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Permalink
https://escholarship.org/uc/item/2604843x

Journal
AMERICAN JOURNAL OF NEPHROLOGY, 46(3)

ISSN
0250-8095

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Publication Date
2017

DOI
10.1159/000480302

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

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Keywords
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
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;
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/m², and BMI ≥25 kg/m².
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 incrementally 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 Gunogor 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-
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.
lipidemia, obesity, inflammation, and incident diabetes. Given that observational studies have shown a relationship between low testosterone and coronary heart disease risk factors such as endothelial dysfunctions, 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 and diabetes; expanded case-mix + laboratory adjusted models 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.

Several studies have shown that testosterone deficiency is more potently associated with 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 levels 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 hemato logic status in this population. For example, an important trial conducted by Johansen et al. [27] examined the impact of nandrolone replacement vs. lower extreme 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 co-

![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 + laboratory adjusted 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.](image)
Correction 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 measurement were collected from a single center.

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.
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.

Acknowledgments

 Portions of these data have been presented as an oral abstract at the 2016 Annual Dialysis Conference, Seattle, WA, USA; February 28 to March 2, 2016.

Disclosure Statement

 None of the authors have any disclosures to report.

Funding Sources

 The authors are supported by the research grants from the NIH/NIDDK including K23-DK102903 (C.M.R.), K24-DK091419 (K.K.Z.), R01-DK09568 (K.K.Z.), R01-DK096920 (C.P.K. and K.K.Z.), and U01-DK102163 (K.K.Z. and C.P.K.), and philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, and Dr. Joseph Lee.

References


Funding Sources

The authors are supported by the research grants from the NIH/NIDDK including K23-DK102903 (C.M.R.), K24-DK091419 (K.K.Z.), R01-DK09568 (K.K.Z.), R01-DK096920 (C.P.K. and K.K.Z.), and U01-DK102163 (K.K.Z. and C.P.K.), and philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, and Dr. Joseph Lee.
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