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CLINICAL RESEARCH

Associations Between Low Serum Testosterone and All-Cause Mortality and Infection-Related Hospitalization in Male Hemodialysis Patients: A Prospective Cohort Study

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Introduction: Infectious diseases are the second highest cause of death in patients on dialysis. In addition, testosterone deficiency or hypogonadism is prevalent in dialysis patients. However, to our knowledge, no studies have investigated the association between testosterone levels and infectious events. We aimed to evaluate whether serum testosterone levels are associated with infection-related hospitalization in male hemodialysis patients in a prospective cohort study.

Methods: We divided the study population into 3 groups based on serum testosterone levels. Associations between testosterone levels and clinical outcomes of infection-related hospitalization, all-cause mortality, and cardiovascular disease (CVD) events were analyzed using the Cox proportional hazard model.

Results: Nine hundred two male patients were enrolled and followed up for a median of 24.7 months. Their mean ± SD age was 63.4 ± 11.8 years, and their median (interquartile range) of total testosterone was 11.7 nmol/l (7.9–14.9 nmol/l). During follow-up, 123 participants died. Infection-related hospitalization and CVD events occurred in 116 and 151 patients, respectively. Infection-related hospitalization was more frequent in the lower testosterone tertile than in the higher testosterone tertile (hazard ratio [HR]: 2.12; 95% confidence interval [CI]: 1.18–3.79; $P = 0.01$) in adjusted models. Moreover, all-cause mortality was significantly greater in the lower testosterone tertile than in the higher testosterone tertile in adjusted analysis (HR: 2.26; 95% CI: 1.21–4.23; $P = 0.01$). In contrast, there were no significant differences in CVD events by testosterone level.

Discussion: Low levels of testosterone may be associated with higher rates of infection-related hospitalization and all-cause mortality in male hemodialysis patients.

Kidney Int Rep (2017) **2,** 1160–1168; http://dx.doi.org/10.1016/j.ekir.2017.07.015
KEYWORDS: hemodialysis; infection; mortality

Infectious diseases are the second highest cause of mortality in patients on dialysis, and the occurrence of infectious events in dialysis patients is increasing worldwide.[1–3] Factors that increase the risk for infectious events in hemodialysis patients include advanced age, malnutrition, diabetes mellitus, and vascular access. However, detailed mechanisms of infection in dialysis patients have not yet been confirmed, and preventive strategies are limited.

Testosterone deficiency or hypogonadism is prevalent in patients with chronic kidney disease; approximately 40% to 60% of end-stage renal disease patients have testosterone deficiency.[4–7] Earlier studies reported that the sex hormone testosterone is associated with the immune system and antibacterial activity.[8,9] Testosterone deficiency may also cause a decrease in bone mineral density, muscle mass, libido, and energy, and an increase in fat mass and insulin resistance.[10] Low serum testosterone has been reported as a risk factor for all-cause mortality and cardiovascular disease (CVD) events in the general population[11,12] and in hemodialysis patients.[4–7] However, previous studies that investigated the relationship between testosterone and mortality in dialysis patients had a relatively small sample size and enrolled participants from a single

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Received 7 March 2017; revised 13 July 2017; accepted 24 July 2017; published online 3 August 2017

center.[4–7] Therefore, we designed a large-scale, multi-institute, prospective cohort study to confirm the role of testosterone in infection-related hospitalization, as well as in all-cause mortality and CVD events, among male hemodialysis patients.

MATERIALS AND METHODS

Study Design

In this multi-institute, prospective cohort study, we recruited male hemodialysis patents from dialysis outpatient units of 15 medical institutions in Tokyo, Japan. Baseline visits for patient enrollment were conducted between May 1, 2011 and March 31, 2012, and enrolled patients were followed up until June 1, 2015. Patients were older than 20 years of age, had spent at least 3 months on dialysis therapy, and regularly received hemodialysis (3–5 h/session) 3 times a week. We excluded patients with acute gastrointestinal bleeding, acute coronary syndrome, liver dysfunction, and a history of prostate cancer at baseline. At all participating hospitals, acute coronary syndrome was defined as acute heart failure, acute myocardial infarction, and unstable angina. We also excluded patients who had currently experienced an active infection or were prescribed antibiotics at the time of inclusion in the study. None of the patients were receiving sex hormone therapy or taking sex hormone antagonists. The study protocol was reviewed and approved by the ethics committee of the Jikei Institutional Review Board at Jikei University School of Medicine. In addition, this study was approved by each participating institution's review board. All study procedures were in accordance with the Declaration of Helsinki and its revisions. Signed informed consent was obtained from all patients before inclusion in the study.

Data Collection

Age, sex, length of dialysis, primary illness leading to kidney dysfunction, and medical history were extracted from medical records. Medication information (use of antiplatelet drugs, vitamin K antagonists, phosphate binders, vitamin D receptor agonists, cinacalcet, antihypertensive medications, and statins) was obtained from prescription records. Comorbidity and medication were determined by chart review and standardized interviews at baseline.

Blood samples were collected at study entry, before the hemodialysis session after the longest interdialysis period. Routine biochemical measurements included serum sodium, potassium, phosphorus, calcium, magnesium, serum albumin, blood urea nitrogen, alkaline phosphatase, creatinine, hematocrit, intact parathyroid hormone, and C-reactive protein levels. The delivered dialysis dose was measured by single pool Kt/V.

Testosterone status was analyzed at a later date using frozen blood samples. The total testosterone level was measured by electrochemiluminescence immunoassay at SRL Tokyo Hachioji Laboratories, Tokyo, Japan. Sex hormone–binding globulin was analyzed by an enzyme-linked immunosorbent assay kit (R&D Systems Inc., Minneapolis, Minnesota, USA).

Outcomes

Clinical outcomes were prospectively recorded and coded, blinded from clinical and biochemical data. These data were collected by study investigators. After review of available information, the cause of death was classified as either cardiovascular, infectious, malignancy, or other. The primary outcome assessed was infectious events requiring hospitalization, defined as a composite of death due to infectious diseases and the first infectious event requiring hospitalization. Infection-related hospitalizations were categorized into 8 mutually exclusive categories: respiratory, gastrointestinal, genitourinary, musculoskeletal, vascular access, septicemia, skin, and others. The secondary outcomes were all-cause mortality and CVD events, which were defined as sudden death, acute coronary syndrome that did not include angina pectoris but included acute myocardial infarction and unstable angina, and stroke that did not include transient cerebral ischemia but included ischemic infarction and cerebral hemorrhage. We set the recruited date for each patient as the time origin of the survival analysis. We counted only the first event for each patient and did not count repeated events in the survival analysis. In all analyses, we censored follow-up at loss to follow-up, renal transplantation, or the end of the study.

Statistical Analysis

Non-normally distributed data were expressed as median (25th and 75th percentiles), and normally distributed data were summarized as mean $\pm$ SD, as appropriate. Binary data were summarized as percentages. Total testosterone levels were divided into 3 groups: lower tertile ($<$9.05 nmol/l), middle tertile (9.05–13.7 nmol/l), and higher tertile ($>$13.7 nmol/l). Differences among $>$3 groups were analyzed by analysis of variance or the Kruskal-Wallis test, as appropriate. Nominal variables were analyzed by the χ^2 test.

To investigate the associations between total testosterone levels and all-cause mortality, we applied Kaplan-Meier survival curves and the Cox proportional hazard model. Univariate and multivariate Cox regression analyses are presented as the hazard ratio (HR) and 95% confidence interval (CI). We used age, body mass