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Low serum testosterone levels and the incidence of chronic kidney disease among male adults: A prospective population-based study

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Abstract

Background: Despite existing evidence regarding the role of testosterone as a pro- tective factor for the kidney function in male adults, there are conflicting and in- conclusive results on the influence of testosterone deficiency on developing chronic kidney disease (CKD).

Objective: This study aimed to investigate the incidence and hazard ratio of CKD among male adults with low testosterone levels compared to controls with normal testosterone levels.

Materials and Methods: During a 15-year follow-up study, a total of 1277 eligible male adults aged 20-80 year consisting of 605 males with low testosterone levels (< 350 ng/dL) and 672 controls with normal levels participating in the Tehran Lipid and Glucose Study were recruited. Cox's proportional hazards models were applied to estimate hazard ratios of CKD between the groups after adjusting for confounders. **Results:** The total cumulative incidence rate of CKD at the median follow-up time of approximately 11.2 years was 21/1000 (95% CI: 18/1000, 25/1000) and 18/1000 (95% CI: 16/1000, 22/1000) in the low and normal testosterone groups, respectively (P = .2). The multivariate Cox model adjusted for age, body mass index, dyslipidemia, hypertension, diabetes, and smoking showed that HR of developing CKD in the male adults with low testosterone levels was significantly higher than those with normal levels (HR = 1.38; 95% CI: 1.05, 1.80).

Discussion and conclusion: This study shows a higher hazard ratio of CKD progres- sion in male adults with hypogonadism compared to those with normal levels in their later life. Therefore, timely diagnosis and treatment of kidney diseases in hypogo- nadal men can prevent the morbidity and mortality from CKD.

Key words: Chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR), testosterone

INTRODUCTION

Chronic kidney disease (CKD), a serious public health disorder, is characterized by the progressive impairment of glomerular function,[1] which affects over 10% of the general population.[2] This systemic disorder is often associated with an increased risk of cardiovascular events and hospitalization.[3,4]

Although the pathophysiology of CKD is yet unknown, some major risk factors of this disease are diabetes mellitus (T2DM), obesity, hypertension, older age, and smoking.[5] In addition, previ- ous study has been suggested that a disturbance in the sex steroid hormone secretion, in particular, testosterone insufficiency, has an important role in the progression of CKD in male adults.[6,7] There is evidence demonstrating that impaired gonadal function (hypogo- nadism) and sexual dysfunction are common findings in uremic men and those with CKD.[8] Indeed, the influence of sex steroid hormones on the progression of CKD is complicated by inverse causation. Accordingly, men with CKD experience disturbances in their sex steroid hormone concentrations.[7] Earlier researches demonstrated that disturbances in the hypothalamus-pituitary-gonadal axis are preva- lent in men with CKD.[5,9] A large case-control study on over 10,000 men with prostate cancer showed that androgen suppression therapy increased the risk of acute kidney injury.[10] Another study conducted by Shoskes et al [11] revealed that low testosterone concen- trations were associated with the increased risk of graft loss in male kidney transplant recipients.[11] The mechanism responsible for the protection of kidneys by testosterone is not completely understood, but it can be attributed to the induction of vasodilation in renal vessels, enhancement of the production of nitric oxide, attenuation of inflammation, and reduction of ischemia mediators, that is, vascular endothelial growth factor (VEGF).[12,13] Some studies have revealed a strong reverse relationship between the testosterone level and the surrogates of inflammation in different CKD populations.[6,14]

Testosterone deficiency has been suggested as a novel risk factor to induce uremic condition in men.[6] Previous studies reported that approximately 50%-70% of men with severe CKD have hypogonadism based on the low levels of total and free testosterone.[15,16] A re- cent study suggested that the early diagnosis of both hypogonadism and related comorbidities may be helpful for the patients in terms of changing lifestyle and appropriate treatment.[17]

Despite existing strong evidence demonstrating the role of testosterone as a protective hormone on the kidney function in men, there are controversies on the influence of decreased levels of endogenous testosterone on developing CKD in men.[4,7,18] This long term follow-up study aimed to investigate the incidence and hazard ratio of CKD among male adults with low concentrations of testosterone compared to controls with normal concentrations.

MATERIAL S AND METHODS

Ethics considerations

This study was approved by the Medical Ethics Committee of the Research Institute for Endocrine Sciences (Code: IR.SBMU. ENDOCRINE.REC.1398.028). All subjects signed a written informed consent.

Subjects

In this ongoing population-based prospective cohort with 15 years of follow-up, study population were recruited from the Tehran Lipid and Glucose Study (TLGS), which was initiated since 1998 to assess the prevalence and risk factors of non-communicable diseases. In the TLGS, a total of 15 005 subjects aged ≥3 years were followed within a three-year interval to obtain data on demographic, anthropometric, reproductive, hormonal, and metabolic characteristics, general physical examinations, and laboratory measurements. Details of the TLGS have been reported previously.[19] All subjects were visited at the outpatient endocrinology clinic of the TLGS between February 1999 and August 2001. The TLGS has five phases, including phase 1(baseline): 1999-2001; phase 2: 2002-2005; phase 3: 2005-2008; phase 4: 2008-2011; and phase 5: 2011-2014.

Figure 1 shows the study flow diagram. All male adults aged 20-80 years were assessed using eligibility criteria (n = 1462), and 678 male adults had low testosterone levels and 784 had normal testosterone levels. All subjects who were visited at the baseline of the study and completed at least one follow-up visit were included. None of the subjects had taken supplemental testosterone. The sub-jects with CKD at baseline (n = 158) and lost to follow-up (n = 27) were excluded. Finally, a total of 1277 men were recruited.

Measurements

At baseline and follow-up visits, the subjects were evaluated for clini-cal, and anthropometric, and biochemical parameters by a well-trainedinterviewer. Bodyweight was assessed with at the least clothes by a digital scale (Seca® 707, Seca GmbH) and rounded to the nearest 100grams. In the same way, height was assessed without shoes in the standing position and normal posture of shoulders by a tape measure.We calculated body mass index (BMI) based on the following formula:weight in kilograms (kg) divided by height squared (m^2). Waist circumference was assessed with an unstretched tape measure at the level ofthe umbilicus, without any pressure to the body surface. Hip circumference was assessed at the level of the anterior-superior iliac spine without any pressure to the body surface. We also assessed the systolic and diastolic blood pressure twice on the right arm in the seatedposture using a standard mercury sphygmomanometer after 15 minesof rest; then, the mean of these measurements was recorded. For this study, serum samples were taken after 12 h of overnight fasting between 7:00 and 9:00 AM; all analyses

were conductedat the TLGS laboratory on the same time of blood collection. We stored all sera at −80°C until use (testing). We measured fasting blood sugar (FBS) by an enzymatic colorimetric method using the glucose oxidase. Serum triglyceride (TG) concentrations were measured using glycerol phosphate. Total cholesterol (TC) was assayed using the enzymatic colorimetric method using cholesterol esterase and cholesterol oxidase. The level of high-density lipoprotein cho- lesterol (HDL-C) was assayed after precipitation of the apolipoprotein B (apo B)–containing lipoproteins using phosphotungstic acid. We used a modified Friedewald to estimate LDL-C. All metabolic parameters were assessed using related kits (Pars Azmon® Inc, Tehran, Iran) and a Selectra 2 autoanalyzer (Vital Scientific®, Spankeren, theNetherlands). The intra- and inter-assay coefficients of variations (CVs) were both 2.2% for glucose. For total and HDL cholesterol, intra- and inter-assay CVs were 0.5 and 2%, respectively. Intra- andinter-assay CVs were 0.6 and 1.6% for TG, respectively.

We assayed testosterone and SHBG levels using enzyme immunoassay (DRG, diagnostic®, GmbH, Germany) by the sunrise ELISA reader (Tecan Co®, Salzburg, Austria); the intra- and inter-assay CVswere 5.7, 8.4, and 9.6, 8.6% with the detection limit of 0.022 ng/ml and 0.1 ng/ml, respectively. We also calculated free testosterone index (FTI) based on the following formula: testosterone (nmol/L)/ SHBG (nmol/L) × 100.

Finally, we measured levels of serum creatinine (Cr) using the kinetic colorimetric Jaffe. The sensitivity of the assay was 0.2 mg/dl (range, 18-1330 µmol/L (0.2-15 mg/dl)). Reference intervals based on the manufacturer's recommendation were 53-97 µmol/L (0.6-1.1 mg/dL) in male adults. Intra-assay and in- ter-assay CVs were less than 3.1% in both baseline and follow-up visits. We carried out all biochemical assays through commercial kits (Pars Azmoon Inc ®, Tehran, Iran) by a Selectra 2 autoanalyzer (Vital Scientific®, Spankeren, the Netherlands). Assay perfor- mance was monitored after every 25 tests by lyophilized serum controls in normal and pathologic ranges, and all samples were analyzed when internal quality control met the standard accept- able criteria.[20,21]

Definitions

According to the recommendations of the International Society for the Study of the Aging Male (ISSAM)[22] and the International Society for Sexual Medicine (ISSM),[23] low testosterone was determined as concentrations of total testosterone <350 ng/dL, otherwise as to thenormal total testosterone.

Based on the Kidney Disease Outcome Quality Initiative (K/ DOQI) guidelines, CKD was defined as either kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for >3 months.[24] We estimated GFR based on the abbreviated prediction equation provided by the Modification of Diet in Renal Disease (MDRD) study as follows:

$$GFR = 186 \times SCr^{-1.154} \times Age^{-0.203}$$

In this equation, eGFR (estimated GFR) and serum creatinine (Scr) levels are expressed as mL/min per 1.73 m^2 and mg/dL. According to guidelines, CKD was considered an eGFR below than 60 mL/ min/1.73 m^2 happening at any time during the follow-ups.[25]

We also classified men based on their GFR; those with GFR ≥ 90 ml/min/1.73 m^2 were defined as normal or high GFR, 60-89as mildly decreased, 45-59 as mildly to moderately decreased, 30-44as moderately to severely decreased, 15-29 severely decreased, and <15 as kidney failure.[26]

Hypertension was diagnosed based on the JNC-VI criteria [27] in- cluding a mean SBP ≥ 140 mm Hg, mean DBP ≥ 90 mm Hg, or the current use of anti-hypertensive medicine.[28,29]

We considered type 2 diabetes mellitus as fasting blood sugar (FBS) ≥7 mmol/L (measured twice), 2-h post-challenge plasma glucose (PCPG) ≥11.1 mmol/L, or taking anti-diabetic drugs.[30]

Men participating in the study were classified based on the smoking status; smokers were defined as those who were cigarette smokers, if not as non-smokers.

Statistical methods

We investigated continuous variables for normality based onthe one-sample Kolmogorov-Smirnov test; they presented as mean ± standard deviation if they had a normal distribution, or median with inter-quartile range (IQ25-75) for variables with skewed distribution. Categorical variables were presented as percentages.All comparisons between the low and normal total testosterone concentration groups were carried out using Student's unpaired *t* test, Mann-Whitney U test, and chi-square test. Exact test method for two-way contingency table was used to get p-values comparing severity of CKD in testosterone categories (low vs. normal). We used the following formula to estimate the person-time incidence rate of CKD: the number of new events in the study time dividedby the sum of person-time (person * year) at risk. The Kaplan-Meierplots and log-rank tests were used to investigate the relationship of testosterone levels with time to CKD progression. We applied the multivariable Cox proportional hazards regression model to estimate the hazard ratio (HR) with a 95% confidence interval (CI) between the low and normal testosterone concentration groups, which was adjusted for age, BMI, dyslipidemia, hypertension, diabetes, and smoking. We tested the proportionality of the model as a whole and get a test of proportionality for each predictor using goodness-of-fit (GOF) tests. The follow-up time was drawn from the difference between the calculated mid-time date and the date at which the subjects entered the study. For the censored or lost to follow-up subjects, the survival time was the interval between the first andlast observation

dates.

We assessed the relationship between total testosterone andCKD using three separate models. The first model compared low (<350 ng/dL) vs. normal total testosterone levels as a grouping variable. The second survival model used continuous log testosterone, and the third model used testosterone quintiles adjusted for potential covariates. The testosterone was selected in a binary manner because it was more beneficial to clinicians.

Statistical analysis was performed using software package STATA(version 14; STATA Inc, College Station, TX, USA) with a significancelevel of $P < .05$ and the confidence interval (CI) of 95%.

RESULTS

During up to 15 years of follow-up, 1277 eligible subjects met inclusion criteria and were recruited (Figure 1). The median andinter-quartile ranges for follow-up years of the low and normal testosterone level groups were 11.0 (10.2-11.9) and 11.4 (10.4-12.4), respectively. At baseline, mean age and BMI were 42.0 ± 12.6 yearsand 25.3 ± 3.9 kg/m^2. Also, 12.6% and 68.8% of the subjects had ahistory of hypertension and dyslipidemia, respectively.

At baseline, 74 (5.8%) had a history of diabetes. Of these, 63 (85.1%) had normal testosterone and 11 (14.9%) had low testoster-one. At the end of follow-up, the number of diabetic men reached 122 with 88 subjects in normal testosterone and 34 subjects in low testosterone group. In addition, of these 122 diabetic patients, 43 men developed CKD. Out of these 43 subjects, 36 men were in nor- mal T category and 7 men were in low T category. The median and inter-quartile ranges for duration of developing CKD in diabeticswere 6.4 (4.1-11.9) years.

Median (IQR) of total testosterone, SHBG, and FTI was 3.7 (3.0-5.2), 31.0 (20.4-43.2), and 40.6 (25.9-63.9), respectively. In this prospective study whose total testosterone was assayed for clinical indications, 605 of 1277 (47.4%) men had low total testosterone levels. Table 1 illustrates the comparison of baseline features for male adults with low and normal total testosterone levels. There were significant differences in markers of SHBG, LDL, FTI, diabetes, and hypertension among men with low versus normal total testosterone levels.

According to classification system GRF in CKD, 109 men classified as normal and 1168 men as mildly decreased GFR category. However, at the end of follow-up with 1048 available data for GFR, there were 48, 794, 194,10, and 2 men in categories of normal, mildlydecreased, mildly to moderately decreased, moderately to severely decreased, and severely decreased, respectively. *P*-values obtained from exact test method for two-way contingency table showed no association between severity of CKD and testosterone levels (Table S1).

The total cumulative incidence rate of CKD at the median follow-up time of almost 11.2 years was 21/1000 (95% CI: 18/1000, 25/1000) and 18/1000 (95% CI: 16/1000, 22/1000) in the low and normal testosterone groups,

respectively ($P = .2$).

Of 1277 eligible men participating in the study, 293 (22.9%) developed CKD during the median follow-up time. The survival curves illustrated the time to the development of CKD for male adultswith low *vs.* normal testosterone levels. Based on log-rank *P*-value, the survival curves for men with low testosterone concentrations were significantly different from those of normal levels ($P = .045$) (Figure 2).

The multivariate Cox model adjusted for age, body mass index, dyslipidemia, hypertension, diabetes, and smoking showed that HR of developing CKD in males with low testosterone levels was significantly higher than those with normal levels (HR = 1.38; 95% CI: 1.05, 1.80). We included age in the multivariate Cox model as a time-de- pendent variable as the GOF test for the age variable was significant(*P*-value = 0.01).

Although in the model adjusted for the previously mentioned variables, the log testosterone concentration was not significantly related to CKD [HR = 0.82; 95% CI: 0.61, 1.10]; in the unadjusted model, every unit increase in the log testosterone level revealed thatthe HR of CKD decreased by 25% (HR = 0.75; 95% CI: 0.57, 0.98).

In the quintile model, the lowest quintile of total testosterone (66-288 ng/dl) was associated with higher HR of CKD progression comparison with the highest quintile (550-1500 ng/dl) (HR = 1.58; 95% CI: 1.04, 2.40). When using a Bonferroni correction to adjust for 3 ways, testosterone was evaluated ($P = .05/3 = 0.017$), and the comparison between the low (<350 ng/dl) and normal total testosterone analysis ($P = .016$) was the only result suggesting a significant relationship of the testosterone level with CKD (Table 2).

In addition, we considered interaction term between diabetesand testosterone groups in our Cox model, but the statistically significant was not observed.

DISCUSSION

Findings from earlier investigations suggest a protective effect of testosterone on the kidney function, although strong evidence onthe relationship between testosterone deficiency and progression of CKD was scarce. This long-term population-based follow-up study provides evidence on the incidence and hazard ratio of CKD in male adults with testosterone deficiency in comparison with those with normal testosterone levels.

Over an approximate median follow-up of 11 years, this study demonstrated that the hazard ratio of developing CKD in males with low endogenous testosterone concentrations was 1.26-fold (95% CI: 1.02, 1.60) higher than those with normal levels. Our findings were significant even after multiple adjustments for potential con- founders related to CKD including age, BMI, smoking, dyslipidemia, diabetes, and hypertension (HRadjusted: 1.38; 95% CI: 1.05, 1.80). This study found that the hazard ratio of progressing CKD was significantly higher in the lowest quintile of testosterone than the highest quintile (the reference range) (HR adjusted = 1.58; 95% CI: 1.04, 2.40).

The mechanism responsible for the protection of kidneys by testosterone is not completely understood, although it can be at- tributed to the induction of vasodilation in renal vessels, enhancing the production of nitric oxide, attenuation of inflammation, and the reduction of ischemia mediators, that is, VEGF.[12,13] There is a strong document demonstrating a strong inverse relationship between the testosterone level and surrogates of inflammation in various populations of CKD.[6,14] On the other hand, treatment of androgen deprivation can induce an increased risk of damage to the glomerulus through antagonizing testosterone. Some animal models have shown that testosterone repletion keeps from harm the kidney, whereas castration promotes renal dysfunction and injury that is independent of conversion to estradiol. Data from experimental investigations suggest that testosterone may protect against ischemia-reperfusion–induced acute kidney injury, possibly through the attenuation of inflammation and mediators of ischemia.[31] An in vitro research demonstrated that mesangial cells derived from male rats produced more fibronectin, TNF-a, and IL-b involved in inflammation and fibrosis, than cells derived from female rats.[32] In addition, some investigators reported that the exogenous administration of testosterone may induce the activation of the renin-angiotensin system (RAS), the production of endothelin, and the regulation of anti- or/ and proinflammatory cytokines involved in the pathogenesis of hypertension and kidney damage,[33,34] suggesting a potential contributing androgens in developing kidney impairment and supporting the hypothesis that the decrease in renal function in men occurs at a faster rate than in women.[9] Further clinical studies confirmed the role of inflammatory mechanisms in developing CKD caused by testosterone insufficiency. For example, a cross-sectional study by Yilmaz et al35 showed that advanced CKD is inversely associated with hypertension, endothelial disturbance, and the increased risk of cardiovascular events.[35] Another investigation by Carrero et al [36] on a cohort of 126 men undergoing hemodialysis showed that independent of age, serum creatinine, and sexual hormone–binding globulin (SHBG), testosterone levels were inversely and strongly related to the inflammatory markers IL-6 and CRP.36

Despite existing several investigations on testosterone deficiency and kidney diseases, no other prospective study is available on the influence of decreased levels of testosterone on progression of CKD in male adults. Observations from a cross-sectional study by Yi et al7 in the United States on 1400 adult men were in contrast with our results. They showed that the mean free testosterone concentration was higher in men with an eGFR < 60 mL/min/ 1.73m^2 than in men with a higher eGFR.[7] As those studies had a cross-section de- sign, reverse causation could not be ruled out. Similar to our findings, a recent cross-sectional study by Kurita et al[18] demonstrated that having low free testosterone levels were related to reduced eGFR in adult men after adjustment for potential confounders such as sociodemographic characteristics, comorbidities, and blood

pressure. A prospective follow-up study by Maric et al[37] demonstrated that developing diabetic nephropathy in male adults with type I diabetes was related to lower endogenous testosterone levels and increased circulating estradiol levels. These findings were in line with our findings and highlighted the role of steroid imbalance in the progressionof kidney diseases.

Hypogonadism in male adults with CKD may associate with a higher risk of cardiovascular events and mortality, particularly in those undergoing hemodialysis.[4] Haring et al[3] using a prospective population-based study with a median follow-up of 9 years found that men with CKD and low total testosterone significantly hadhigher all-cause mortality compared to those with normal levels (HR,1.42,95% CI, 1.09-1.84),[3] confirming the effect of testosterone deficiency on developing CKD. Also, a recent retrospective study by Khurana et al[4] on 2419 men with severe CKD showed that a higher total testosterone level was associated with lower mortality when it was examined as a continuous variable, but they did not observe anysignificant difference in the mortality and survival of patients when testosterone was classified as a qualitative variable (low *vs.* normal).However, it should be considered that these two cohort studies assessed all-cause mortality and hence could not infer causality. In this study, total testosterone was considered a preferred androgenic marker. Although theoretically, bioavailable testosterone is the most accurate parameter to identify testosterone deficiency, because a standard method to measure this parameter has not been established, total testosterone is the most widely accepted substitute parameter.[38,39] However, it should be noted that the use of total testosterone level for the diagnosis of hypogonadism in elder indi- viduals may result in under-diagnosis because SHBG increases with age and albumin decreases.[40]

Although testosterone levels in male adults decrease with aging (approximately 0.12 nmol/L per year),[41,42] it is progressive through- out life and there is no set point in women during menopause. In ad-dition, there is a variation in testosterone assays. For such reasons, no precise cutoff value is available for deficient endogenous testos-terone in male adults. However, in this study, based on the recom- mendations of the ISSAM[22] and the ISSM,[23] a cutoff value < 350 ng/dl was considered as a low testosterone level.

To the best of our knowledge, this is the first prospective study with a long-term follow-up duration evaluating the influence of testosterone deficiency on the progression of CKD in male adults. The strength of this study is its design as a population-based prospectivestudy with over a decade of follow-up and short-term intervals. In addition, the acceptable level of lost to follow-up, accurate measurements, and statistical analysis adjusted for age, body mass index, dyslipidemia, hypertension, diabetes, and smoking status at baselinecould help to reach more precise results.

However, this study has also some limitations, which should be considered to interpret the results. In the current study similar to most epidemiologic studies, CKD was defined based on a limited number of creatinine measurements and these measurements could not be repeated within 3 months to confirm a chronic reduction in GFR. In addition, testosterone levels were measured only once inthis study as at baseline, which can result in variability in hormone concentrations.[22] Finally, although we tried to run different models to control all major confounders for which data were available, possibly confounding factors such as physical activity could not be assessed because of limitations in data collection.

CONCLUSION

In this study, a higher hazard ratio of CKD progression was reportedin male adults with hypogonadism compared to those with normal levels in their later life. In addition, faster development of CKD was observed compared with those with normal testosterone levels. Our results suggest that the early diagnosis and managing subsequent kidney diseases in hypogonadal men can potentially prevent the morbidity and mortality from CKD.

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AUTHOR CONTRIBUTIONS

MA contributed to the study design, analyzing data, manuscript drafting, interpreting data, and critical discussion. FRT contributed to study design, execution, analyzing data, interpreting data, and critical discussion. M.R participated in the analyzing data and manuscript writing. SAS, SBG, and ZS participated in the interpreting data and criticaldiscussion. F.A participated in study design, execution, and critical discussion. All authors have read and approved the final manuscript.

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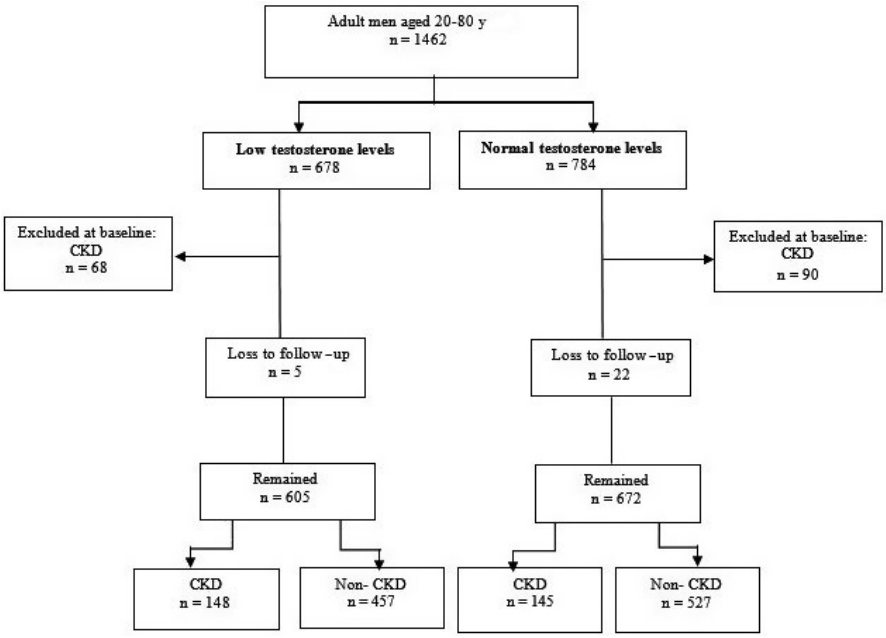
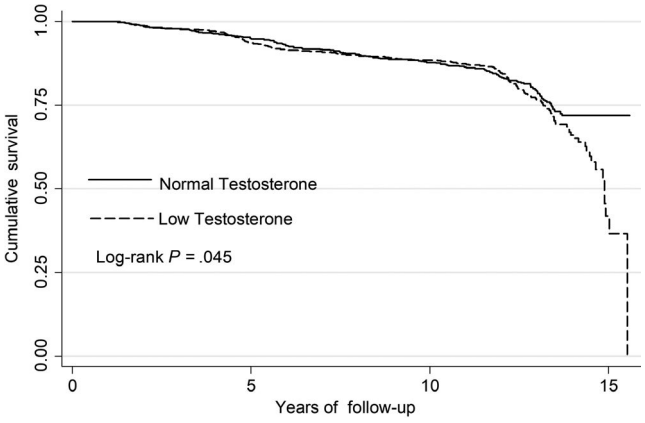
FIGURE 1 Flowchart of the study



FI G U R E 2 Kaplan-Meier plot indicates survival (time toCKD) curves for normal testosterone (≥350 ng/dl) vs. low (testosterone < 350 ng/dL)



TA B L E 1 Baseline characteristics ofthe subjects in the groups

Characteristics	Low testosterone (<350 ng/dl) N = 605	Normal testosterone (≥350 ng/dl) N = 672	*P*-value[d]
Age (year)[a]	42.1 ± 12.6	41.8 ± 12.6	.7
Follow-up time (year)[b]	11.0 (10.2-11.9)	11.4 (10.4-12.4)	<.001
Body mass index (kg/m^2)[a]	25.3 ± 3.6	25.3 ± 4.2	.9
Systolic blood pressure (mm/Hg)[a]	115.2 ± 14	118.6 ± 17.8	<.001
Diastolic blood pressure (mm/Hg)[a]	75.4 ± 9.5	77.1 ± 10.8	.002
Waist Circumference (cm)[a]	86.9 ± 9.7	86.7 ± 11.4	.7
Waist-hip ratio[a]	0.9 ± 0.1	0.9 ± 0.1	.2
Smoking history[c], n (%)	237 (39.2)	288 (42.9)	.1
Dyslipidemia[c], n (%)	412 (68.1)	467 (70.1)	.2
Sex hormone–binding globulin(nmol/L)[b]	30 (19.1-41.7)	33.7 (22.3-46.2)	.002
Free testosterone index[b]	34 (23.6-51.2)	56.3 (39.1-90.4)	<.001
Total cholesterol[a]	203.7 ± 39.7	200 ± 39.8	.1
High-density lipoprotein (mg/dl)[a]	39.5 ± 9.4	39.2 ± 9.6	.6
Low-density lipoprotein (mg/dl)[a]	132.2 ± 33.6	128 ± 34.7	.03
Triglyceride (mg/dl)[b]	140 (102-196.5)	146 (97-207)	.5

[a]Values are presented as mean ± SD.

[b]Presented as median (inter-quartile range).[c]Data shown as percentage.

[d]Significant differences (*P*-value < .05), analyzed using independent *t* test for superscripts [a], Mann-Whitney *U* test for superscripts[b], and Pearson's chi-square test for superscripts[c].

TABLE 2 Cox proportional models of total testosterone vs. CKD

	Unadjusted	Adjusted*
Low (<350 ng/dL) vs. nor-mal (≥350 ng/dl)	1.26 (1.02, 1.60)	1.38 (1.05, 1.80)
Continuous log testosterone	0.75 (0.57, 0.98)	0.82 (0.61, 1.10)
Quintiles of testosterone		
66-288	1.60 (1.12, 2.26)	1.58 (1.04, 2.40)
289-336	1.08 (0.74, 1.58)	1.20 (0.77, 1.85)
337-426	0.99 (0.68, 1.46)	1.14 (0.73, 1.77)
427-549	1.12 (0.77, 1.62)	1.07 (0.70, 1.66)
550-1500	1.00 (reference)	1.00 (reference)

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

*Adjusted for age, BMI, smoking history, diabetes, dyslipidemia,hypertension.