



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 \pm 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.

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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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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 patients 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, anti-hypertensive 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

index, albumin, creatinine, C-reactive protein, sex hormone-binding globulin, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diabetes mellitus, and a history of CVD for multiple regression analysis. At the study outset, we divided patients into 3 age groups: younger than 60 years, 60 to younger than 70 years, and 70 years or older for subgroup analysis. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using STATA 14.0 (STATA Corp., College Station, Texas, USA).

RESULTS

Patient Characteristics

Of 931 initially evaluated patients, 25 patients were excluded at entry for the following reasons: acute gastrointestinal bleeding ($n = 2$), acute coronary syndrome ($n = 2$), liver dysfunction ($n = 10$), history of prostate cancer ($n = 8$), and infection or antibiotic therapy ($n = 3$). As a result, we included 902 patients in this study. Their mean \pm SD age was 63.4 ± 11.8 years, and their median time on dialysis was 81 months (range: 38–144 months). Diabetes mellitus was observed in 366 patients (40.6%). Median (interquartile range) of total testosterone was 11.7 nmol/l (7.9–14.9 nmol/l). Testosterone deficiency (< 10 nmol/l) was seen in 365 (40.5%) patients. Patients in the lower testosterone tertile tended to be older; had lower serum albumin, hemoglobin, and creatinine levels; and had higher body mass index and potassium, and higher C-reactive protein levels than those in the higher testosterone tertile (Table 1). However, there were no significant differences in the prevalence of diabetes mellitus, history of CVD, phosphorus levels, and total cholesterol levels among the tertiles. Thirteen patients were lost to follow-up.

Testosterone and Infectious Events Requiring Hospitalization

During a median follow-up of 24.7 months, 116 infectious events required hospitalization (12.9%). The types of infectious events were as follows: respiratory ($n = 47$), gastrointestinal ($n = 34$), cystic infection ($n = 4$), vascular access infection ($n = 3$), and others ($n = 28$). Infection-related hospitalization was significantly associated with testosterone levels by both unadjusted (HR: 2.82; 95% CI: 1.72–4.61; $P < 0.01$) and adjusted Cox proportional hazard models (HR: 2.12; 95% CI: 1.18–3.79; $P = 0.01$) (Table 2, Figure 1a). A consistent trend toward decreased risk for infectious events that required hospitalization was observed in patients with higher testosterone levels, even after multivariate adjustment.

Table 1. Patient characteristics

Characteristic	Lower tertile (< 9.05 nmol/l) $n = 302$	Middle tertile (9.05 – 13.7 nmol/l) $n = 299$	Higher tertile (> 13.7 nmol/l) $n = 301$	P value
Age (yr)	65.4 ± 11.6	62.7 ± 12.4	61.8 ± 11.4	< 0.01
BMI (kg/m^2)	22.9 ± 4.6	22.8 ± 3.4	21.6 ± 3.4	< 0.01
Dialysis vintage (mo)	106 ± 87	99 ± 83	111 ± 96	0.21
Diabetes mellitus (%)	42.7	41.1	37.2	0.37
CVD (%)	21.5	18.9	19.1	0.67
SBP (mm Hg)	153 ± 21	152 ± 23	153 ± 21	0.82
DBP (mm Hg)	80 ± 14	79 ± 14	81 ± 14	0.26
Blood urea nitrogen (mg/dl)	66.2 ± 13.7	66.4 ± 13.7	63.1 ± 13.8	< 0.01
Creatinine (mg/dl)	11.7 ± 3.1	12.4 ± 3.1	12.3 ± 3.3	0.02
Sodium (mEq/l)	139 ± 3	139 ± 3	139 ± 3	0.24
Potassium (mEq/l)	5.1 ± 0.7	5 ± 0.7	4.9 ± 0.7	0.01
Uric acid (mg/dl)	7.9 ± 1.5	7.7 ± 1.3	7.6 ± 1.3	0.07
Albumin (g/dl)	3.7 ± 0.4	3.8 ± 0.4	3.8 ± 0.3	< 0.01
Total cholesterol (mg/dl)	155 ± 69	154 ± 32	151 ± 30	0.67
Triglyceride (mg/dl)	150 ± 134	131 ± 91	103 ± 56	< 0.01
Alkaline phosphatase (U/l)	250 ± 114	223 ± 91	224 ± 99	< 0.01
Calcium (mg/dl)	8.7 ± 0.7	8.9 ± 0.7	8.9 ± 0.6	< 0.01
Phosphate (mg/dl)	5.7 ± 1.5	5.5 ± 1.3	5.4 ± 1.3	0.04
Intact PTH (pg/ml)	152 (80–240)	139 (82–212)	140 (87–240)	0.35
C-reactive protein (mg/dl)	0.21 (0.07–0.53)	0.13 (0.06–0.4)	0.13 (0.06–0.33)	< 0.01
Hemoglobin (g/dl)	10.4 ± 1.0	10.6 ± 1.0	10.6 ± 1.0	0.01
Total testosterone (nmol/l)	6.28 (4.23–7.97)	11.02 (9.99–12.2)	17.06 (14.9–19.7)	< 0.01
SHBG (nmol/l)	18.5 (10.7–27.5)	19.7 (11.6–28.9)	27.9 (16.9–41.5)	< 0.01

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; PTH, parathyroid hormone; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin.

Data are expressed as mean \pm SD or median (interquartile range) for continuous variables and percentage for categorical variables.

Testosterone and All-Cause Mortality

One hundred twenty-three patients died during the study period (13.6%). The distribution of cause of death was as follows: CVD ($n = 59$), infections ($n = 22$), malignancy ($n = 21$), and others ($n = 21$). Lower total testosterone levels were significantly associated with all-cause mortality than higher levels according to unadjusted analysis (HR: 2.80; 95% CI: 1.73–4.59; $P < 0.01$) and Cox proportional hazard models (HR: 2.26; 95% CI: 1.21–4.23; $P = 0.01$) (Table 2, Figure 1b).

Testosterone and CVD Events

One hundred fifty-one CVD events occurred during the study period (16.7%). The distribution of CVD

Table 2. Cox proportional hazard models of low serum levels of testosterone with infectious events, all-cause mortality, and cardiovascular disease events in male hemodialysis patients

Variable	Baseline total testosterone		
	Lower tertile (< 9.05 nmol/l) n = 302	Middle tertile (9.05–13.7 nmol/l) n = 299	Higher tertile (>13.7 nmol/l) n = 301
Infectious events			
No. of events	55	35	26
Unadjusted HR (95% CI)	2.82 (1.72–4.61)	1.28 (0.73–2.23)	1.00 (reference)
P value	<0.01	0.39	–
Adjusted HR (95% CI)	2.12 (1.18–3.79)	1.27 (0.68–2.37)	1.00 (reference)
P value	0.01	0.46	–
All-cause mortality			
No. of events	61	36	26
Unadjusted HR (95% CI)	2.80 (1.73–4.59)	1.49 (0.87–2.56)	1.00 (reference)
P value	<0.01	0.42	–
Adjusted HR (95% CI)	2.26 (1.21–4.23)	1.69 (0.87–3.28)	1.00 (reference)
P value	0.01	0.12	–
CVD events			
No. of events	57	51	43
Unadjusted HR (95% CI)	1.49 (0.99–2.24)	1.38 (0.92–2.01)	1.00 (reference)
P value	0.06	0.12	–
Adjusted HR (95% CI)	1.19 (0.74–1.91)	1.35 (0.86–2.15)	1.00 (reference)
P value	0.47	0.19	–

CI, confidence interval; HR, hazard ratio.

Data were adjusted for age, body mass index, albumin, creatinine, C-reactive protein, sex hormone-binding globulin protein, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, diabetes, and history of cardiovascular disease (CVD).

events was as follows: sudden death (n = 37), acute coronary syndrome (n = 74), cerebral infarction (n = 27), and cerebral hemorrhage (n = 13). No statistically significant associations were observed between baseline testosterone levels and CVD events in both unadjusted (Figure 1c) and fully adjusted models (Table 2).

Infectious Events and Mortality in Older Patients

We divided patients' characteristics according to age (younger than 60 years, 60 to younger than 70 years, and 70 years or older) (Table 3). There were significant differences among the age groups in body mass index, length of dialysis, creatinine, and C-reactive protein. Although total testosterone decreased with age, sex hormone-binding globulin increased with age. There were no significant differences in the prevalence of diabetes mellitus, albumin, calcium, phosphate, and hemoglobin. The association between serum testosterone level and all-cause mortality varied with age. The P value for interaction between age younger than 60 years, 60 to younger than 70 years, and 70 years or older and serum testosterone level was 0.03. However, in stratified analysis, an association between adjusted risk of mortality and low serum testosterone levels was observed in older participants (70 years or older), but not in those younger than 60 years and those 60 to

younger than 70 years (HR: 2.71; 95% CI: 1.15–6.40; P = 0.02) (Table 4) (Figure 2a–c).

Interactions between serum testosterone levels and infectious events requiring hospitalization also varied with age (P = 0.01). In stratified analysis, an association between adjusted risk of infection-related hospitalization and low serum testosterone levels was observed in older participants 60 to younger than 70 years but not in those younger than 60 years (HR: 4.87; 95% CI: 1.74–13.6; P < 0.01) (Table 4) (Figure 2d–f). There were no significant associations between testosterone levels and CVD events, irrespective of age.

DISCUSSION

The results of this study showed that lower levels of serum testosterone were associated with infection-related hospitalization and all-cause mortality in male hemodialysis patients. CVD events were not significantly associated with testosterone levels. We confirmed the association between testosterone and infection-related hospitalization and all-cause mortality in older patients. To our knowledge, this study was the first to show an association between testosterone and infectious events that required hospitalization. In addition, our study was the largest study to investigate the association between serum testosterone levels and adverse clinical outcomes in dialysis patients.

A novel observation of our study was the association between testosterone levels and infection-related hospitalization. In addition, these results were found among older dialysis patients. Testosterone regulates the immune system to produce anti-infection and anti-inflammatory cytokines. Previous studies showed that testosterone regulates responses to immunological stimuli through androgen receptors in immune cells.^{13,14} Another study reported that exogenous treatment of young adult male mice with testosterone generally reduced the synthesis of proinflammatory cytokines (e.g., interferon gamma and tumor necrosis factor- α), increased anti-inflammatory cytokines (e.g., interleukin-10), and reduced helper T-cell type 1 activity.¹⁵ A recent study reported that reduced testosterone levels contributed to age-associated increases in influenza infection in experimental murine models, and treatment of these reduced testosterone levels improved survival rates.¹⁶ The association between infectious disease and declining testosterone levels was previously reported for influenza virus,¹⁷ HIV,¹⁸ and tapeworm infections.¹⁹ However, to our knowledge, no study has investigated whether administration of testosterone prevents infectious events.

In our study, the most frequent type of infection was respiratory infection (40.5%), such as pneumonia,

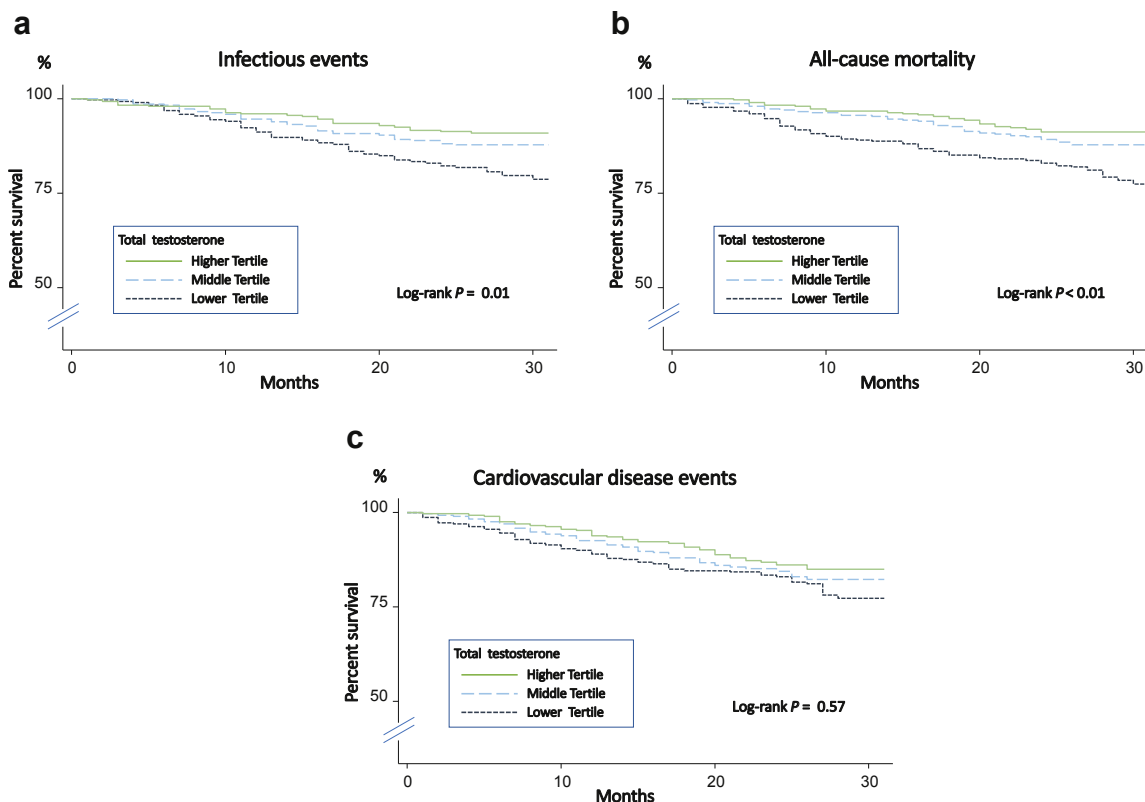


Figure 1. Kaplan-Meier survival analysis for (a) infectious events, (b) all-cause mortality, and (c) cardiovascular disease events.

sinusitis, lung abscess, and pleuritis. Previous studies also revealed a relationship between androgen deprivation therapy and community-acquired respiratory infections in patients with prostate cancer.^{20,21} Another study reported that surgical and pharmacological castration induced morphological changes in the lung, similar to those observed in human lung emphysema.²² In addition, testosterone levels were lower in severe chronic obstructive pulmonary disease, in patients with severe hypoxemia (partial pressure of oxygen in arterial blood <60 mm Hg), and in hypercapnic patients.²³ Another study also reported hypogonadism in aged male patients as a risk factor for respiratory tract disease.²⁴ Therefore, it is possible that testosterone is associated with the immune system of respiratory organs, and low levels of testosterone may increase the risk of respiratory infections.

There are several other possible mechanisms for the association between testosterone deficiency and infectious events. Testosterone is strongly associated with muscle mass and strength,²⁵ and sarcopenia, which is a state of decreased muscle mass, is a risk factor for mortality and infectious events.^{26,27} Low levels of plasma gelsolin, which is produced primarily by skeletal muscle and has antimicrobial actions through inactivation of bioactive lipid mediators, have been associated with increased mortality in hemodialysis

patients.²⁸ A previous study showed an association between androgen and gelsolin.²⁹ In addition, vitamin D has recently been considered a key factor in the expression of bactericidal proteins (e.g., cathelicidin) and immune defense.³⁰ Because previous clinical studies showed that serum testosterone levels and vitamin D levels are significantly associated,^{31–33} it is possible that testosterone influences the anti-infectious effect of vitamin D.

Several mechanisms have been proposed to explain the association between testosterone and mortality. First, a decrease in testosterone levels is associated with an increase in risk factors for CVD, such as hyperlipidemia,³⁴ metabolic syndrome,³⁵ obesity,³⁶ and insulin resistance.³⁷ Second, low levels of testosterone are associated with decreased muscle mass³⁸ and are considered a risk factor for frailty.³⁹ Testosterone plays an important role in muscle health by promoting synthesis of muscle cells and suppressing inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α , which activate muscle atrophy through the ubiquitin-proteasome system.^{25,40} Third, suppressive androgen receptors influence bone reabsorption,⁴¹ and testosterone deficiency has been reported as a risk factor for fracture events⁴² and falls.⁴³ In our study, associations between low levels of serum testosterone and infectious events and all-cause mortality were

Table 3. Patients' characteristics divided by age

Variable	Age <60 yr n = 339	Age 60 to <70 yr n = 312	Age ≥70 yr n = 280	P value
Age (yr)	50.7 ± 7.3	65.5 ± 3.0	76.5 ± 4.4	<0.01
BMI (kg/m ²)	24 ± 4.6	21.7 ± 3.0	21.3 ± 3.1	<0.01
Dialysis vintage (mo)	102 ± 86	121 ± 99	91 ± 76	<0.01
Diabetes mellitus (%)	38.9	43.9	39.1	0.35
CVD (%)	13.1	24	23.2	<0.01
SBP (mm Hg)	156 ± 21	152 ± 22	150 ± 22	0.63
DBP (mm Hg)	85 ± 15	80 ± 12	74 ± 12	<0.01
Blood urea nitrogen (mg/dl)	67.6 ± 13.2	65.7 ± 14.3	61.9 ± 13.4	0.36
Creatinine (mg/dl)	13.7 ± 3.3	11.9 ± 2.8	10.5 ± 2.4	<0.01
Sodium (mEq/l)	139 ± 3	139 ± 3	139 ± 3	0.51
Potassium (mEq/l)	5.0 ± 0.7	5.1 ± 0.7	4.9 ± 0.7	0.54
Uric acid (mg/dl)	8.0 ± 1.4	7.6 ± 1.3	7.3 ± 1.3	0.70
Albumin (g/dl)	3.9 ± 0.3	3.7 ± 0.3	3.6 ± 0.3	0.64
Total cholesterol (mg/dl)	157 ± 32	153 ± 32	156 ± 98	<0.01
Triglyceride (mg/dl)	146 ± 122	118 ± 80	105 ± 59	<0.01
Alkaline phosphatase (U/l)	221 ± 93	232 ± 105	243 ± 109	0.01
Calcium (mg/dl)	9.0 ± 0.7	8.8 ± 0.6	8.7 ± 0.7	0.35
Phosphate (mg/dl)	5.8 ± 1.4	5.5 ± 1.4	5.3 ± 1.3	0.34
Intact PTH (pg/ml)	151 (93–264)	150 (87–222)	122 (73–207)	<0.01
C-reactive protein (mg/dl)	0.13 (0.05–0.34)	0.15 (0.07–0.43)	0.19 (0.07–0.54)	<0.01
Hemoglobin (g/dl)	10.7 ± 1.1	10.5 ± 1.1	10.4 ± 1.0	0.09
Total testosterone (nmol/l)	3.36 (2.42–4.59)	3.31 (2.32–4.38)	2.84 (1.94–3.96)	<0.01
SHBG (nmol/l)	18.3 (10.7–28.7)	23.5 (13.7–34.7)	24.6 (14.9–33.6)	0.01

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; PTH, parathyroid hormone; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin.

Data are expressed as mean ± SD or median (interquartile range) for continuous variables and percentage for categorical variables.

confirmed only in older patients (70 years or older). A previous study also reported that adverse outcomes of low testosterone levels were especially seen in older populations.¹² Thus, the effects of testosterone deficiency are particularly important in older patients who are more vulnerable to these effects.

Our results did not indicate a significant association between testosterone levels and CVD events. The prevalence of CVD events in Japanese dialysis patients was lower than that in Caucasian and African American patients.⁴⁴ Hence, it was possible that our sample size was not large enough to detect an effect of testosterone on CVD events. Conversely, it was also possible that lower testosterone levels are not a risk factor for CVD events in hemodialysis patients. In general, hyperlipidemia, metabolic syndrome, and obesity, all of which are influenced by testosterone, are risk factors for CVD events.⁴⁵ However, in patients on dialysis, these factors are related to a better prognosis, which is referred to as paradoxical epidemiology.^{46,47} Although some studies showed an association between testosterone deficiency

Table 4. Cox proportional hazard models of hospitalized infectious events and all-cause mortality by total testosterone and age

Variable	Baseline total testosterone		
	Lower tertile (< 9.05 nmol/l)	Middle tertile (9.05–13.7 nmol/l)	Higher tertile (> 13.7 nmol/l)
All-cause mortality			
Age <60 yr			
Adjusted HR (95% CI)	2.89 (0.81–10.3)	1.07 (0.25–4.59)	1.00 (reference)
P value	0.11	0.92	–
Age 60 to <70 yr			
Adjusted HR (95% CI)	2.54 (0.85–7.57)	2.26 (0.75–6.8)	1.00 (reference)
P value	0.09	0.15	–
Age ≥70 yr			
Adjusted HR (95% CI)	2.71 (1.15–6.40)	1.78 (0.67–4.67)	1.00 (reference)
P value	0.02	0.24	–
Infectious events			
Age <60 yr			
Adjusted HR (95% CI)	1.32 (0.44–3.93)	0.40 (0.98–1.66)	1.00 (reference)
P value	0.62	0.21	–
Age 60 to <70 yr			
Adjusted HR (95% CI)	4.87 (1.74–13.6)	3.81 (1.31–11.1)	1.00 (reference)
P value	< 0.01	0.01	–
Age ≥70 yr			
Adjusted HR (95% CI)	2.30 (0.95–5.57)	1.53 (0.60–3.91)	1.00 (reference)
P value	0.07	0.37	–

CI, confidence interval; HR, hazard ratio.

Data were adjusted for age, body mass index, albumin, creatinine, C-reactive protein, sex hormone-binding globulin protein, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, diabetes, and history of cardiovascular disease.

and CVD events among hemodialysis patients,^{4,5} another study did not find any association.⁷ This suggests that the association between testosterone and CVD events in hemodialysis patients may be weaker than that in the general population.

There were several limitations associated with our study. First, because this study was an observational study, we could not confirm a causal relationship between testosterone levels and the primary and secondary study outcomes. Second, we did not investigate clinical signs of hypogonadism, such as decreased libido, erectile dysfunction, and depression. Third, we only measured testosterone levels at baseline. However, a previous general population study reported that a single measurement of testosterone reflected mean annual testosterone levels.⁴⁸ Fourth, we did not have information about vascular access. The use of a central venous catheter is a risk factor for infectious events.⁴⁹ However, because arteriovenous fistulas are the main type of vascular access for hemodialysis in Japan (~90% of all cases),⁵⁰ the influence of vascular access on infectious events might have been relatively small in this study. Because only 3 patients in this study developed vascular access infections, the types of vascular access might not influence the overall results.

In conclusion, our study showed that testosterone levels were associated with infectious events

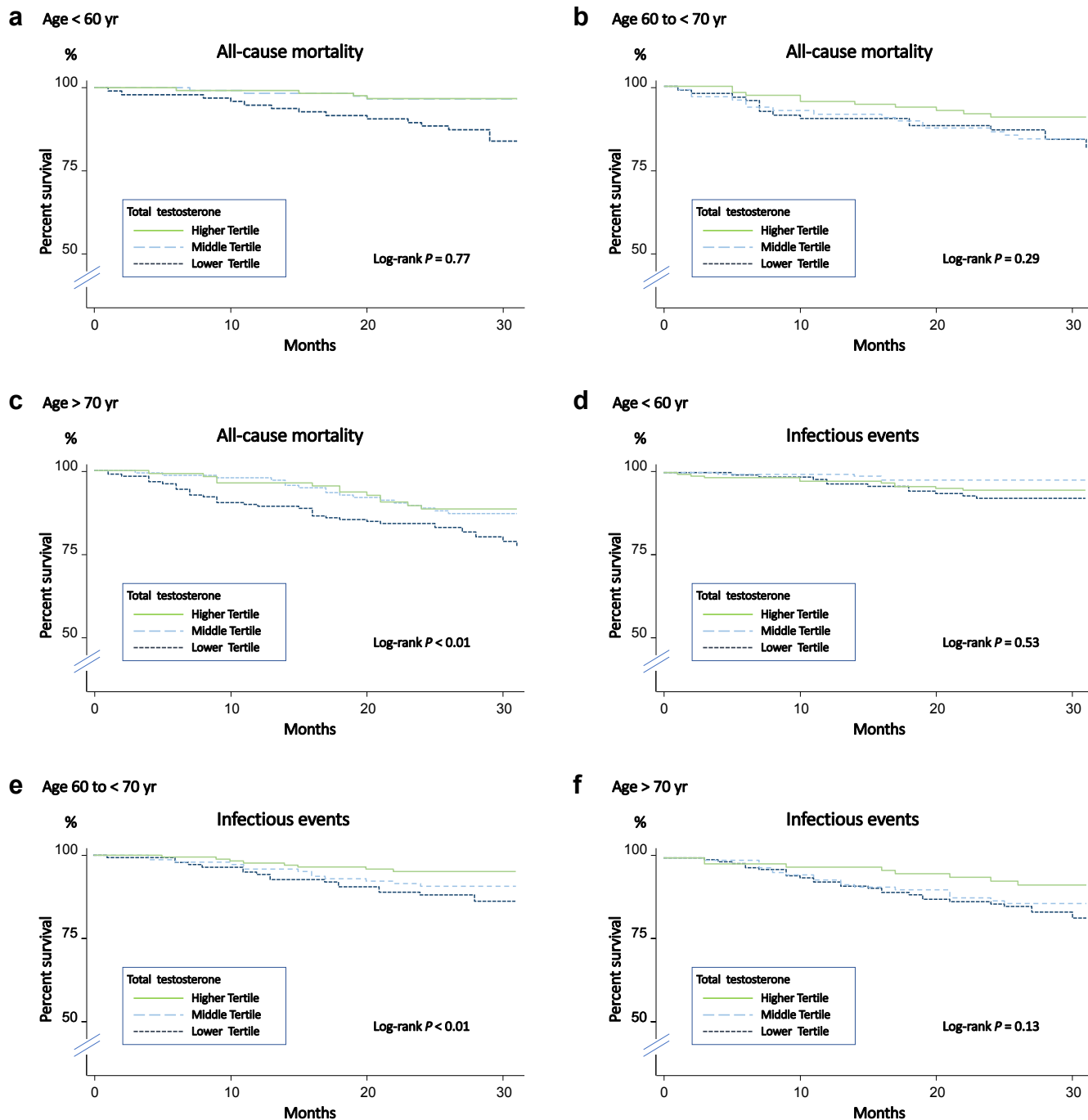


Figure 2. Kaplan-Meier survival analysis for infectious events and all-cause mortality divided by age. All-cause mortality: (a) age younger than 60 years, (b) age 60 to younger than 70 years, and (c) age older than 70 years. Infectious events: (d) age younger than 60 years, (e) age 60 to younger than 70 years, and (f) age older than 70 years.

and all-cause mortality in male hemodialysis patients. However, the underlying mechanisms remain to be explored. Future large-scale prospective and interventional studies are required to clarify the need for testosterone replacement in dialysis patients.

DISCLOSURE

All the authors declared no competing interests.

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