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Serum Testosterone Levels and Mortality in Men With CKD Stages 3–4

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Abstract

Background—Hypogonadism in men (total testosterone level < 350 ng/dL) is associated with higher risk of cardiovascular disease and mortality in men on dialysis. We evaluated the association of hypogonadism with all-cause mortality in men with non–dialysis-dependent CKD.

Study Design—Retrospective, cohort study.

Setting & Participants—2419 men with CKD stages 3–4 (estimated glomerular filtration rate [eGFR], 15–59 mL/min/1.73 m^2) who had total testosterone measured for-cause between January 1, 2005 and October 31, 2011 at a tertiary care center in Cleveland, Ohio.

Predictors—Total testosterone measured using an immunoassay measurement in 3 forms: a) categorized as low or testosterone replacement therapy versus normal, b) continuous log testosterone, and c) quintiles (100–226, 227–305, 306–392, 393–511, 512–3153 ng/dL).

Outcomes—Factors associated with low total testosterone, and association between low total testosterone and all-cause mortality were evaluated using logistic regression, Cox proportional hazard models, and Kaplan-Meier survival curves.

Results—Hypogonadism was found in 1288/2419 (53%) of men. In a multivariable logistic regression analysis, African American ethnicity and higher eGFR were associated with lower odds

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Supplementary Material

Table S1: Characteristics of patients with and without testosterone measurement.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Descriptive Text for Online Delivery of Supplementary Material

Supplementary Table S1 (PDF)

Characteristics of patients with and without testosterone measurement.

of having hypogonadism. Diabetes and higher body mass index were associated with higher odds of having hypogonadism. 357/2419 (15%) patients died during a median follow up of 2.3 years. In the multivariate Cox model, testosterone <350 ng/dL or testosterone replacement therapy were not associated with mortality. In a multivariable model also adjusted for testosterone supplementation, higher log testosterone was associated with significantly lower mortality (HR per 1 log unit, 0.70; 95% CI, 0.55–0.89). When compared to the highest quintile, the second lowest quintile of testosterone was associated with higher mortality (HR, 1.53; 95% CI, 1.09–2.16).

Limitations—Single center study, timing of testosterone testing, lack of adjustment for proteinuria, and sampling bias.

Conclusions—Low total testosterone may be associated with higher mortality in men with CKD stages 3–4 but more studies are needed.

Index words

hypogonadism; low testosterone; chronic kidney disease (CKD); mortality risk; testosterone replacement therapy (TRT); CKD registry

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Diagnosis of low testosterone (“hypogonadism”) and the indications, risks and benefits of testosterone replacement therapy (TRT) are controversial. While the greatest focus has been on men with sexually related symptoms such as low libido and erectile dysfunction (ED)[1], there are clear associations between hypogonadism and systemic conditions such as HIV/AIDS, type II diabetes mellitus, metabolic syndrome, and osteoporosis and chronic use of steroids or opioids[2–4]. Some of these associations may be coincidental while others may have direct cause-and-effect relationships in either direction. Several studies have shown a high incidence of hypogonadism in male dialysis patients.

In addition, low total testosterone levels have been associated with higher all-cause mortality in these men[5–8]. A study including 1822 men found that men with chronic kidney disease (CKD) and low total testosterone had significantly increased all-cause mortality[9]. Cigarran et al[10] reported lower muscle mass in those with low testosterone levels but did not evaluate mortality. Causality has not been shown in prior studies, but they are consistent in their finding of a strong association between low total testosterone and death in this cohort. The scope of the problem in men with non–dialysis-dependent CKD is less studied.

The most important issue is whether total testosterone represents a therapeutic target for early intervention in men with CKD stages 3–4, and whether there is a window of opportunity for affecting outcomes. Thus, the objective of our study was to investigate the association between total testosterone and all-cause mortality in men with CKD stages 3–4.

METHODS

Study Cohort

We extracted data from our electronic health record–based CKD registry from a tertiary care center in Cleveland, Ohio, which has been developed and validated at our institution[7]. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[39A] statement guidelines in conducting analyses. Females were excluded. Men

with the following inclusion criteria starting January 1, 2005 and ending October 31, 2011 were selected: (1) men with two eGFR values < 60 mL/min/1.73m^2 (using the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation[39B]) more than 90 days apart, and (2) men with measurement of outpatient total testosterone level. Men with eGFR < 15 mL/min/1.73m^2, receiving renal replacement therapy, and with total testosterone < 100 ng/dL were excluded (group we excluded the last group because there was high likelihood that these men were on androgen ablation therapy for advanced prostate cancer). We also excluded men who had improved kidney function with eGFR >60 mL/min/1.73m^2 at the time of first testosterone measurement. In the current study inception time was the start of time for survival analysis which corresponded to second eGFR <60 mL/min/1.73m^2 or first testosterone value, whichever was last. Information in the registry includes demographics, laboratory data, eGFR, and comorbidities. ICD-9 codes for comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, and hyperlipidemia have been validated using prespecified criteria. Our CKD registry has been linked with the Social Security Death Index where information regarding deaths was gathered.

Definitions and Outcome Measures

Exposure of Interest

Kidney function: Men with CKD stages 3–4 qualified for the study. Creatinine was measured using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, www.roche.com). We verified that patients were not on dialysis by merging our data with data from the US Renal Data System. However, those data were only available until September 15, 2009, and not available from September 15, 2009 to October 31, 2011, so we excluded patients with second or study inception (see below) eGFR < 15 mL/min/1.73m^2 to avoid including patients with the highest risk of being on dialysis without our knowledge.

Total testosterone: Total testosterone was measured using Siemens ADVIA Centaur CP immunoassay system (Siemens Healthcare Diagnostics, www.usa.healthcare.siemens.com). Only outpatient laboratory values between January 1, 2005 and October 31, 2011 and prior to end-stage renal disease were considered for analysis. For uniformity, we only used total testosterone results from assays with reference values of 220-1000 ng/dL. Greater than 90% of our cohort had testing within this reference range. Since we lacked the time of specimen collection, we selected a random sample of 40 patients and all their total testosterone results for chart review to ensure that most values were obtained in the morning before 12:00 PM (testosterone should be measured in the morning for the most accurate values, as it declines as the day passes). Overall, 54% of test results were collected between 7:00 AM and noon. We defined low testosterone as any value <350 ng/dL[11–13] or presence of testosterone supplementation. Testosterone was only measured in patients with a clinical indication; however, it is unknown whether testing was done due to presence of symptoms or another cause. Possible symptoms that may prompt testosterone testing include decreased libido, erectile dysfunction, generalized fatigue, weakness, and others. Information regarding testosterone supplements was extracted from our electronic medical record and included the following supplements: testosterone patch/gel/intramuscular/buccal/implanted pellet, oral methyltestosterone, fluoxymesterone, intramuscular nandrolone decanoate or nandrolone

phenpropionate, clomiphene, anastrozole, and stanozolol. Forty random charts were reviewed to confirm the use of testosterone supplementation.

Outcome of Interest

Mortality: The primary endpoint was all-cause mortality, which was obtained from our electronic medical record and by linking our registry with the Social Security Death Index. Mortality data up to October 31, 2011 were obtained.

Additional Covariates—Demographic information and laboratory results included age, race/ethnicity, BMI, and albumin level, which were extracted from electronic health records. Comorbidities, including diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, hyperlipidemia, malignancy, and smoking, were defined using prespecified criteria and validated previously[8]. The validation was done as of March 2010 by using ICD-9 codes.

Statistical Analysis

To evaluate the type of patients having testosterone measured in our CKD registry and their representativeness, we compared characteristics of patients with and without testosterone data using t-tests for continuous variables and Chi-square tests for categorical variables. We also compared characteristics of patients with low and normal testosterone levels using t-tests for continuous variables and Chi-square tests for categorical variables. We used a logistic regression analysis to evaluate whether age, ethnicity, eGFR, BMI group, smoking and comorbidities were associated with low testosterone level.

We used Kaplan-Meier plots and log-rank tests to evaluate the association between low testosterone level and survival. Cox proportional hazards models were used to evaluate whether low testosterone was associated with survival while adjusting for age, eGFR, race, BMI group, albumin and comorbidities (diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, hyperlipidemia, malignancy, and smoking). Albumin was missing in 8% of the patients, and, in order to include all patients in the analysis, we used mean value imputation along with a dummy indicator for missing data. We evaluated the relationship of total testosterone and allcause mortality in three separate models. The first model compared low (<350 ng/dL or presence of testosterone supplementation) versus normal total testosterone as a time-dependent variable. Patients with low testosterone or testosterone supplementation remained in the low group for the entire follow up whereas patients who had normal testosterone level at the start of the study but had a low value or started testosterone supplementation during follow up were switched to the low group at that time. The second survival model used continuous log testosterone, and the third model used testosterone quintiles while adjusting for the previously mentioned covariates plus testosterone supplementation. The continuous and quintile models used the lowest testosterone result before study inception. We chose to model testosterone in a binary manner because this is most clinically useful to primary care physicians as well as nephrologists, urologists, and endocrinologists. The other two models (continuous and categorical [quintiles]) were used as exploratory analyses to evaluate for underlying association. Binary[14] and categorical[5, 6] models have been used in the literature. In the

continuous and quintile models study, inception was the date of first testosterone measurement or date of second eGFR<60 mL/min/1.73m^2, whichever was last. In the binary model, inception was the first date of testosterone measurement or testosterone supplement, or date of second eGFR<60 mL/min/1.73m^2, whichever was last.

RESULTS

Patient Characteristics

There were 338,154 patients with 2 eGFR values 90 days apart between January 1, 2005 and October 31, 2011. Then 279,819 patients were excluded because their second eGFR value was either <15 mL/min/1.73m^2 or >60 mL/min/1.73m^2. There were 58,335 patients left who had two eGFR values between 15–59 mL/min/1.73 m^2 at least 90 days apart, but 31,943 were female and thus excluded. Of the remaining 26,392 male patients in our registry during the study period, 23,973 were excluded as follows: 23,281, lack of testosterone measurement; 466, testosterone <100 ng/dL; 12, eGFR value at inception <15 mL/min/1.73m^2; and 214, eGFR value at inception >60 mL/min/1.73m^2.

Therefore, 2,419 patients met inclusion criteria for the current study (Figure 1). Mean ± standard deviation age of patients included in the study was 67.3 ±11.3 (range, 22–95) years, eGFR at study inception was 49.1 ± 9.5 (range, 15.3–59.95) mL/min/1.73m^2, and BMI was 29.4 ± 5.4 (range, 14.4–64.3) kg/m^2. 11% were African American. In this cohort whose testosterone was measured for clinical indications, 1288 of 2419 (53%) men had low total testosterone levels or were receiving testosterone medication. An additional 97 patients who had a normal testosterone at study inception had a low value during follow-up or started to receive testosterone medication. Low total testosterone was found in approximately half the men in each decade of life from 20–90 years of age. At study inception, 301 patients had a prescription for testosterone medication. By the end of the study, 447 patients had a prescription for testosterone medication.

Table S1 (provided as online supplementary material) shows the comparison of clinical characteristics for patients with versus without testosterone measurement. Patients without total testosterone measurement were older, had lower eGFR, lower BMI, and had less diabetes, hypertension, congestive heart failure, and hyperlipidemia. Table 1 compares patients with low total testosterone and normal total testosterone. Patients with low versus normal total testosterone were significantly different in their eGFR, CKD stage, BMI, diabetes and cerebrovascular disease.

Predictors of Low Testosterone

In a multivariable logistic regression analysis, African American ethnicity and higher eGFR were associated with lower odds of having low total testosterone. Diabetes mellitus and higher BMI were associated with significantly higher odds of having lower total testosterone (Table 2).

Associations With Death

There were 357 of 2419 (14.8%) patients who died during a median follow-up of 2.3 (range, 0.003–6.5) years. Figure 2 shows a Kaplan-Meier survival curve of men with normal testosterone level compared with those having low testosterone or testosterone supplementation. The two groups did not have significantly different survival. In a multivariable Cox model adjusted for age, eGFR, BMI, comorbidities, and albumin, time-dependent low testosterone (<350 ng/dL or presence of testosterone supplementation) was not significantly associated with mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.93–1.64). In a model adjusted for the previously mentioned variables plus testosterone medication, higher log testosterone was associated with significantly lower mortality (HR per 1 log unit, 0.70; 95% CI, 0.55–0.89). In the quintile model, the two lowest quintiles of total testosterone (100–226 and 227–305 ng/dL) were associated with higher mortality when compared to the highest quintile (512–3153 ng/dL [the reference range]), but the association for the lowest quintile did not reach statistical significance (Table 3). When using a Bonferroni correction to adjust for the 3 ways we evaluated testosterone (P=0.05/3=0.017), the log testosterone analysis (P=0.003) and the comparison between the second lowest and the highest quintiles (P=0.01) were the only results suggesting a significant association between testosterone level and mortality.

DISCUSSION

The popularity of testosterone replacement therapy is rapidly growing, with huge increases in utilization and costs over the past 10 years[15]. As a panacea for erectile dysfunction, general malaise and “lost youth”, testosterone is almost certainly being overprescribed in ways that do not follow best practice guidelines. On the other hand, men with serious systemic health conditions often associated with low testosterone and its effects are seldom screened and treated. In addition, early evidence suggests an association between low testosterone and mortality in some patient populations. The objective of this study was to investigate whether low total testosterone was associated with increased all-cause mortality in men with kidney disease who were not receiving dialysis. We found that higher testosterone level may be associated with significantly lower mortality when examined as a continuous variable or comparing second lowest quintile to highest quintile [the reference range], but not when using a cutoff of <350 ng/dL.

Studies investigating testosterone levels in men with non–dialysis-dependent CKD are limited. Previous studies have been done mainly in the hemodialysis population, and have found that low testosterone is associated with increased cardiovascular disease and all-cause mortality[7]. One study of 239 men assessed the association of testosterone level and cardiovascular disease, and found that an increase of 1 nmol/L (or 28.8 ng/dL) decreased the likelihood of cardiovascular event by 22%[16]. A recent study of 126 dialysis-dependent males with total testosterone measured prospectively and followed up for a mean of 41 months found that the lowest tertile of total testosterone (≤ 233 ng/dL) was associated with significantly increased all-cause mortality (HR, 2.03; 95% CI, 1.24–3.31) as well as death due to cardiovascular disease (HR, 3.19; 95% CI, 1.49–6.83)[5]. Another study of 111 hemodialysis-dependent males had similar findings[6]. In this study, 54 men with low total

testosterone (< 369 ng/dL [12.8 nmol/L]) were compared to 57 men with normal total testosterone. There were 49 deaths during a median follow-up of 37 months. Low total testosterone was associated with increased cardiovascular disease and all-cause mortality (HRs of 3.14 [95% CI, 1.21–8.16] and 3.09 [95% CI, 1.53–6.25], respectively). This study also found that men with total testosterone below 231 ng/dL [8 nmol/L] were at higher risk of cardiovascular disease and all-cause mortality, and the lowest tertile of total testosterone (<150 ng/dL [5.2 nmol/L]) had the highest risk.

These studies reflect a strong association between total testosterone level, cardiovascular disease, and all-cause mortality in men with CKD. The risk for cardiovascular disease and/or death seems to increase for decreasing levels of total testosterone. The evidence is stronger for dialysis-dependent men than non–dialysis-dependent men; however, the study by Yilmaz et al[16] and our study point to a similarly strong association between testosterone and death in men who are not yet on dialysis.

Some of the potential mechanisms that may be responsible for the association between low testosterone and mortality include the effect on the cardiovascular system, and cognitive function, and other less well studied phenomena. Several studies have investigated the pathophysiological effects of testosterone on the cardiovascular system that may be contributing to decreased overall survival. Testosterone has been associated with heart failure, and a double-blind randomized controlled trial showed that TRT increased exercise capacity and symptoms in men with moderately severe heart failure[17]. Another randomized controlled trial showed that TRT improved exercise capacity, muscle strength, and insulin resistance in men with moderately severe chronic heart failure[18]. A recent meta-analysis supported these findings[19]. These effects have been linked to a vasodilatory property of testosterone[20] resulting in increase in cardiac output and decrease in systemic vascular resistance[21]. Similarly, greater endothelial dysfunction was seen in castrated rats in one study, and administration of testosterone resulted in lower apoptosis, fibrosis, and angiotensin II receptor expression[22]. Several studies have shown a strong association between depression, cognitive function and mortality in CKD patients[23], and testosterone has been known to be associated with depression[24]

In our study, there was an association of increased BMI and diabetes mellitus with lower total testosterone. This association has been seen in the other studies of men with CKD[16] as well as in men with hypogonadism without CKD[25, 26]. In a study of 1059 men, total testosterone decreased with increasing quartiles of BMI (<25, 25–29.9, 30–34.9, and ≥35 kg/m^2). The cause is still unclear, but sex hormone binding globulin has been suggested[26]. Similarly, diabetes mellitus has been shown to be associated with low testosterone in the normal population. A study of 1413 men showed that the lowest tertile of free testosterone was highly associated with diabetes mellitus (HR, 4.12; 95% CI, 1.25–13.55) after adjusting for age, ethnicity, and BMI[27]. Alterations in glucose metabolism and insulin resistance have been discussed as possible mechanisms[27].

Our study also found that higher eGFR was associated with higher total testosterone. This is in agreement with another study with a similar finding[16]. Progression to more severe CKD

stages is well known to be associated with worse cardiovascular and allcause mortality[28]. However, in our study, greater all-cause mortality was found even after adjusting for eGFR.

African American ethnicity was associated with improved total testosterone level in our study. Previous studies assessing the relationship between ethnicity and total testosterone levels provided conflicting results. In a study of 1475 community-dwelling men in Boston, equal proportions of Caucasian, Hispanic, and African-American men were interviewed and had blood samples collected for total and free testosterone measurements[29]. The prevalence of symptomatic hypogonadism was 5.6%, and there was equal distribution among all three ethnic groups. A study of 1413 African-American, Caucasian, and Hispanic-American men found that total testosterone did not differ between African-American and Caucasian men, but was higher in Hispanic-American men[30]. Since these papers did not adjust for comorbidities and other confounding factors, it is difficult to discern the true relationship of ethnicity with total testosterone levels.

The benefits of testosterone replacement in men with CKD are severely understudied. One study found that testosterone replacement restored sexual function in 11% of men, with partial response in 70%, but the effects were not long lasting[31]. Hypogonadism has been shown to be associated with anemia and hyporesponsiveness to erythropoiesis-stimulating agents[32]. In a study of 84 patients, nandrolone decanoate, 200 mg, was given intramuscularly weekly for six months[33]. Hematocrit increased from 6.9 to 8.7 g/dL, with the greatest increase in patients older than 55 years. A follow-up study by the same group showed that the increase in hemoglobin was similar with erythropoietin as compared to nandrolone decanoate[34]. Another benefit of androgen therapy was seen in a randomized controlled trial that reported significant increase in lean body mass, functional status, and quality of life in dialysis patients treated with nandrolone decanoate[35]. Though these effects may not be causal, there is evidence of an association between androgen therapy and improvement in sexual function, anemia, muscle mass, and functional status. However, the effect of TRT on cardiovascular status and mortality are yet to be proven. An important finding in our study is that among men found to have low total testosterone, only 31.6% were ever on TRT. The low usage of therapy in this cohort may be due to the unproven benefit of TRT in CKD[36, 37].

Our study has several strengths. This is one of the few studies investigating the role of low total testosterone in men with CKD stages 3–4. Our registry is validated, and we were able to study a large cohort of patients. We adjusted for variety of comorbidities in addition to age, race, and eGFR.

The study is not without limitations. The study was done at a single tertiary care center, and may not be applicable in other clinical settings. We also restricted analysis to men with eGFR less than 60 ml/min/1.73m^2, and are unable to state whether these findings hold true in men with less severe stages of CKD. Additionally, though our data shows an association between low total testosterone and all-cause mortality, we cannot infer causality. Other limitations include not adjusting for inflammatory markers such as C-reactive protein as these data were not available for majority of our study population, for the time of total testosterone blood draw, or for other medications that may affect testosterone level. We

were unable to adjust for proteinuria since majority of study participants did not have proteinuria assessed around the time of serum testosterone measurements. It is quite possible that testosterone may be a marker of illness rather than on the pathogenetic pathway to mortality. One study showed that over half of all patients admitted to the hospital had hypogonadism[38]. Another paper showed that testosterone was associated with metabolic syndrome in elderly men, but lost its association when adjusted for lipids, C-reactive protein, BMI and insulin level[39]. Further investigation of these factors may be important for future studies. Moreover, since not all men were tested, our results might not be generalizable to entire CKD population, and we are unable to comment on the prevalence of symptomatic hypogonadism in men with non–dialysis-dependent CKD. We found that only 11.8% of men in our registry were tested for clinical indications, and 54% of those men (6.4% of the entire cohort) were found to have low total testosterone. It is unknown whether these men were symptomatic or if total testosterone levels were checked for another reason. Despite selective testing, it is important to note that in our cohort a clinically significant number of men tested had hypogonadism.

In summary, this study shows that low total testosterone may be associated with all-cause mortality in men with CKD stages 3–4. The findings of this study should be confirmed in other cohorts. It remains to be seen whether replacing testosterone will improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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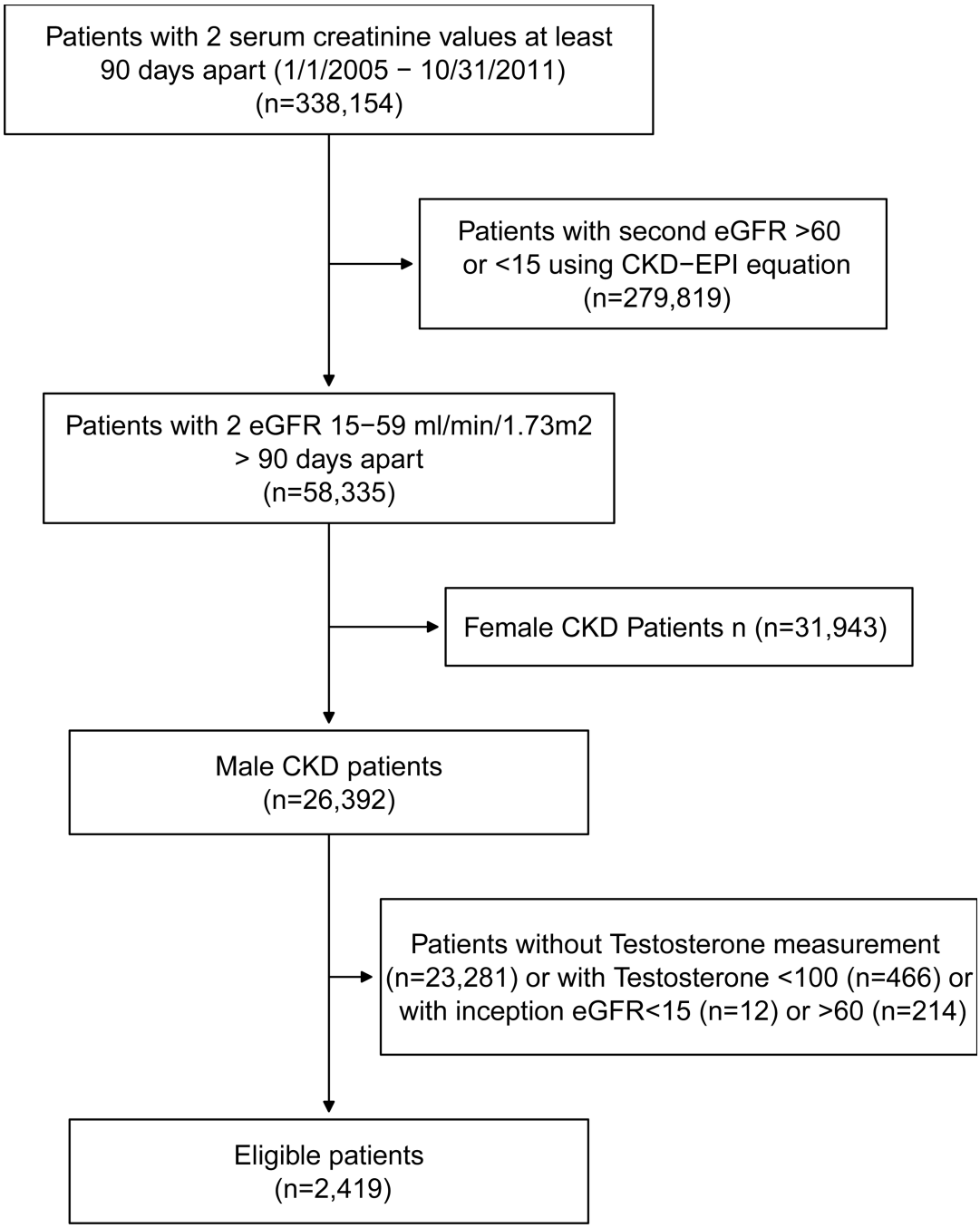

Figure 1.

Flowchart of patient selection for study inclusion

(CKD: chronic kidney disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation, eGFR: estimated glomerular filtration rate)

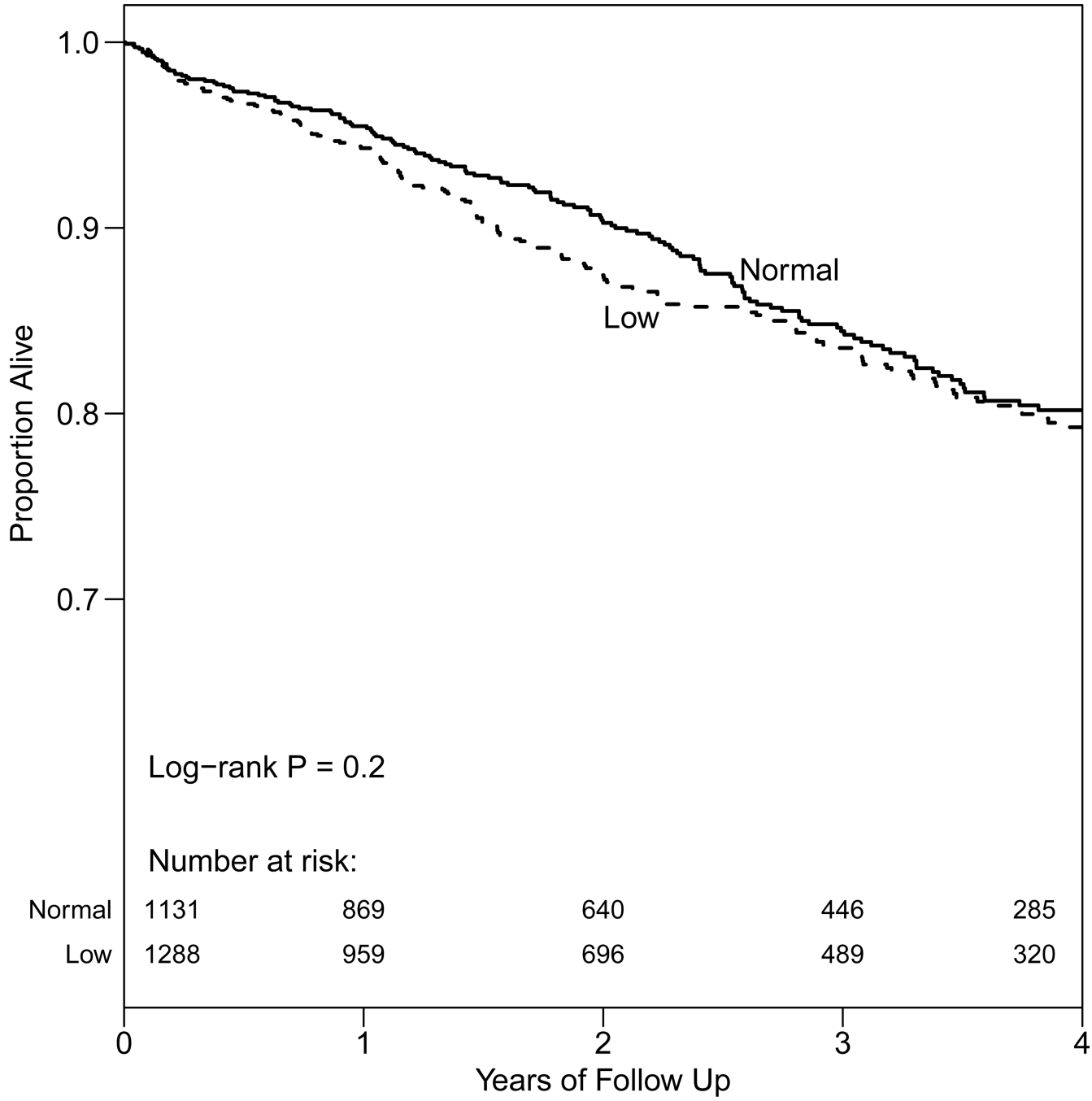

Figure 2.
Kaplan-Meier survival curve of men with chronic kidney disease stages 3–4 categorized as normal testosterone vs. low (testosterone <350 ng/dL or testosterone supplementation)

Table 1

Characteristics of patients with low and normal total testosterone levels

Factor	Low (n=1288)	Normal (n=1131)
Age (y)	67.5±11.3	67.0±11.3
African American	128(9.9)	140(12.4)
eGFR at inception (mL/min/1.73m^2)*	48.4±9.8	49.8±9.1
eGFR category*		
45–59 mL/min/1.73m^2	906(70.3)	870(76.9)
30–44 mL/min/1.73m^2	303(23.5)	208(18.4)
15–29 mL/min/1.73m^2	79(6.1)	53(4.7)
BMI (kg/m^2)*	30.3±5.7	28.4±5.0
BMI category*		
<18.5 kg/m^2	3(0.23)	7(0.62)
18.5–24.9 kg/m^2	189(14.7)	268(23.7)
25–29.9 kg/m^2	496(38.5)	501(44.3)
≥30 kg/m2	588(45.7)	343(30.3)
Missing	12(0.93)	12(1.1)
Smoking Status		
No	1144(88.8)	979(86.6)
Yes	81(6.3)	95(8.4)
Missing	63(4.9)	57(5.0)
Diabetes *	459(35.6)	285(25.2)
Hypertension	1206(93.6)	1037(91.7)
Cerebrovascular disease *	150(11.6)	102(9.0)
Malignancy	367(28.5)	306(27.1)
Coronary artery disease	390(30.3)	324(28.6)
Chronic heart failure	178(13.8)	152(13.4)
Hyperlipidemia	1102(85.6)	953(84.3)
Lowest testosterone before inception (ng/dL)	253.5[199.0–303.0]	478.0[405.0–562.0]
Albumin (g/dL)^	4.2±0.40	4.2±0.41

Note: Values for categorical variables are given as number (percentage) with chi-square test; values for continuous variables are given as mean ± standard deviation with t-test or median [interquartile range] with Kruskal-Wallis test.

BMI: body mass index, eGFR, estimated glomerular filtration rate

^Albumin data missing for 207 (9%) patients

*Significantly different between patients with low and normal testosterone.

Table 2

Multivariable logistic regression of factors associated with low testosterone[a]

Factor	OR (95% CI)
Age, per 10-y increase	1.06 (0.98, 1.15)
African American	0.65 (0.50, 0.85)[b]
eGFR, per 5-ml/min/1.73 m^2 greater	0.92 (0.88, 0.96) [b]
Diabetes	1.47 (1.21, 1.78) [b]
Hypertension	1.07 (0.77, 1.49)
Cerebrovascular disease	1.32 (0.996, 1.74)
Malignancy	1.10 (0.91, 1.33)
Coronary artery disease	0.96 (0.79, 1.17)
Chronic heart failure	1.00 (0.77, 1.30)
Hyperlipidemia	0.89 (0.70, 1.14)
BMI	
<18.5 vs 18.5–24.9 kg/m^2	0.52 (0.13, 2.08)
25–29.9 vs 18.5–24.9 kg/m^2	1.41 (1.12, 1.77)[b]
≥30 vs 18.5–24.9 kg/m^2	2.40 (1.89, 3.06) [b]
Missing vs 18.5–24.9 kg/m^2	1.53 (0.66, 3.56)
Smoking	
Yes vs. no	0.77 (0.56, 1.06)
Missing vs. no	1.01 (0.68, 1.51)

eGFR: estimated glomerular filtration rate, BMI: body mass index; OR, odds ratio; CI, confidence interval.

[a] Model was also adjusted for year of inclusion in study

[b] Statistically significant.

Table 3

Cox proportional models of total testosterone vs. all-cause mortality

	Unadjusted	Adjusted for age, African American race, and eGFR	Multivariable adjusted model
Low(<350 mg/dL or medication) vs. normal	1.14 (0.92, 1.41)	1.10 (0.89, 1.36)	1.16 (0.93, 1.44)*
Continuous Log Testosterone	0.65 (0.52, 0.82)	0.71 (0.56, 0.89)	0.70 (0.55, 0.89)**
Quintiles of testosterone			
100–226 ng/dL	1.58 (1.13, 2.21)	1.36 (0.97, 1.91)	1.42 (0.995, 2.02) **
227–305 ng/dL	1.52 (1.09, 2.13)	1.43 (1.02, 2.00)	1.53 (1.09, 2.16) **
306–392 ng/dL	1.18 (0.84, 1.67)	1.17 (0.83, 1.65)	1.22 (0.86, 1.73) **
393–511 ng/dL	1.01 (0.71, 1.45)	0.93 (0.65, 1.33)	1.01 (0.70, 1.45) **
512–3153 ng/dL	1.00 (reference)	1.00 (reference)	1.00 (reference)

Note: Associations given as hazard ratio (95% confidence interval).

eGFR, estimated glomerular filtration rate

*Adjusted for age, African American race, eGFR, diabetes, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, hyperlipidemia, malignancy, body mass index category, smoking status and albumin

**Adjusted for age, African American race, eGFR, diabetes, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, hyperlipidemia, malignancy, body mass index category, smoking status, albumin and testosterone medication