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


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 or-
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/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 increas-ingly 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 Gun-gor et al. [9], crude analyses showed a significant association between the lowest total testosterone tertile (<6.8 nmol/L < 288 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.
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 dys-
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...
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

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