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Original Investigation

Serum Testosterone Levels and Clinical Outcomes in Male Hemodialysis Patients

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Background: Studies linking low serum testosterone concentration to adverse clinical outcomes in hemodialysis patients have been relatively small. We investigated the role of testosterone in adverse outcomes and quality of life in an incident cohort of male Canadian hemodialysis patients.

Study Design: A prospectively designed multicenter observational study using data from the Canadian Kidney Disease Cohort Study (CKDCS).

Setting & Participants: Male patients initiating hemodialysis therapy since February 14, 2005, in 3 Canadian centers serving ethnically diverse populations were studied (N = 623).

Predictor: Serum testosterone levels using the International Society of Andrology, International Society for the Study of the Aging Male, and European Association of Urology cutoffs (low, <231 ng/dL; borderline, 231-346 ng/dL; normal, >346 ng/dL).

Outcomes: All-cause mortality, fatal and nonfatal cardiovascular (CV) events, and Health Utility Index (HUI)-assessed health-related quality of life.

Measurements: Participants completed a structured interview on demographics and medical history and an HUI questionnaire (version 3). Routine laboratory test results captured into the study database, and serum testosterone measured within 3 months after initiation of the baseline hemodialysis session.

Results: During a median follow-up of 20 (range, 1-81) months, 166 (27%) died and 98 (20%) had a CV event. Mean serum testosterone level was 234.1 ± 146.1 (SD) ng/dL. Higher serum testosterone levels were associated with significantly decreased unadjusted risk of death (HR per 10-ng/dL increase, 0.58; 95% CI, 0.37-0.90). There was a statistically significant trend for higher all-cause mortality with low serum testosterone levels in adjusted analyses ($P < 0.001$). Higher levels of log-transformed testosterone were associated with significantly higher HUI scores (P for trend <0.001), and low levels of serum testosterone were associated significantly with lower HUI scores (P for trend <0.001). Although there was a significant trend in the unadjusted risk of CV events among participants with low serum testosterone levels ($P < 0.001$), the risk was no longer significant after adjustment for age. There was no significant interaction with age and serum testosterone level tested as continuous variables ($P = 0.07$).

Limitations: A short follow-up period and serum testosterone measured on a single occasion.

Conclusions: Low serum testosterone concentration may be a modifiable risk factor for adverse outcomes and poor quality of life in male hemodialysis patients. This hypothesis should be tested in randomized controlled trials.
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INDEX WORDS: Serum testosterone; dialysis; adverse clinical outcomes; health-related quality of life (HRQoL).

Low serum testosterone concentration is common in the general population and present in up to 30% of men[1-3] older than 40 years.[4] There is accumulating evidence linking low testosterone levels and increased risk of adverse clinical outcomes[1-3,5-14] due to direct effects on vascular remodeling and function and its association with classic cardiovascular (CV) disease (CVD) risk factors.[1,4,5,13] Experimental and clinical data suggest that low testosterone levels may be associated with excess risk of CVD and mortality in high-risk patients with increasing age and comorbid conditions, such as those with diabetes, metabolic syndrome, chronic kidney disease (CKD), and various inflammatory states.[1,2,13-20]

About 40%-60% of patients with advanced CKD have evidence of low testosterone levels.[8,11,19,20] Given the high mortality (due to a combination of CVD, protein-energy wasting, and infectious complications) and poor quality of life associated with dialysis treatment, identification of novel treatments for advanced kidney disease and kidney failure is a high clinical priority.[1,2,20]

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A few studies have investigated the role of serum testosterone and its relation to excess risk of CVD in patients with non−dialysis-dependent and dialysis-dependent CKD.[5,6,19-21] These studies are relatively small, have enrolled patients from a single center, and have tended to evaluate a limited spectrum of outcomes. Using a large-scale, prospective, and multicenter study, we investigated the role of testosterone on all-cause mortality, CVD events, and quality of life in an incident cohort of male hemodialysis (HD) patients in Canada.

METHODS

Study Design

This was a prospective multicenter observational study using data from the Canadian Kidney Disease Cohort Study (CKDCS).[22] Patients initiating HD therapy since February 14, 2005, in 3 Canadian centers serving ethnically mixed populations (Vancouver, Calgary, and Edmonton) were eligible for inclusion in the CKDCS[22] (Fig 1). A principal investigator at each site took responsibility for recruitment, data collection, and follow-up until the cutoff date (November 26, 2011). The institutional review boards at the participating centers approved the study, which was conducted according to the Declaration of Helsinki for medical research in humans.[22]

Study Patients

The inclusion criteria were all male incident adult (aged ≥18 years) HD patients from the 3 participating renal programs.[22] All eligible patients initiating maintenance HD therapy were approached by the study staff within 8 weeks. The exclusion criteria were failure to provide informed consent for blood collection (n = 23), switching of dialysis modality before testosterone sample collection (n = 28), or missing serum sample collection (n = 48; Fig 1).

Data Collection

Consenting participants underwent a structured interview at baseline to collect detailed data for demographic characteristics and medical history and to complete a Health Utility Index (HUI; version 3; HU) questionnaire.[22] The HUI captures information on overall health status and health-related quality of life and is based on clinically meaningful utility scores.[23]

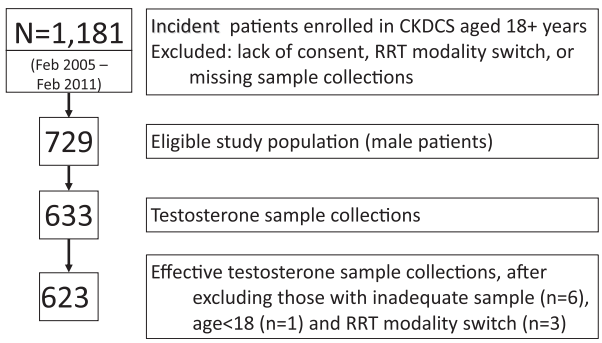

Figure 1. Participant flow chart. Abbreviations: CKDCS, Canadian Kidney Disease Cohort Study; RRT, renal replacement therapy.

Information from the clinical record was used to supplement the history. Follow-up visits were conducted at month 6; years 1, 2, 3, 4, and 5; and then every 5 years thereafter. The baseline study visit was conducted within 8 weeks of initiating HD therapy, with follow-up visits completed within ±2 months of the scheduled visit date.[22]

Routine laboratory test results from dialysis monthly blood tests (white blood cell count, creatinine, albumin, calcium, phosphate, hemoglobin, bicarbonate, and parathyroid hormone) were captured in the study database using either a direct data link or entered manually by study personnel.[22]

Serum from blood samples was collected within 3 months after initiation of the baseline HD session and sera were processed and frozen in 0.5-mL cryovials at −85°C within 72 hours of sample collection.[22] Frozen serum samples from eligible participants were sent to the Karolinska Institute in Stockholm, Sweden, for testing of total testosterone and sex hormone−binding globulin using certified routine methods at the Department of Laboratory Medicine in Karolinska University Hospital.

Serum testosterone levels were classified for analyses using predefined categories according to the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association of Urology (EAU) revised consensus criteria for diagnosis[7,11,19,21,24,25] as follows: serum testosterone levels <231, 231-346, and >346 ng/dL defined as low, borderline, and normal, respectively. In addition, we also have classified serum testosterone based on previous reports as continuous with and without log transformation and tertiles.

Outcome Measures

The primary outcome for this study was all-cause mortality. Study participants who died were identified by monthly follow-up by study coordinators; date of death was obtained from each respective renal program. A prospectively defined method was used to ascertain the cause of death.[25] Primary and secondary causes of death were identified by 2 independent physicians (with agreement by consensus) and classified using a standardized classification scheme adapted for use in HD patients.[25]

A composite outcome of incident fatal and nonfatal CV events including myocardial infarction, coronary artery disease (myocardial infarction, angioplasty, stent, or coronary artery bypass surgery), and CVD (coronary artery disease, stroke, or peripheral vascular disease [amputation, peripheral vascular intervention, and gangrene]) was identified by follow-up medical history interviews. Total composite CV events represent the number of fatal and nonfatal CV-specific events, including death; the total number of deaths includes both CV- and non–CV-related mortality. The formula of the dead-perfect health scale was used to ascertain HUI3 multiattribute utility function.[23]

Statistical Analysis

Baseline demographic and clinical characteristics, stratified by levels of serum testosterone by standard criteria, are presented as means or proportions. Cox proportional hazards models were used for time-to-event analyses (all-cause mortality). The proportional hazards assumptions were tested using log–negative-log survival plots; logistic regression analyses were used to test the associations between serum testosterone levels and incident CV events. Longitudinal mixed-effect models were used for HUI analyses, with intercepts and slopes as random effects, and unstructured covariance was specified to allow an intercept-slope covariance to be estimated. All models to assess the associations between serum testosterone levels and outcomes were adjusted for significant