterone (95% CI)	P-value
	1.55 (1.09–2.02)	0.004	1.72 (1.13–2.33)	0.002

[a]Adjusted for age, race, history of CAD, history of DM, albumin concentration, BMI and time of HD session.

Table 3. Association between free testosterone and measures of physical function and muscle mass[a]

Muscle function and muscle mass measures	Physical function		Change in physical function over 12 months	
	Difference, per 50% lower free testosterone (95% CI)	P-value	Change, per 50% lower free testosterone (95% CI)	P-value
Grip strength, kg	−0.96 (−1.62 to −0.31)	0.004	−1.06 (−1.80 to−0.32)	0.005
Gait speed, m/s	−0.03 (−0.05 to −0.01)	0.006	−0.04 (−0.06 to −0.01)	0.003
Creatinine, mg/dL	−0.29 (−0.51 to −0.08)	0.007	−0.35 (−0.57 to −0.12)	0.002
TBMM/BMI, m^2	−0.02 (−0.03 to −0.01)	0.008	−0.02 (−0.03 to −0.01)	0.001

[a]Adjusted for age, race, history of CAD, history of DM, albumin, BMI and time of HD session.

concentrations were not significantly associated with other components of frailty (i.e. exhaustion, weight loss and physical activity; Table 2).

Over 12 months, each 50% lower baseline free testosterone was associated with 1.40-fold higher odds of becoming frail [OR 1.40 (95% CI 1.07–1.73)]. Each 50% lower baseline serum free testosterone was associated with 1.38-fold higher odds of developing a slow walk time [OR 1.38 (95% CI 1.03–1.71)]. Each 50% lower baseline free testosterone was associated with 1.29-fold higher odds for developing weak grip strength over 12 months [OR 1.29 (95% CI 1.02–1.56)]. Serum free testosterone concentration was not significantly associated with the development of exhaustion, weight loss or low physical activity over 12 months (Table 2).

Association between free testosterone, physical performance and muscle mass among men, and sarcopenia

Among men, lower serum free testosterone was associated with weaker grip strength [−0.04 kg/50% lower testosterone (95% CI −1.62 to −0.27)] as well as slower gait speed [−0.04 m/s/50% lower testosterone (95% CI −0.06 to −0.01)] (Table 3). Lower serum free testosterone was also associated with a decrease in grip strength [−1.01 kg/50% lower testosterone (95% CI −1.74 to −0.28)] as well as a decrease in gait speed [−0.04 m/s/50% lower testosterone (95% CI −0.06 to −0.02)] over 12 months. Each 50% lower free testosterone concentration was associated with a 0.44 lower SPPB score [−0.44 points/50% lower free testosterone (95% CI −0.67 to −0.22)]. Over 12 months, a 50% lower free testosterone concentration at baseline was also associated with a decrease in SPPB score [−0.24 points/50% lower free testosterone (95% CI −0.45 to −0.05)] (Table 2). Lower serum free testosterone concentration was also associated with lower serum creatinine, a proxy for muscle mass [−0.38 mg/dL/50% lower testosterone (95% CI −0.60 to −0.16)], as well as with a decrease in serum creatinine over 12 months [−0.37 mg/dL/50% lower testosterone (95% CI −0.61 to −0.14)] (Table 3). Lower serum free testosterone concentration was also associated with lower TBMM/BMI [−0.02 m^2/50% lower testosterone (95% CI −0.03 to −0.01)] as well as a decrease in TBMM/BMI over 12 months [−0.02 m^2/50% lower testosterone (95% CI −0.03 to −0.01)] (Table 3). A 50% lower free testosterone concentration was associated with 1.55-fold higher odds of meeting the diagnosis of sarcopenia [OR 1.55 (95% CI 1.09–2.02)]. Over 12 months, each 50% lower baseline free testosterone was also associated with 1.72-fold higher odds of meeting the diagnosis of sarcopenia [OR 1.72 (95% CI 1.13–2.33); Table 2].

Association between low free testosterone (dichotomous) and frailty, physical function and muscle mass among men

A serum free testosterone concentration <147 pmol/L was associated with higher odds of being frail [OR 1.48 (95% CI 1.04–2.13)] and higher odds of having a slow walk time [OR 1.62 (95% CI 1.10–2.38)] at baseline. In addition, among men with low free testosterone at baseline, the odds of becoming frail over 12 months were higher [OR 1.58 (95% CI 1.06–2.34)] and odds of developing a slow gait speed were also higher [OR 1.64 (95% CI 1.07–2.52); Table 4].

Considering grip strength, gait speed and serum creatinine as continuous variables, low serum free testosterone was associated with significantly lower grip strength [−1.02 kg (95% CI −2.01–0.01)], slower gait speed [−1.14 m/s (95% CI −2.22 to −0.06)] and lower serum creatinine concentration [−0.64 mg/dL (95% CI −1.06 to −0.26)]. In addition, over 12 months, low free testosterone was associated with a decrease in grip strength of −1.14 kg (95% CI −2.22 to −0.06), a decrease in gait speed of −0.05 m/s (95% CI −0.08 to −0.01) and a decrease in serum creatinine concentration of −0.54 mg/dL (95% CI −0.93 to −0.15).

Sensitivity analyses considering total testosterone and bioavailable testosterone produced similar results (Supplementary data, Tables S1–S4). Sensitivity analyses excluding participants who were prescribed testosterone replacement did not differ from the primary analysis. In an additional sensitivity analysis considering hemoglobin as a possible covariate and potential mediator, results remained similar to the primary analysis.

DISCUSSION

We found that lower levels of serum free testosterone were associated with higher odds of being frail and of becoming frail over 12 months among men receiving HD. This association was mainly due to an association with the physical function components of frailty, grip strength and gait speed. In addition, lower free testosterone was associated with lower other indicators of physical performance and with lower estimates of muscle mass and a decline in muscle mass over 12 months.

Relatively few studies have examined the relations among testosterone, muscle mass, physical function and frailty in ESRD. Observational studies in patients undergoing dialysis have

Table 4. Association of low free testosterone concentration (<147 pmol/L) with physical function, muscle mass and frailty[a]

Frailty and Components	Frailty			
	Frailty		Change in frailty over 12 months	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Frail	1.38 (0.96–1.99)	0.08	1.56 (1.04–2.33)	0.03
Exhaustion	0.80 (0.57–1.12)	0.20	0.79 (0.55–1.14)	0.22
Grip strength	1.44 (1.05–1.98)	0.03	1.44 (1.02–2.04)	0.03
Activity	0.97 (0.70–1.34)	0.83	0.99 (0.69–1.40)	0.95
Walk time	1.53 (1.02–2.28)	0.04	1.59 (1.02–2.47)	0.04
Weight loss	0.99 (0.69–1.43)	0.97	1.09 (0.72–1.65)	0.69

Muscle function and muscle mass measures	Physical function			
	Physical function		Change in physical function over 12 months	
	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Grip strength, kg	−1.06 (−2.08 to −0.04)	0.04	−1.25 (−2.32 to −0.19)	0.02
Gait speed, m/s	−0.03 (−0.07 to −0.01)	0.04	−0.04 (−0.07 to −0.01)	0.01
Creatinine, mg/dL	−0.56 (−0.93 to −0.19)	0.003	−0.54 (−0.92 to −0.16)	0.006
TBMM/BMI, m^2	−0.20 (−0.32 to −0.83)	0.001	−0.18 (−0.31 to −0.05)	0.005

[a]Adjusted for age, history of CAD, history of DM, albumin, BMI and time of HD session.

demonstrated an association between total serum testosterone concentration and muscle mass estimated by computed tomography [21] and by serum creatinine concentration [22]. Several interventional studies in patients on dialysis have explored the effects of testosterone or testosterone derivatives on muscle mass and physical function. A randomized controlled trial in 29 patients on HD demonstrated that treatment with nandrolone decanoate for 6 months led to increased lean body mass and a decrease in walk and stair-climbing time, as well as an increase in serum creatinine concentration when compared to treatment with placebo injections [23]. A larger follow-up study that also incorporated exercise showed improvements in body composition with nandrolone over 3 months but showed no improvement in self-reported physical function or measured strength in the absence of exercise [24]. Thus the extent to which androgen treatment improves physical function is unclear. In addition, endogenous testosterone production decreased with the administration of synthetic androgen in these studies, and follow-up time was limited. Therefore data from larger and longer observational studies such as those presented here can supplement what we have learned from interventional trials.

The association of lower serum free testosterone with higher odds of becoming frail over 12 months in patients on HD in our study is in agreement with a study of a community-dwelling elderly population in which lower serum free testosterone was associated with higher odds of developing frailty over 4–7 years [25]. Although clinical cutoffs for normal serum free testosterone have not been well established, particularly in the ESRD population, an approach using a testosterone threshold may be of greater potential clinical utility. Therefore we used an unbiased cutoff derived from nonparametric models. Patients with serum free testosterone below the median had 1.58-fold higher odds of becoming frail over 12 months than those with testosterone levels above the median.

Of the five components of frailty, lower testosterone was associated with higher odds of having, and developing, weak grip strength and slow walk time. These associations are especially noteworthy since slow gait speed and low grip strength have been shown to be associated with mortality in patients on dialysis [26] and may be important for maintaining independence. Muscle mass is an important contributor to physical function, and the associations between free testosterone and serum creatinine and BIS-derived muscle mass we observed are consistent with the hypothesis that testosterone may be associated with components of frailty because of its effects on muscle. Specifically, we hypothesize that low free testosterone may lead to a decrease in muscle mass in men receiving HD, which in turn leads to deterioration in grip strength and gait speed. We further tested this hypothesis in two ways. First, we found that lower testosterone was associated with the presence of sarcopenia and with the development of sarcopenia over 12 months. To the best of our knowledge, prior studies have not examined the longitudinal association of testosterone concentration and development of sarcopenia. Second, we found that lower testosterone was also associated with lower SPPB score and a decrease in SPPB score over 12 months, indicating that lower extremity strength and integrated physical function may also be deteriorating in those with low testosterone concentration.

In addition to increasing muscle mass as a possible pathway to increasing muscle function, testosterone is also well described to increase erythropoiesis, and synthetic derivatives were widely used to treat anemia in patients with ESRD prior to the availability of recombinant erythropoietin. In our cohort, those with lower testosterone concentration had a statistically significant lower (though not clinically significantly lower) hemoglobin concentration at baseline. The small difference in hemoglobin may likely be related to clinical practice guidelines that recommend actively managing hemoglobin levels to be within the set ranges in the HD population [27]. In our sensitivity analysis, we found that adjustment for hemoglobin had minimal effect on the association between testosterone concentration and muscle function outcomes. Therefore lower

erythropoiesis in participants with lower testosterone may be a small contributor to lower muscle strength and physical function seen in the cohort. We had initially hypothesized that lower serum free testosterone concentrations would also be associated with other frailty components, such as exhaustion and low physical activity, which are common clinical manifestations of hypogonadism in healthy men. On the other hand, the lack of association we observed is in agreement with results of the Testosterone Trials, in which Snyder *et al.* [28] found that testosterone treatment did not improve fatigue, which was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, in community-dwelling older men. Therefore the lack of association of testosterone concentration with fatigue and physical activity may suggest that other factors associated with aging or chronic illness or its treatment may be more important drivers of exhaustion and low physical activity than testosterone concentration.

The safety and efficacy of testosterone replacement therapy are controversial. Despite benefits shown in the Testosterone Trial, including improved sexual function and physical function, there are also risks to replacement [28], especially in older men, that still need to be considered. Testosterone administration is associated with erythrocytosis in a dose-dependent manner, an effect that is greater in men 60–75 years of age than in younger men [29]. Although excessive erythropoiesis has a potentially harmful side effect in the general population, it could be a beneficial effect in the HD population. Prostate disease and cancer are also potential concerns related to testosterone replacement therapy. Although prostate-specific antigen (PSA) levels and detection of subclinical prostate disease have been shown to increase [30] in the setting of testosterone therapy, there is no evidence to suggest that testosterone causes prostate cancer [31]. Guidelines from the Endocrine Society recommend avoiding testosterone replacement in those with prostate cancer and referring patients whose PSA increases >1.4 ng/mL above baseline for urology evaluation [32]. Obstructive sleep apnea has been reported to worsen during testosterone therapy [32], possibly due to the depression of hypercapnic ventilator drive. Perhaps the biggest concern in recent studies has been the possibility of cardiovascular adverse events with testosterone therapy. Observational studies have reported higher rates of cardiovascular events and cardiovascular death among individuals with lower serum testosterone [33–35]. However, in the randomized Testosterone in Older Men with Mobility Limitations trial [36], men assigned to receive testosterone experienced a higher frequency of cardiovascular events when compared with those on placebo. Those in the study who had cardiovascular adverse events had a greater increase in testosterone than those who did not, with more achieving supraphysiological levels than those who did not [36]. However, the Testosterone Trial investigators did not find any difference in cardiovascular event rates between those on testosterone and those on placebo [28]. Thus data from randomized trials in older men have yielded conflicting information about the potential cardiovascular risks of testosterone therapy. Given that the dialysis population has a higher risk of cardiovascular events than otherwise healthy older men [37], but could be less susceptible to testosterone-related risk because of underlying anemia, extrapolation from trials in the general population may not be appropriate. However, there are no trials in the HD population of sufficient size to address this question.

The strengths of our study include the size of the cohort and its prospective and longitudinal design. Another strength lies in the measurement of SHBG and the use of free testosterone in our analysis. More than 95% of testosterone is bound to SHBG and it is the unbound, or free, testosterone that exerts its biological effects. In ESRD, there are many factors that may affect the SHBG concentration, including diabetes, obesity and age. Therefore serum total testosterone may be low as a result of low SHBG and free testosterone is expected to be a more accurate reflection of biologically active testosterone at the tissue level. Although the gold standard of free testosterone measurement is equilibrium dialysis, this test is not always available in commercial laboratories so we used the method of calculating free testosterone from total testosterone and SHBG recommended by the Endocrine Society [5, 11].

There are limitations of our study that should also be acknowledged. Although we utilized a longitudinal cohort design to assess change within individuals over time, and we adjusted for possible confounders, the study was observational. Therefore the observed associations between free testosterone, physical function, muscle mass and frailty could be confounded by factors we did not measure, so we cannot prove causality. Another limitation is that the gold standard of testosterone measurement is a fasting, morning blood collection, but we collected blood prior to the participants' dialysis sessions. However, given that the majority of the cohort (78%) had a dialysis start time in the morning, the timing of measurement was unlikely to have had a major impact on the associations we observed. Moreover, we adjusted for the time of dialysis in all of our analyses. There were only four men who were prescribed testosterone replacement therapy at the time of enrollment. These individuals were included in the analyses, as the association between testosterone concentration and frailty was of interest to us regardless of whether testosterone was endogenous or exogenous. Our sensitivity analyses did not show any difference in the results between including versus excluding these individuals. The accuracy of serum creatinine as a proxy for muscle mass could be affected by varying degrees of residual kidney function. Therefore we also included results using BIS-derived measures of muscle mass, which were similar to the analyses using serum creatinine.

In conclusion, the high prevalence of frailty and its associated morbidity and mortality among patients with ESRD make frailty an important but difficult target for therapeutic or preventative interventions. We showed that in men receiving HD, serum free testosterone concentration was associated with muscle mass, physical function and frailty as well as the change in these outcomes over 12 months. Given the high prevalence and clinical consequences associated with frailty in ESRD, additional, larger and longer-term clinical trials testing the efficacy and safety of testosterone replacement in men are warranted.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.M.C. was involved in study design and primary data analysis and interpretation and drafted the manuscript. G.A.K. was involved in study design, acquisition of data and analysis and critical revision of the manuscript. M.S. advised on statistical analysis and interpretation and critical revision of the manuscript. G.C. was involved in study design and critical revision of the manuscript for important intellectual content. C.D. was responsible for critical revision of the manuscript for important intellectual content. K.J. was involved in study concept, design and supervision, acquisition of data and critical revision of the manuscript for important intellectual content. All authors provided final approval for publication.

CONFLICT OF INTEREST STATEMENT

None of the authors has any financial conflict of interest with the information presented in this article. The results presented in this article have not been published previously in whole or part, except in abstract format.

(See related article by Garibotto *et al.* Testosterone deficiency, frailty and muscle wasting in CKD: a converging paradigm? *Nephrol Dial Transplant* 2019; 34: 723–726)

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High and low estimated glomerular filtration rates are associated with adverse outcomes in patients undergoing surgery for gastrointestinal malignancies

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ABSTRACT

Background. Abnormally high estimated glomerular filtration rates (eGFRs) are associated with endothelial dysfunction and frailty. Previous studies have shown that low eGFR is associated with increased morbidity, but few reports address high eGFR. The purpose of this study is to evaluate the association of high eGFR with surgical outcomes in patients undergoing surgery for gastrointestinal malignancies.

Methods. We identified patients who underwent elective surgery for gastrointestinal malignancies from 2005 to 2015 in the American College of Surgeons National Surgical Quality Improvement Program database. We evaluated associations of eGFR with surgical outcomes by Cox or logistic models with restricted cubic spline functions, adjusting for case mix variables (i.e. age, gender, race and diabetes).

Results. The median eGFR is 83 (interquartile range 67–96) mL/min/1.73 m^2. Thirty-day mortality was 1.9% (2555/136 896). There is a U-shaped relationship between eGFR and 30-day mortality. The adjusted hazard ratios (95% confidence intervals) for eGFRs of 30, 60, 105 and 120 mL/min/1.73 m^2 (versus 90 mL/min/1.73 m^2) are 1.73 (1.52–1.97), 1.00 (0.89–1.11), 1.42 (1.31–1.55) and 2.20 (1.79–2.70), respectively. Similar associations are shown for other surgical outcomes, including return to the operating room and postoperative pneumonia. Subgroup analyses show that eGFRs both higher and lower than the respective medians are consistently associated with a higher risk of adverse outcomes across age, gender and race.

Conclusions. High and low eGFRs are associated with more adverse surgical outcomes in patients undergoing surgery for gastrointestinal malignancies. The eGFR associated with the lowest