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Association between Testosterone and Mortality Risk among U.S. Males Receiving Dialysis

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Testosterone · Mortality · Survival · Dialysis

Abstract

Background: Among the general population, low circulating testosterone levels are associated with higher risk of cardiovascular disease and death. While testosterone deficiency is common in dialysis patients, studies of testosterone and mortality in this population are ambiguous and overlapping. We hypothesized that lower testosterone levels are associated with higher mortality in male dialysis patients. ***Methods:*** We examined a nationally representative cohort of male dialysis patients from a large US dialysis organization who underwent one or more total testosterone measurements from 1/2007 to 12/2011. The association between total testosterone categorized as quartiles and all-cause mortality was studied using Cox models adjusted for expanded case-mix and laboratory covariates. We also examined total testosterone as a continuous predictor of all-cause mortality using restricted cubic splines. ***Results:*** Among 624 male dialysis patients, 51% of patients demonstrated testosterone deficiency (total testosterone <300 ng/dL); median (IQR) total testosterone levels were 297 (190–424) ng/mL. In expanded case-mix + laboratory adjusted Cox analyses, we observed a graded association between lower testosterone levels and higher mortality risk (ref: quartile 3): adjusted hazard ratios (95% CI) 2.32 (1.33–4.06), 1.80 (0.99–3.28), and 0.68 (0.32–1.42) for Quartiles 1, 2, and 4, respectively. In adjusted spline analyses, the lower testosterone-higher mortality risk association declined with higher testosterone levels until the value reached a threshold of 400 ng/dL above which risk plateaued. ***Conclusion:*** Lower testosterone levels were independently associated with higher mortality risk in male dialysis patients. Further studies are needed to determine underlying mechanisms, and whether testosterone replacement ameliorates death risk in this population.

Introduction

In the general population, testosterone deficiency is a highly prevalent condition, affecting 6–12% of men over the age of 30 years and up to 30% of men older than the age of 60 years [1–3]. Observational data have also shown that testosterone supplementation in adult males with testosterone deficiency is associated with a significant reduction in their risk for myocardial infarction, stroke, and all-cause death [4, 5]. These findings may bear particular

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relevance among male end-stage renal disease (ESRD) patients, who commonly manifest low testosterone levels [6], and who have disproportionately high mortality rates due to cardiovascular disease (40% of deaths) [7].

Epidemiologic data have indeed shown a disproportionately high prevalence of testosterone deficiency in ESRD patients. For example, in a study of 260 men with ESRD, it was shown that 44% of patients had testosterone deficiency and 33% had testosterone insufficiency (defined as total testosterone levels <10 nmol/L [<288 ng/dL] and 10–14 nmol/L [288–404 ng/dL], respectively), while only 23% demonstrated normal testosterone concentrations (total testosterone >14 nmol/L [>404 ng/dL]) [8]. Other data suggest that as many as two thirds of ESRD patients have biochemical evidence of testosterone deficiency using these criteria [9]. The etiologic factors for low testosterone levels in kidney disease may be multifactorial and include alterations in the hypothalamic-pituitary-axis and metabolic milieu (i.e., decreased gonadotropin-releasing hormone pulsation, prolactin retention with the inhibition of luteinizing hormone signaling), heightened inflammation (i.e., increased C-reactive protein, interleukin-6, and fibrinogen levels), advanced age, and coexisting comorbidities [10–12].

Given their exceedingly high cardiovascular death risk, there has been considerable interest in understanding the implications of testosterone deficiency upon mortality risk in ESRD patients. Prior studies of testosterone and mortality in European, Canadian, and Australian dialysis cohorts have shown mixed findings, likely due to the heterogeneous study cohort composition and sizes, varying definitions of testosterone deficiency, inconsistent consideration of confounders, and differential follow-up periods [8, 9, 13–16]. To date, there has not been a large population-based study examining the relationship between testosterone deficiency and mortality specifically in US male dialysis patients who manifest a differential racial/ethnic composition and comorbidity burden versus international dialysis populations. Thus, to better inform the field, we sought to examine the association between serum total testosterone levels and mortality risk among a large national cohort of US dialysis patients. We additionally examined predictors of testosterone deficiency in this population.

Materials and Methods

Source Population

We conducted a historical cohort study of incident/prevalent adult male hemodialysis and peritoneal dialysis patients receiving treatment within the outpatient facilities of a large US dialysis organization over the period of January 1, 2007 to December 30, 2011 with detailed information on socio-demographics, comorbidities (ascertained by International Classification of Disease 9th Revision codes), laboratory tests, dialysis treatment characteristics, clinical events, and vital status [17, 18]. Patients were included provided they had undergone at least one or more serum total testosterone measurement(s) anytime during the study period, and were age 18 years or older at the time of study entry (date of testosterone measurement). Patients were excluded if they had undergone treatment with a dialysis modality other than in-center hemodialysis or peritoneal dialysis at the time of study entry. The study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California Irvine Medical Center, and the University of Washington.

Exposure and Outcome Ascertainment

Serum total testosterone levels ascertained at study entry (baseline testosterone level) were the exposure of interest. In primary analyses, we examined total testosterone levels categorized as quartiles defined by the following thresholds: total testosterone ≤190, >190–296, >296–423, and >423 ng/dL for quartiles 1, 2, 3, and 4, respectively. In order to flexibly examine total testosterone as a continuous predictor of mortality, we conducted restricted cubic spline analyses with knots defined at the 33rd and 66th percentiles of observed values (corresponding to total testosterone levels of 227 and 361 ng/dL, respectively) in sensitivity analyses.

The outcome of interest was all-cause mortality. At-risk time began the day after the baseline total testosterone measurement. Patients were censored for kidney transplantation, transfer to a dialysis facility operated by another organization, or at the end of the study (December 31, 2011).

Laboratory Data Collection

Serum samples for total testosterone and other laboratory tests were drawn at the indication of providers using standardized techniques within the outpatient dialysis clinics of the large dialysis organization; they were then transported to a single central laboratory in Deland, Florida typically within 24 h of collection, and measured using automated and standardized methods. Most blood samples were collected before the start of dialysis except post-dialysis serum urea nitrogen levels that were collected after dialysis in order to calculate urea kinetics.

Statistical Analysis

Baseline characteristics between exposure groups were compared using chi-square, analysis of variance, and Kruskal-Wallis tests according to data type. We first examined the association between relevant clinical characteristics with testosterone deficiency (defined as total testosterone <300 ng/dL according to Endocrine Society guidelines [19]; reference: total testosterone ≥300 ng/dL) using logistic regression. We then estimated the association between total testosterone levels and all-cause mortality using Cox proportional hazard models. Logistic and Cox regression models were analyzed using three hierarchical levels of adjustment with covariates ascertained at baseline:

(1) Minimally adjusted model: Adjusted for calendar quarter of study entry;

(2) Case-mix model: Adjusted for minimally adjusted model covariates, as well as age, sex, race/ethnicity, and diabetes;

(3) Expanded case-mix + laboratory model: Adjusted for case-mix model covariates, as well as dialysis vintage, cause of ESRD, modality, dialysis access, congestive heart failure, coronary heart disease, and serum albumin level.

We a priori defined the expanded case-mix + laboratory model as our preferred model, which included core socio-demographic measures and other confounders of the association between total testosterone level and mortality. Proportional hazards assumptions were checked by graphical and formal testing.

We conducted subgroup analyses of testosterone level (dichotomized as total testosterone <300 vs. ≥300 ng/dL [19]; reference: total testosterone ≥300 ng/dL) and mortality across clinically relevant categories of socio-demographics, comorbidity status, and laboratory measures. There were no missing values for any of the covariates, including age, sex, race/ethnicity, diabetes, vintage, cause of ESRD, dialysis access, congestive heart failure, coronary heart disease, or serum albumin levels. Analyses and figures were generated using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), Stata version 13.1 (Stata Corporation, College Station, TX, USA), and SigmaPlot Version 12.5 (Systat Software, San Jose, CA, USA).

Results

Study Cohort

Among 624 patients who met eligibility criteria, the mean ± SD and median (IQR) baseline total testosterone values were 323 ± 193 and 297 (190–424) ng/dL, respectively (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000480302). Fifty-one percent of patients (n = 317) had testosterone deficiency (defined as total testosterone <300 ng/dL). When total testosterone levels were examined across strata of age (<40, 40–60, >60 years of age), there was a dose-response relationship between older age and lower mean ± SD serum testosterone levels: 371 ± 222, 353 ± 179, and 280 ± 192 ng/dL, respectively (online suppl. Table 1).

Compared with patients in the highest testosterone quartile, those in the lowest quartile were of older age; were less likely to be African-American; had shorter dialysis vintage; and were more likely to have diabetes and congestive heart failure (Table 1).

Clinical Characteristics Associated with Testosterone Deficiency

In minimally adjusted logistic regression analyses, patients of older age, underlying congestive heart failure, higher body mass index (BMI), and higher serum ferritin had higher risk of having testosterone deficiency (defined as total testosterone <300 ng/dL), whereas patients with higher hemoglobin levels were less likely to have testosterone deficiency (Table 2). These associations persisted with further adjustment for case-mix and expanded case-mix + laboratory covariates.

Testosterone and All-Cause Mortality

Patients contributed a total of 806 patient-years of follow up, during which time 108 all-cause deaths occurred. The median (IQR) at-risk time was 1.2 (0.5–1.9) years. In minimally adjusted analyses, point estimates for increasingly lower testosterone quartiles were associated with numerically higher mortality risk (ref: quartile 3): hazard ratios (HRs; 95% CI) 2.63 (1.57–4.41), 1.72 (0.99–2.99), and 0.54 (0.26–1.12) for Quartiles 1, 2, and 4, respectively (Fig. 1; online suppl. Table 2). With incremental adjustment for case-mix covariates, the association between quartile 1 and higher mortality remained statistically significant. In both minimally adjusted and case-mix models, quartile 2 was associated with numerically higher mortality risk but did not reach statistical significance. In expanded case-mix + laboratory adjusted analyses, point estimates for increasingly lower testosterone quartiles were associated with numerically higher mortality risk (ref: quartile 3): adjusted HRs (95% CI) 2.32 (1.33–4.06), 1.80 (0.99–3.28), and 0.68 (0.32–1.42) for quartiles 1, 2, and 4, respectively.

In restricted cubic spline analyses of total testosterone as a continuous predictor and all-cause mortality, we observed that mortality risk declined with increasingly higher testosterone levels until reaching a threshold of 400 ng/dL above which risk plateaued in case-mix and expanded case-mix + laboratory models (online suppl Fig. 2).

Subgroup Analyses

In expanded case-mix + laboratory adjusted analyses, there was effect modification on the basis of underlying coronary heart disease, such that the relationship between testosterone deficiency and mortality was stronger in those with coronary heart disease vs. those without coronary heart disease (p-interaction = 0.04; Fig. 2 and online suppl. Table 3). In expanded case-mix + laboratory adjusted analyses, nominal HRs for testosterone deficiency were >1 across all subgroups; nominal associations were statistically significant in the following subgroups: age <55 years, age ≥55 years, Black race, presence of diabetes, presence of congestive heart failure, presence of coronary heart disease, absence of coronary heart disease, receipt of hemodialysis, serum albumin ≥4.0 g/dL, vintage <1 year, vintage ≥1 year, BMI <25 kg/m^2, and BMI ≥25 kg/m^2.

Table 1. Baseline characteristics among dialysis patients according to baseline total testosterone quartile

	Total testosterone level				
	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4
n	624	158	154	156	156
Testosterone range, ng/dL, min–max	0–1,644	0–190	191–296	297–423	425–1,644
Age, years, mean ± SD	58±14	61±14	60±15	56±13	54±14
Race, %					
Black	32	21	29	37	44
Non-Black	68	79	71	63	56
Vintage, days, median (IQR)	370	281 (97–660)	374 (160–720)	396 (167–735)	417 (168–727)
Vascular access, %					
CVC	21	24	19	21	18
AVF/AVG	56	56	58	54	59
PD catheter	29	16	19	22	23
Unknown/missing	3	4	4	2	1
Cause of ESRD, %					
Diabetes	40	42	40	40	37
Hypertension	29	30	25	31	31
Glomerulonephritis	14	11	16	11	19
Cystic disease	2.7	1.9	1.9	5.1	1.9
Other	14	15	16	13	10
Modality, %					
HD	79.6	83.5	81.2	77.6	76.3
PD	20.3	16.5	18.8	22.4	23.7
Diabetes, %	61.9	65.2	60.4	62.8	59.0
CHF, %	47.3	54.4	50.0	40.4	44.2
CHD, %	18.6	18.4	15.6	22.4	18.0
Serum albumin, g/dL, median (IQR)	3.9 (3.6–4.1)	3.9 (3.6–4.1)	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.9 (3.6–4.2)

CVC, central venous catheter; AVF, arteriovenous fistula; AVG, arteriovenous grat; PD, peritoneal dialysis; HD, hemodialysis; CHF, congestive heart failure; CHD, coronary heart disease.

Discussion

In a nationally representative cohort of US dialysis patients, we observed that the prevalence of testosterone deficiency (total testosterone <300 ng/dL) was substantially higher than that of the general population but similar to that of other international dialysis cohorts [8, 9, 13, 14, 16]. In analyses of total testosterone as a categorical predictor, we found that point estimates of incrementally lower testosterone quartiles were associated with increasingly higher mortality risk independent of case-mix and laboratory characteristics. In subgroup analyses that dichotomized testosterone as <300 ng/dL (i.e., testosterone deficiency [19]) vs. ≥300 ng/dL, we found that testosterone deficiency was associated with higher death risk across various subgroups defined by socio-demographic, comorbidity, and nutritional status.

In international, non-US based dialysis cohorts, there have been several studies of total testosterone and mortality that have shown mixed findings [8, 9, 13–16]. In one of the seminal studies that examined a cohort of 126 Swedish hemodialysis patients by Carrero et al. [14], those in the lowest total testosterone tertile (<233 ng/dL) vs. highest tertile (>345 ng/dL) had a higher mortality risk independent of socio-demographics, comorbidities, medications, and laboratory tests; however, upon adjustment for serum creatinine as a proxy of muscle mass, these associations were attenuated to the null. Similarly, in a study of 420 Turkish hemodialysis patients by Gungor et al. [9], crude analyses showed a significant association between the lowest total testosterone tertile (<6.8 nmol/L or <196 ng/dL) and mortality, which was attenuated to the null in adjusted analyses. Yet in two subsequent studies of 260 Swedish ESRD patients by Carrero et al. [8], and 111 Greek hemodialysis patients by Kyriazis et al. [16], those in the lowest total testosterone tertile (<10 nmol/L [288 ng/dL] and <5.2 nmol/L [150 ng/dL], respectively) had a significantly higher mortality risk inde-

Table 2. Clinical characteristics associated with testosterone deficiency (total testosterone <300 ng/dL) using logistic regression

	Minimally adjusted OR (95% CI)	Case-mix adjusted OR (95% CI)	Expanded case-mix + laboratory adjusted OR (95% CI)
Age, Δ10 years	**1.30 (1.15–1.46)**	**1.23 (1.09–1.40)**	**1.23 (1.08–1.40)**
Black race (ref: Non-Black)	0.45 (0.32–0.64)	0.52 (0.36–0.75)	0.51 (0.35–0.76)
Vintage (Δ1 month)	1.00 (0.99–1.02)	1.01 (0.99–1.02)	1.01 (0.99–1.03)
Vascular access (ref: CVC)			
AVF/AVG	1.04 (0.68–1.59)	1.02 (0.66–1.59)	1.03 (0.65–1.64)
PD catheter	0.68 (0.40–1.13)	0.63 (0.37–1.07)	0.66 (0.37–1.16)
Unknown/missing	3.87 (0.99–15.1)	**4.67 (1.14–19.2)**	**4.75 (1.14–19.8)**
Cause of ESRD (ref: Diabetes)			
Hypertension	0.77 (0.52–1.14)	0.82 (0.52–1.30)	0.88 (0.55–1.41)
Glomerulonephritis	0.83 (0.50–1.38)	0.93 (0.53–1.62)	1.07 (0.60–1.91)
Cystic disease	0.54 (0.19–1.54)	0.59 (0.19–1.76)	0.69 (0.22–2.19)
Other	1.25 (0.74–2.11)	1.19 (0.67–2.13)	1.36 (0.75–2.46)
Diabetes	1.11 (0.79–1.56)	1.08 (0.76–1.54)	1.12 (0.73–1.71)
CHF	**1.66 (1.19–2.31)**	**1.62 (1.15–2.28)**	**1.44 (1.00–2.07)**
CHD	0.81 (0.53–1.23)	0.74 (0.48–1.14)	0.69 (0.44–1.08)
Serum albumin, Δ0.5 g/dL	0.86 (0.71–1.03)	0.92 (0.76–1.11)	0.85 (0.69–1.05)
BMI, Δ5 kg/m^2	**1.16 (1.01–1.32)**	**1.23 (1.07–1.41)**	**1.22 (1.05–1.42)**
Serum creatinine, mg/dL	0.94 (0.90–0.99)	1.00 (0.95–1.06)	1.03 (0.96–1.09)
Calcium, mg/dL	1.03 (0.76–1.41)	0.98 (0.71–1.35)	1.06 (0.76–1.48)
Phosphorus, mg/dL	1.00 (0.88–1.14)	1.09 (0.94–1.25)	1.07 (0.93–1.24)
PTH, Δ25 pg/mL	0.98 (0.96–1.00)	0.99 (0.98–1.01)	0.99 (0.97–1.01)
Bicarbonate, Δ5meq/L	0.87 (0.67–1.13)	0.79 (0.60–1.04)	0.82 (0.61–1.10)
Hemoglobin, g/dL	**0.76 (0.65–0.89)**	**0.77 (0.65–0.90)**	**0.76 (0.64–0.91)**
Transferrin saturation, Δ5%	0.97 (0.90–1.04)	0.97 (0.90–1.04)	0.98 (0.91–1.06)
Ferritin, Δ50 ng/mL	**1.03 (1.01–1.06)**	**1.03 (1.00–1.05)**	**1.02 (1.00–1.05)**
Renal urea clearance, mL/min	0.98 (0.88–1.10)	1.00 (0.88–1.15)	0.98 (0.85–1.14)
spKt/V, Δ0.2	1.09 (0.98–1.22)	1.04 (0.93–1.16)	1.07 (0.94–1.22)
nPCR, Δ0.2 g/kg/day	1.11 (0.97–1.28)	1.09 (0.94–1.26)	1.15 (0.98–1.35)

CVC, central venous catheter; AVF, arteriovenous fistula; AVG, arteriovenous graft; PD, peritoneal dialysis; ESRD, end stage renal disease; CHF, congestive heart failure; CHD, coronary heart disease; BMI, body mass index; PTH, parathyroid hormone; nPCR, normalized protein catabolic rate.

Minimally adjusted analyses adjusted for calendar quarter of study entry; Case-mix adjusted analyses adjusted for minimally adjusted model covariates, as well as age, sex, race/ethnicity, and diabetes; Expanded case-mix models adjusted for case-mix model covariates, as well as dialysis vintage, cause of ESRD, dialysis access, modality, CHF, CHD, and serum albumin level. Bold values indicate statistically significant associations.

pendent of socio-demographics, comorbidity status, and inflammatory markers. Most recently, in a study of 623 Canadian hemodialysis patients by Bello et al. [13], the impact of low testosterone levels upon mortality was dependent on age, such that low testosterone levels (<231 ng/dL) were associated with higher mortality in those who were younger (<63 years old) but not in those who were older (≥63 years old).

To our knowledge, this is the largest study of testosterone and mortality among US dialysis patients conducted to date. Our primary analyses of testosterone as a categorical (i.e., quartiles) predictor suggest that levels below ~296 ng/dL are associated with lower survival. In secondary analyses of testosterone as a continuous predictor (i.e., splines), the lower testosterone – higher mortality risk declined with increasingly higher testosterone levels until reaching a threshold value of 400 ng/dL above which risk plateaued. These associations between lower testosterone level and higher mortality risk were independent of age, medical comorbidities, dialysis vintage, and race,

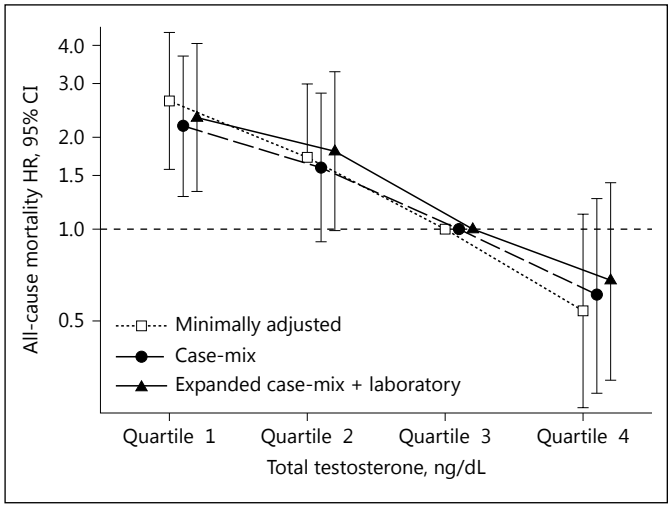

Fig. 1. Association between baseline total testosterone levels and all-cause mortality in dialysis patients in minimally adjusted, case-mix, and expanded case-mix + laboratory adjusted models. Minimally adjusted analyses adjusted for calendar quarter of study entry; case-mix adjusted analyses adjusted for minimally adjusted model covariates, as well as age, sex, race/ethnicity, and diabetes; expanded case-mix models adjusted for case-mix model covariates, as well as dialysis vintage, cause of end-stage renal disease, modality, dialysis access, congestive heart failure, coronary heart disease, and serum albumin level.

thereby suggesting that testosterone plays an independent physiologic role that contributes to the survival of the ESRD population. In addition, compared to the aforementioned international studies [8, 9, 13, 14, 16], our study population was observed to have a high prevalence of Black patients and those with underlying diabetes and cardiovascular disease, which is more reflective of the racial/ethnic diversity and high burden of medical comorbidities typically encountered in the US dialysis population [7]. Despite these case-mix differences, we observed a similar testosterone threshold associated with greater survival as observed in prior dialysis studies [8, 13, 16].

Another novel finding of our study was the potent interaction that occurred due to patient characteristics, such as underlying cardiovascular risk. For example, we observed that stronger testosterone-mortality associations were observed in those with coronary heart disease vs. those without coronary heart disease. In the general population, testosterone deficiency has been associated with multiple atherosclerotic risk factors including dyslipidemia [20], obesity [21], inflammation [22], and incident diabetes [23]. Given that observational studies have shown a relationship between low testosterone and coronary heart disease risk factors such as endothelial dysfunction [24], increased arterial stiffness [16], anemia, and erythropoietin-stimulating agent resistance [25] in chronic kidney disease and ESRD patients, it has been speculated that testosterone deficiency may be linked to higher death risk in these populations via cardiovascular pathways. Thus, it is plausible that dialysis patients with underlying coronary heart disease may be predisposed to cardiovascular mortality associated with testosterone deficiency, resulting from a metabolic milieu conferring heightened vulnerability to testosterone-related perturbations. We also observed a trend toward more potent testosterone-mortality associations among Black vs. non-Black patients, although interaction tests narrowly missed significance. While Black dialysis patients tend to have higher testosterone levels and greater survival [26], these data suggest that testosterone deficiency is more potently associated with death risk in this racial/ethnic subgroup. Notably, although incrementally lower mean testosterone levels were observed with increasingly older age strata, in contrast to the Bello et al. [13] study, we did not observe a differential association between lower testosterone level and mortality across age groups, suggesting that testosterone deficiency may be equally detrimental among younger and older patients.

To date, there has been sparse study of the impact of testosterone replacement upon hard outcomes in dialysis patients. However, limited evidence suggests that correction of testosterone deficiency may improve surrogate endpoints such as body anthropometry, nutritional, and hematologic status in this population. For example, an important trial conducted by Johansen et al. [27] examined the impact of nandrolone replacement vs. lower extremity resistive exercise upon lean body mass among 79 maintenance hemodialysis patients over a 12-week period. Notably, patients randomized to nandrolone replacement were observed to have a statistically significant gain in lean body mass, while those randomized to exercise alone did not. Similarly, an observational study that included hemodialysis patients who were administered nandrolone was observed to exhibit improvements in albumin, cholesterol, and lipoprotein suggestive of nutritional benefits of androgen supplementation in ESRD patients [28]. Finally, as androgen use preceded the advent of erythropoietin, prior research has shown the utility of androgen replacement in correcting anemia of renal disease. Indeed, a recent meta-analysis comparing nandrolone vs. erythropoietin in the treatment of anemia of renal disease showed no significant difference in hemoglobin level across the two groups [29]. These collective data warrant future studies that will examine whether the cor-

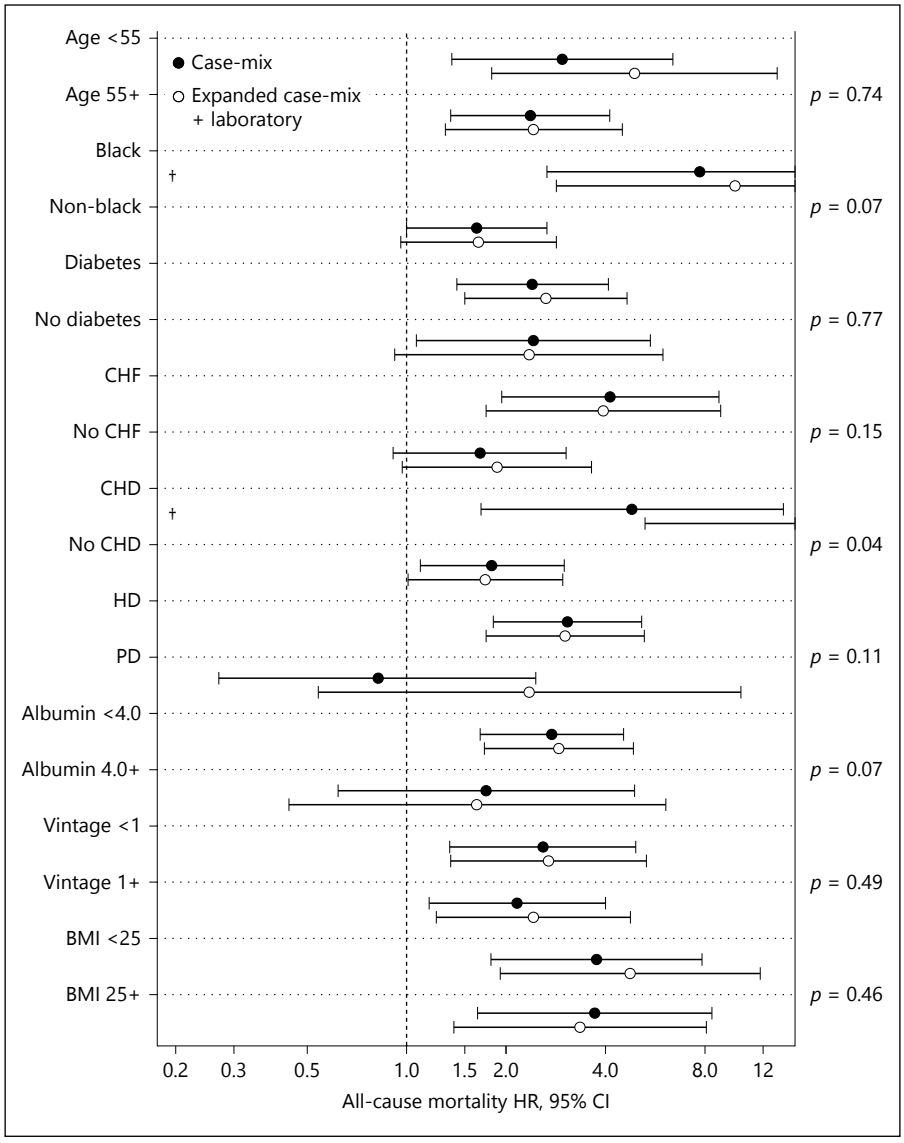

Fig. 2. Associations between baseline total testosterone level (dichotomized as total testosterone level <300 vs. ≥300 ng/dL; reference: total testosterone ≥300 ng/dL) and all-cause mortality. Case-mix adjusted analyses adjusted for calendar quarter of study entry, age, sex, race/ethnicity, and diabetes; Expanded case-mix models adjusted for case-mix model covariates, as well as dialysis vintage, cause of end-stage renal disease, modality, dialysis access, congestive heart failure, coronary heart disease, and serum albumin level. † Upper bound of 95% CI exceeds figure limits.

rection of testosterone deficiency will ameliorate hard outcomes such as cardiovascular disease and death in dialysis patients, as well as the optimal total testosterone target range in this population.

The strengths of our study include its examination of a large, nationally representative cohort of US dialysis patients; comprehensive availability of detailed, longitudinal patient-level comorbidity, laboratory, and dialysis-treatment characteristics; and laboratory data collected in the outpatient setting and uniformly measured at a single center. However, several limitations of our study bear mention. First, an inherent disadvantage of a retrospective analysis using clinical data is that indications for serum testosterone measurement are not evident (i.e., patients who underwent testosterone measurement may have had higher pre-test probability of underlying disease). However, while the indications for testing in this study cohort are unknown, this requirement applied equally to patients irrespective of testosterone status and should not impair the study's internal validity. Second, our study solely relied on total testosterone measurements and did not include analyses of free testosterone. However, it should be noted that the recommended methodologic approach for measuring free testosterone (i.e., equilibrium dialysis) is not routinely available in the clinical setting, and total testosterone is considered to be an accurate metric of testosterone secretion [19]. Third, while all serum samples for total testosterone measure-

ment were collected prior to dialysis, due to data limitations we were unable to determine what time of day samples were drawn and thus could not account for diurnal variations in levels. Fourth, due to data limitations, we were unable to determine which patients were receiving testosterone replacement therapy and certain medications that might impact testosterone levels (e.g., beta blockers). Thus, patients were categorized according to their biochemical total testosterone status irrespective of treatment. However, it should be noted that prior studies of CKD and dialysis patients that excluded recipients of testosterone replacement have observed similar findings [9, 16, 30]. Lastly, given the inherent limitations of an observational study, we cannot exclude the possibility of residual confounding.

In conclusion, our study found that lower total testosterone levels were associated with higher death risk in dialysis patients, and that testosterone deficiency was linked with heightened mortality across multiple subgroups. At this time, future studies are needed to investigate underlying pathways by which low testosterone levels adversely impact survival. Furthermore, interventional studies are needed to determine whether correction of testosterone deficiency leads to improved outcomes, and to clarify the causal relationships between low testosterone and mortality in dialysis patients.

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Disclosure Statement

None of the authors have any disclosures to report.

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References

1 Araujo AB, Kupelian V, Page ST, Handelsman DJ, Bremner WJ, McKinlay JB: Sex steroids and all-cause and cause-specific mortality in men. Arch Intern Med. 2007;167:1252–1260.

2 Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–731.

3 Laughlin GA, Barrett-Connor E, Bergstrom J: Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008;93:68–75.

4 Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, Sharma R, Parashara D, Savin VJ, Ambrose JA, Barua RS: Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36:2706–2715.

5 Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Almeida OP, Golledge J, Norman PE, Flicker L: In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab 2014;99:E9–E18.

6 Kakiya R, Shoji T, Hayashi T, Tatsumi-Shimomura N, Tsujimoto Y, Tabata T, Shima H, Mori K, Fukumoto S, Tahara H, Koyama H, Emoto M, Ishimura E, Nishizawa Y, Inaba M: Decreased serum adrenal androgen dehydroepiandrosterone sulfate and mortality in hemodialysis patients. Nephrol Dial Transplant 2012;27:3915–3922.

7 URD System: USRDS 2013 Annual Data Report: Atlas of Chronic Kidney DIsease and End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013.

8 Carrero JJ, Qureshi AR, Nakashima A, Arver S, Parini P, Lindholm B, Barany P, Heimburger O, Stenvinkel P: Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. Nephrol Dial Transplant 2011;26:184–190.

9 Gungor O, Kircelli F, Carrero JJ, Asci G, Toz H, Tatar E, Hur E, Sever MS, Arinsoy T, Ok E: Endogenous testosterone and mortality in male hemodialysis patients: is it the result of aging? Clin J Am Soc Nephrol 2010;5:2018–2023.

10 Carrero JJ: Testosterone deficiency at the crossroads of cardiometabolic complications in CKD. Am J Kidney Dis 2014;64:322–325.

11 Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH: The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004;89:3313–3318.

12 Schmidt A, Luger A, Horl WH: Sexual hormone abnormalities in male patients with renal failure. Nephrol Dial Transplant 2002;17:368–371.

13 Bello AK, Stenvinkel P, Lin M, Hemmelgarn B, Thadhani R, Klarenbach S, Chan C, Zimmerman D, Cembrowski G, Strippoli G, Carrero JJ, Tonelli M: Serum testosterone levels and clinical outcomes in male hemodialysis patients. Am J Kidney Dis 2014;63:268–275.

14 Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Barany P, Heimburger O, Stenvinkel P: Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol 2009;20:613–620.

15 Grossmann M, Hoermann R, Ng Tang Fui M, Zajac JD, Ierino FL, Roberts MA: Sex steroids levels in chronic kidney disease and kidney transplant recipients: associations with disease severity and prediction of mortality. Clin Endocrinol (Oxf) 2015;82:767–775.

16 Kyriazis J, Tzanakis I, Stylianou K, Katsipi I, Moisiadis D, Papadaki A, Mavroeidi V, Kagia S, Karkavitsas N, Daphnis E: Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients. Nephrol Dial Transplant 2011;26:2971–2977.

17 Kuttykrishnan S, Kalantar-Zadeh K, Arah OA, Cheung AK, Brunelli S, Heagerty PJ, Katz R, Molnar MZ, Nissenson A, Ravel V, Streja E, Himmelfarb J, Mehrotra R: Predictors of treatment with dialysis modalities in observational studies for comparative effectiveness research. Nephrol Dial Transplant 2015;30:1208–1217.
18 Rhee CM, Kim S, Gillen DL, Oztan T, Wang J, Mehrotra R, Kuttykrishnan S, Nguyen DV, Brunelli SM, Kovesdy CP, Brent GA, Kalantar-Zadeh K: Association of thyroid functional disease with mortality in a national cohort of incident hemodialysis patients. J Clin Endocrinol Metab 2015;100:1386–1395.
19 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM: Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–2559.
20 Haffner SM, Mykkanen L, Valdez RA, Katz MS: Relationship of sex hormones to lipids and lipoproteins in nondiabetic men. J Clin Endocrinol Metab 1993;77:1610–1615.
21 Ohlsson C, Barrett-Connor E, Bhasin S, Orwoll E, Labrie F, Karlsson MK, Ljunggren O, Vandenput L, Mellstrom D, Tivesten A: High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol 2011;58:1674–1681.
22 Kaplan SA, Johnson-Levonas AO, Lin J, Shah AK, Meehan AG: Elevated high sensitivity C-reactive protein levels in aging men with low testosterone. Aging Male 2010;13:108–112.
23 Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT: Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes care. 2004;27:1036–1041.
24 Yilmaz MI, Sonmez A, Qureshi AR, Saglam M, Stenvinkel P, Yaman H, Eyileten T, Caglar K, Oguz Y, Taslipinar A, Vural A, Gok M, Unal HU, Yenicesu M, Carrero JJ: Endogenous testosterone, endothelial dysfunction, and cardiovascular events in men with nondialysis chronic kidney disease. Clin J Am Soc Nephrol 2011;6:1617–1625.
25 Carrero JJ, Barany P, Yilmaz MI, Qureshi AR, Sonmez A, Heimburger O, Ozgurtas T, Yenicesu M, Lindholm B, Stenvinkel P: Testosterone deficiency is a cause of anaemia and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. Nephrol Dial Transplant. 2012;27:709–715.
26 Rhee CM, Lertdumrongluk P, Streja E, Park J, Moradi H, Lau WL, Norris KC, Nissenson AR, Amin AN, Kovesdy CP, Kalantar-Zadeh K: Impact of age, race and ethnicity on dialysis patient survival and kidney transplantation disparities. Am J Nephrol 2014;39:183–194.
27 Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA 1999;281:1275–1281.
28 Ghorbanihaghjo A, Argani H, Rohbaninoubar M, Rashtchizadeh N: Effect of Nandrolone Decanoate on serum lipoprotein (a) and its isoforms in hemodialysis patients. Lipids Health Dis 2004;3:16.
29 Adamu B, Ma'aji SM, Erwin PJ, Tleyjeh IM: Meta-Analysis of Randomized controlled trials on androgens versus erythropoietin for anaemia of chronic kidney disease: implications for developing Countries. Int J Nephrol 2012;2012:580437.
30 Haring R, Nauck M, Volzke H, Endlich K, Lendeckel U, Friedrich N, Dorr M, Rettig R, Kroemer HK, Wallaschofski H Low serum testosterone is associated with increased mortality in men with stage 3 or greater nephropathy. Am J Nephrol 2011;33:209–217.