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Low Serum Testosterone Is Associated with Increased Mortality in Men with Stage 3 or Greater Nephropathy

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Key Words

Kidney disease · Total testosterone · Estimated glomerular filtration rate · Albuminuria · The Study of Health in Pomerania

Abstract

Background: Chronic kidney disease (CKD) and low serum total testosterone (TT) concentrations are independent predictors of mortality risk in the general population, but their combined potential for improved mortality risk stratification is unknown. ***Methods:*** We used data of 1,822 men from the population-based Study of Health in Pomerania followed-up for 9.9 years (median). The direct effects of kidney dysfunction (estimated glomerular filtration rate <60 ml/min/1.73 m^2), albuminuria (urinary albumin-creatinine ratio ≥2.5 mg/mmol) and their combination (CKD) on all-cause and cardiovascular mortality were analyzed using multivariable Cox regression models. Serum TT concentrations below the age-specific 10th percentile (by decades) were considered low and were used for further risk stratification. ***Results:*** Kidney dysfunction (hazard ratio, HR, 1.40; 95% confidence interval, CI, 1.02–1.92), albuminuria (HR, 1.38; 95% CI, 1.06–1.79), and CKD (HR, 1.42; 95% CI, 1.09–1.84) were associated with increased all-cause mortality risk, while only kidney dysfunction (HR, 2.01; 95% CI, 1.21–3.34) was associated with increased cardiovascular mortality risk after multivariable adjustment. Men with kidney dysfunction and low TT concentrations were identified as high-risk individuals showing a more than 2-fold increased all-cause mortality risk (HR, 2.52; 95% CI, 1.08–5.85). Added to multivariable models, nonsignificant interaction terms suggest that kidney dysfunction and low TT are primarily additive rather than synergistic mortality risk factors. ***Conclusion:*** In the case of early loss of kidney function, measured TT concentrations might help to detect high-risk individuals for potential therapeutic interventions and to improve mortality risk assessment and outcome.

Introduction

Chronic kidney disease (CKD) is a major and growing public health issue of considerable socioeconomic and medical importance. Increasing CKD prevalence and incidence rates can be confirmed worldwide, reflecting similar increases in shared cardiovascular disease (CVD) risk factors including obesity, diabetes mellitus, and hypertension [1]. The associations of non-dialysis-dependent CKD

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with all-cause and cardiovascular mortality has been shown in different populations, age-groups, and study settings [2], and were consolidated by a large meta-analysis of 21 general population cohorts [3]. Furthermore, even mild kidney dysfunction was identified to substantially increase the risk of cardiovascular events, hospitalization, and death in a large community-based population [4].

The altered metabolic milieu in CKD affects the secretion of hormones and the hormone-induced response of target tissues, causing endocrine dysfunctions [5]. As many as 50–70% of male patients with severe CKD may be hypogonadal on the basis of low concentrations of total and free testosterone [6]. Furthermore, alterations of sex hormone production and metabolism are already seen when moderate reductions in the glomerular filtration rate arise [7]. We have recently demonstrated that low concentrations of total testosterone (TT) were independently associated with increased risk of all-cause and cardiovascular mortality in a population-based sample of 1,954 men [8].

Based on the interrelationship between CKD and TT, it is reasonable to expect an impact of low TT concentrations on CKD-related mortality associations. But to date, there are only clinical studies reporting that low TT concentrations were associated with increased cardiovascular comorbidity and overall mortality risk in male end-stage renal disease and dialysis patients [9, 10]. Due to the lack of systematic investigations in larger population-based samples, it is currently unknown whether a combined assessment of CKD measures and TT status would yield improved mortality risk profiles. This is even more intriguing, given the increasing body of evidence suggesting low TT concentrations as a meaningful biomarker of pre-existing metabolic disturbances and adverse cardiovascular risk factor profiles [11–13]. Therefore, we used data from the population-based Study of Health in Pomerania (SHIP) including 1,822 men with long term follow-up, to explore the direct effects of kidney dysfunction, albuminuria and their combination on all-cause and cardiovascular mortality, and to investigate if a combined assessment of CKD measures and TT status would yield improved mortality risk profiles.

Methods

Study Population

SHIP is a population-based cohort study in West Pomerania, a region in northeastern Germany. Details on the SHIP study design, recruitment, and procedures have been published previously [14]. The net sample (without migrated or deceased persons) comprised 6,265 eligible subjects, whereof 4,308 finally participated (response rate 68.7%). All participants gave written informed consent. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in an a priori approval by the local Ethics Committee of the University of Greifswald. From the 2,116 male baseline participants, we excluded men due to unmeasured concentrations of serum creatinine (n = 12), urine creatinine (n = 19), urine albumin (n = 149), or TT (n = 76). We also excluded men with measured urine creatinine concentrations <1.0 mmol/l or >100 mmol/l (n = 29), adenomas (n = 2), or self-reported intake of sex steroids (Anatomical Therapeutic Chemical, ATC, code G03; n = 2), testosterone 5α reductase inhibitors (ATC code G04CB; n = 4), or sex steroid antagonists (ATC code L02B; n = 1). The final study population comprised 1,822 men.

Clinical Evaluation

Computer-assisted personal interviews assessed information regarding age, smoking (current, former, and never smokers), as well as subjects' self-reported medical history of diabetes mellitus. After a resting period of at least 5 min, systolic and diastolic blood pressure was measured three times at the right arm of seated subjects by use of an oscillometric digital blood pressure monitor (HEM-705CP; Omron Corporation, Tokyo, Japan). The interval between the readings was 3 min. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined by systolic blood pressure or diastolic blood pressure of ≥140 and ≥90 mm Hg, respectively, or use of antihypertensive medication (ATC codes: C02, C03, C04, C07, C08, or C09). Waist circumference (WC) was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet.

Laboratory Examinations

Non-fasting blood samples were taken from the cubital vein in the supine position between 07:00 a.m. and 06:00 p.m. and prepared for immediate analysis or for storage at –80°C for further analysis. Serum creatinine concentrations were determined with the Jaffé method (Hitachi 717; Roche Diagnostics, Germany), and the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation [15]: eGFR (ml/min/1.73 m^2) = 186 × serum creatinine (mg/dl)$^{-1.154}$ × age (years)$^{-0.203}$. Kidney dysfunction was defined as eGFR <60 ml/min/1.73 m^2. Concentrations of urine albumin and creatinine were determined on a Behring Nephelometer (Siemens BN albumin; Siemens Healthcare, Marburg, Germany) and a Hitachi 717 (Roche Diagnostics), respectively. The urinary albumin-creatinine ratio (UACR) following the equation: UACR (mg/mmol) = urine albumin concentration (mg/l)/urine creatinine concentration (mmol/l) was used as a measure of albumin excretion. Albuminuria was defined as an UACR of ≥2.5 mg/mmol [16]. According to the Kidney Disease Outcomes Quality Initiative guidelines, CKD was defined as presence of kidney dysfunction and/or albuminuria [17].

Low-density lipoprotein cholesterol (LDL-C) was measured by applying a precipitation procedure using dextran sulphate (Immuno, Heidelberg, Germany) on an Epos 5060 (Eppendorf, Hamburg, Germany). TT concentrations were measured from frozen serum aliquots using competitive chemiluminescent enzyme immunoassays on an Immulite 2500 analyzer (Siemens

Healthcare Medical Diagnostics, Bad Nauheim, Germany). Measurements were carried out from December 2005 to January 2006. The inter-assay coefficient of variation was 13.2% with a systematic deviation of +2.3% at the 3.2 nmol/l level, and 8.9% with a systematic deviation of +0.24% at the 22.5 nmol/l level [18]. Low TT concentrations were defined according to the 10th percentile in every 10-year age group.

Mortality Follow-Up

During 17,243 person-years (median, 9.9 years; 25th, 9.2; 75th, 10.7) of follow-up, 282 individuals (15.5%) died, reflecting an overall crude mortality rate of 16.4 deaths per 1,000 person-years. Information on vital status was collected from population registries at annual intervals from time of enrollment into the study through December 15, 2009. Subjects were censored at either death or loss to follow-up and the number of months between baseline examination and censoring was used as follow-up length. Death certificates were requested from the local health authority at the place of death. Causes of deaths were coded by a certified nosologist according to the International Classification of Diseases, 10th revision (ICD-10). Additionally, 2 internists (H.W. and M.D.) independently validated the underlying cause of death, and performed a joint reading in cases of disagreement. A third internist (H.V.) finally decided in cases of still existing disagreement. Cardiovascular mortality comprised the ICD-10 codes I10–I79 (I10–I15 hypertensive diseases, I20–I25 ischemic heart diseases, I26–I28 pulmonary heart disease and diseases of pulmonary circulation, I30–I52 other forms of heart disease, I60–I69 cerebrovascular diseases, and I70–I79 diseases of arteries, arterioles and capillaries).

Statistical Analyses

Baseline characteristics of the study population are expressed as median and interquartile range for qualitative data and as percent values for qualitative data as indicated. In a first step, we used multivariable Cox proportional hazards regression models adjusted for age, WC, smoking, diabetes mellitus, hypertension, and LDL-C concentrations to analyze the associations between measures of impaired kidney function and all-cause as well as cardiovascular mortality. We used an established threshold at the age of 70 years to repeat the conducted models stratified by age [19]. We graphically explored log-log plots to satisfy the proportional hazards assumption. To evaluate possible non-response bias due to missing data, we additionally included inverse probability weights into the multivariable models calculated with respect to baseline information regarding age, WC, physical activity, diabetes mellitus, and hypertension [20]. To account for potentially confounding effects of acute illness, sensitivity analyses were performed by excluding first-year decedents (n = 17). Further sensitivity analyses included the additional adjustment for blood sampling time and statin use (ATC code C10AA), both factors known to affect GFR and albumin excretion [21], as well as testosterone concentrations [22].

In a second step, we reassessed the multivariable Cox models stratified by TT status. Kaplan-Meier analyses were graphed and survival curves compared by log-rank test. To avoid arbitrariness in the definition of low TT concentrations, we also applied alternative cutoffs. We tested multiplicative interaction terms for eGFR, UACR, and CKD with continuous TT concentrations: (1) in parsimonious bivariate models including the respective interaction, (2) additionally adjusted for age, and (3) in fully adjusted multivariable models. A significant interaction term ($p < 0.05$) indicates that the effect of one exposure (low TT) on mortality varies according to the value of the second exposure (eGFR, UACR, or CKD, respectively). Furthermore, we aimed to compare the predictive ability between multivariable Cox models without and with continuous TT concentrations using receiver-operating characteristic (ROC) curves, C-statistics, and the integrated discrimination improvement (IDI) [23]. The IDI is based on continuous differences in the predicted risk between the two estimated models based on multivariable logistic regression models that examined deaths through 10-years of follow-up. Hazard ratios (HR) were calculated with 95% confidence intervals (95% CI), and two-sided probability values <0.05 were considered statistically significant. All statistical analyses were performed using Stata 11.0 (Stata Corporation, College Station, Tex., USA).

Table 1. Baseline characteristics of the study population

N	1,822
Sex	male
Age, years	51.8 (37.2; 65.4)[1]
WC, cm	95.5 (87.5; 103.2)[1]
Serum creatinine, mmol/l	90.0 (83.3; 98.4)[1]
eGFR, ml/min/1.73 m^2	83.2 (73.8; 92.9)[1]
Urine creatinine, mmol/l	10.0 (6.8; 13.8)[1]
Urine albumin, mg/l	8.5 (4.8; 18.5)[1]
Kidney dysfunction, %	6.4
Albuminuria, %	19.1
CKD, %	22.8
Serum TT, nmol/l	15.9 (12.5; 19.9)[1]
Low TT (<age-dependent 10th percentile), %	10.2
LDL-C, mmol/l	3.6 (2.8; 4.3)[1]
Diabetes mellitus, %	8.8
Hypertension, %	64.4
Current smoking, %	33.4

[1] Median (25th; 75th percentile).

Results

Baseline data for the study population are given in table 1. The overall prevalence of kidney dysfunction, albuminuria, and CKD was 6.4, 19.1, and 22.8%, respectively. Median TT concentrations were significantly lower in men with kidney dysfunction (14.6 nmol/l), albuminuria (15.9 nmol/l), and CKD (15.8 nmol/l) compared to men without these conditions ($p < 0.05$). Prevalence estimates for low TT concentrations ranged from 12.0% among men with kidney dysfunction to 13.2% (albuminuria) and 14.1% (CKD). Graphed Kaplan-Meier analyses for all-cause and cardiovascular mortality indicate that men

Table 2. Association of measures of impaired kidney function with all-cause and cardiovascular mortality

Models	Kidney dysfunction		Albuminuria		CKD	
	all-cause mortality	cardiovascular mortality	all-cause mortality	cardiovascular mortality	all-cause mortality	cardiovascular mortality
1 Age-adjusted model	1.49 (1.09–2.03)*	2.16 (1.32–3.52)*	1.46 (1.14–1.88)*	1.40 (0.90–2.17)	1.51 (1.18–1.92)*	1.74 (1.12–2.68)*
2 Multiple-adjusted model	1.40 (1.02–1.93)*	2.01 (1.21–3.34)*	1.38 (1.06–1.79)*	1.18 (0.74–1.89)	1.42 (1.09–1.84)*	1.46 (0.92–2.33)
29–69 years (n = 1,564)	2.19 (1.34–3.59)*	4.34 (1.91–9.87)*	1.62 (1.14–2.31)*	1.30 (0.63–2.66)	1.66 (1.17–2.35)*	1.91 (0.97–3.74)
70–79 years (n = 258)	1.13 (0.75–1.73)	1.45 (0.76–2.77)	1.19 (0.80–1.78)	1.08 (0.57–2.04)	1.22 (0.81–1.82)	1.13 (0.58–2.18)
2 + Non-response weights	1.34 (0.98–1.85)	2.10 (1.25–3.53)*	1.32 (1.01–1.73)*	1.26 (0.78–2.03)	1.36 (1.04–1.77)*	1.55 (0.97–2.48)
2 Excluding first-year deaths	1.32 (0.94–1.83)	1.72 (1.01–2.93)*	1.37 (1.05–1.81)*	1.28 (0.79–2.06)	1.34 (1.03–1.76)*	1.36 (0.84–2.19)

Multiple-adjusted model included adjustment for age, WC, diabetes mellitus, hypertension, smoking (3 categories), and LDL-C concentrations.
* $p < 0.05$. Figures represent hazard ratios (95% CI).

Table 3. Association of measures of impaired kidney function with all-cause mortality stratified by low TT concentrations

Models	Kidney dysfunction		Albuminuria		CKD	
	TT ≤10th	TT >10th	TT ≤10th	TT >10th	TT ≤10th	TT >10th
All-cause mortality						
1 Age-adjusted model	2.80 (1.33–5.85)*	1.32 (0.94–1.86)	1.01 (0.51–1.99)	1.49 (1.14–1.95)*	1.37 (0.68–2.77)	1.48 (1.13–1.92)*
2 Multiple-adjusted model	2.52 (1.08–5.85)*	1.26 (0.89–1.80)	0.58 (0.24–1.41)	1.46 (1.11–1.94)*	1.00 (0.43–2.32)	1.43 (1.08–1.89)*
29–69 years	17.01 (3.90–74.1)*	1.67 (0.94–2.99)	0.67 (0.17–2.59)	1.73 (1.19–2.52)*	1.96 (0.58–6.68)	1.64 (1.13–2.38)*
70–79 years	1.24 (0.31–5.01)	1.13 (0.72–1.80)	0.37 (0.09–1.48)	1.26 (0.82–1.94)	0.49 (0.14–1.72)	1.26 (0.81–1.95)
2 + Non-response weights	3.82 (1.63–8.94)*	1.15 (0.81–1.64)	0.50 (0.21–1.21)	1.40 (1.05–1.86)*	0.90 (0.38–2.14)	1.35 (1.02–1.79)*
2 Excluding first-year deaths	2.20 (0.93–5.23)*	1.19 (0.82–1.73)	0.54 (0.21–1.35)	1.48 (1.10–1.97)*	0.96 (0.41–2.26)	1.36 (1.02–1.81)*
Cardiovascular mortality						
1 Age-adjusted model	3.97 (1.31–12.01)*	1.87 (1.08–3.24)*	0.97 (0.33–2.88)	1.36 (0.83–2.22)	2.14 (0.62–7.36)	1.57 (0.98–2.53)
2 Multiple-adjusted model	2.93 (0.88–9.86)	1.63 (0.92–2.90)	0.30 (0.05–1.66)	1.21 (0.72–2.02)	1.44 (0.30–6.94)	1.30 (0.79–2.16)
29–69 years	12.64 (0.51–314.2)	2.89 (1.10–7.59)*	0.47 (0.03–7.52)	1.37 (0.63–3.02)	3.07 (0.24–38.6)	1.66 (0.79–3.48)
70–79 years	2.97 (0.41–21.45)	1.23 (0.59–2.56)	0.13 (0.01–1.76)	1.11 (0.55–2.26)	0.45 (0.04–4.47)	1.03 (0.50–2.14)
2 + Non-response weights	4.58 (1.14–18.32)*	1.62 (0.90–2.90)	0.46 (0.08–2.51)	1.25 (0.74–2.11)	1.67 (0.32–8.84)	1.34 (0.81–2.23)
2 Excluding first-year deaths	2.94 (0.86–9.86)	1.32 (0.71–2.43)	0.30 (0.05–1.66)	1.32 (0.79–2.23)	1.44 (0.30–6.94)	1.18 (0.70–2.00)

Multiple-adjusted model included adjustment for age, WC, diabetes mellitus, hypertension, smoking (3 categories), and LDL-C concentrations. Low TT concentrations were defined according to the 10th percentile in every 10-year age group. * $p < 0.05$. Figures represent hazard ratios (95% CI).

with kidney dysfunction, albuminuria, or CKD had significantly shorter survival times ($p < 0.001$) compared to men without these conditions (graphs not shown). Multivariable Cox models presented in table 2 indicate an increased all-cause mortality risk from kidney dysfunction (HR, 1.40; 95% CI, 1.02–1.92), albuminuria (HR, 1.38; 95% CI, 1.06–1.79), and CKD (HR, 1.42; 95% CI, 1.09–1.84), respectively. Of the 270 men with available death certificates, 89 (33.0%) died from cardiovascular causes. After multivariable adjustment, only kidney dysfunction (HR, 2.01; 95% CI, 1.21–3.34) was associated with increased risk of cardiovascular mortality independent of traditional risk factors (table 2). In age-stratified analyses, we found men aged 29–69 to be particularly responsive to the revealed association of kidney dysfunction with all-cause (HR, 2.19; 95% CI, 1.34–3.59) and cardiovascular mortality (HR, 4.34; 95% CI, 1.91–9.87).

Sensitivity analyses slightly decreased the revealed estimates by the exclusion of first-year decedents and the inclusion of inverse probability weights, respectively (table 2), whereas the additional adjustment for blood sampling time and statin use showed no overall impact on the revealed estimates (data not shown). Interaction terms for eGFR, UACR, and CKD suggested overlapping interrelationships in bivariate ($p < 0.001$, <0.001, and 0.040, respectively) and age-adjusted models (0.046, 0.001, and

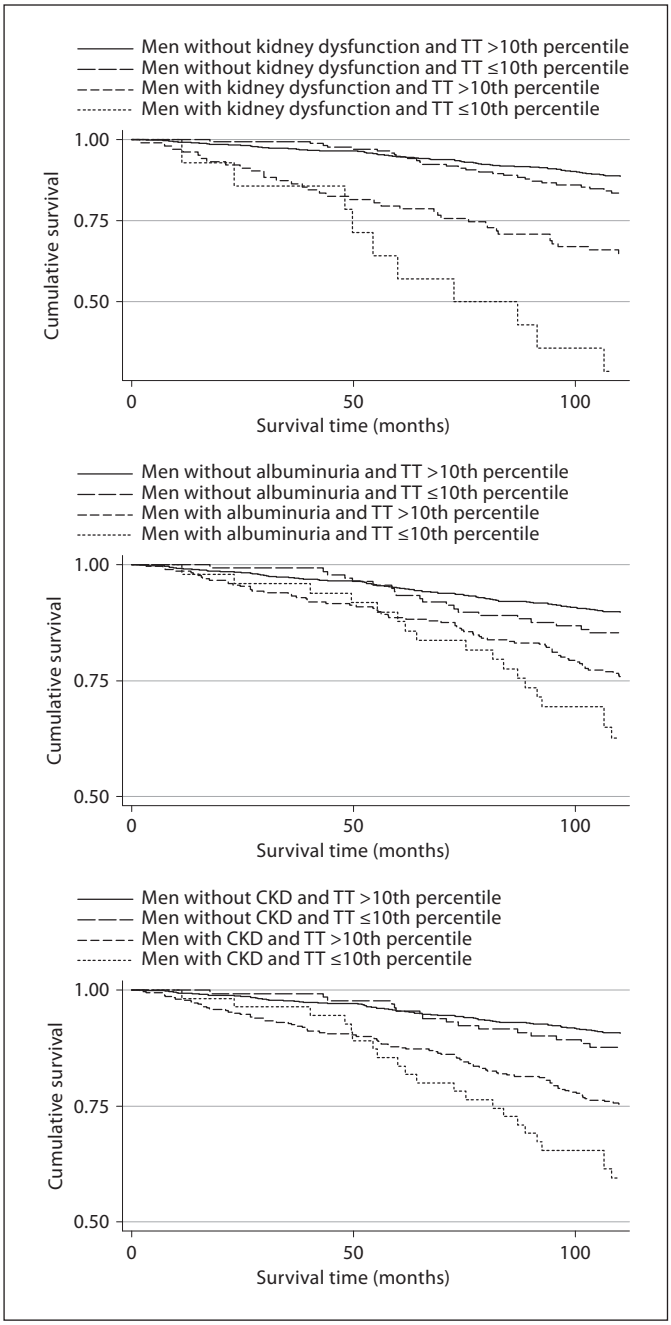

Fig. 1. Kaplan-Meier survival curves for men with and without kidney dysfunction, albuminuria, and CKD stratified by low and higher TT concentrations. Survival times differed significantly between groups (log-rank test, $p < 0.001$).

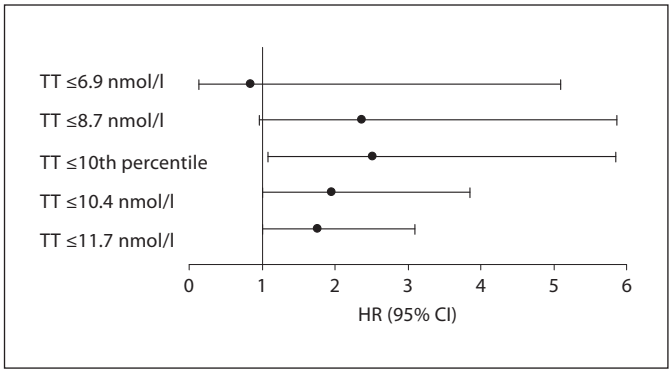

Fig. 2. Estimates for the association of kidney dysfunction with all-cause mortality risk by different cutoffs for the definition of low TT concentrations. Models were adjusted for age, WC, diabetes mellitus, hypertension, smoking (3 categories), and LDL-C concentrations.

0.022, respectively), but not in multivariable models (0.120, 0.152, and 0.111, respectively). The additional inclusion of continuous TT concentrations to the multivariable model associating kidney dysfunction, albuminuria, and CKD with increased all-cause and cardiovascular mortality showed no significant improvement ($p < 0.05$) in the overall predictive ability, as indicated by ROC analyses, C-statistics, and IDI.

In a next step, we used TT concentrations to conduct stratified analyses. Kaplan-Meier analyses depicted in figure 1 show that the subgroup of men with kidney dysfunction, albuminuria, or CKD, together with low TT concentrations experienced the shortest survival time (log-rank test, $p < 0.001$). Multivariable Cox models presented in table 3 revealed that men with kidney dysfunction and low TT concentrations had a more than 2-fold increased all-cause mortality risk (HR, 2.52; 95% CI, 1.08–5.85). In contrast, kidney dysfunction was not associated with a higher mortality risk among men with higher TT concentrations (HR, 1.26; 95% CI, 0.89–1.80). When we used alternative cutoffs for the definition of low TT concentrations, we found comparable risk estimates for the association of kidney dysfunction with all-cause mortality (fig. 2). With regard to albuminuria and CKD, refined mortality risk stratification by using TT status did not reveal any substantial deviations from the previous, unstratified estimates (table 3). We did not detect any association of kidney dysfunction, albuminuria, or CKD with increased cardiovascular mortality risk after multivariable adjustment (table 3). The additional inclusion of non-response weights considerably increased the revealed estimates for the association of kidney dysfunction with all-cause and cardiovascular mortality risk among men with low TT concentrations, while the exclusion of 17 first-year decedents showed no major impact on the revealed multivariable estimates (table 3).

Discussion

The present population-based study among 1,822 men demonstrates that kidney dysfunction is associated with all-cause mortality and cardiovascular mortality after adjustment for traditional risk factors. Furthermore, we reported improved mortality risk stratification through the combined assessment of eGFR and TT concentrations. Although several previous studies have reported associations of kidney dysfunction and albuminuria with mortality risk in the general population, the present population-based investigation is the first one to demonstrate how the mortality risk attributable to kidney dysfunction varies as a function of low TT concentrations.

In a first step, we analyzed the independent and combined associations of kidney dysfunction and albuminuria with all-cause and cardiovascular mortality. While we found all three conditions predictive of all-cause mortality, only kidney dysfunction was associated with higher cardiovascular mortality. These findings are consistent with a recent meta-analysis of 21 general population cohorts [3] and other large-scale community-based studies [4, 24]. The absence of associations of albuminuria and CKD with cardiovascular mortality after multivariable adjustment in our study is most likely explained by the comparably low number of cardiovascular deaths and by differences in the categorizations used for the definition of albuminuria. Furthermore, our findings suggest eGFR and UACR as biomarkers of mortality risk with a higher prognostic significance particularly among middle-aged men (29–69 years), as we were not able to detect these associations in the elderly (70–79 years).

Next, we considered serum TT concentrations for prevalence estimates, further risk stratification, and potential risk prediction improvements. In comparison with previous prevalence estimates (TT <10.0 nmol/l) of 52% among male dialysis patients [10] or 44% among men with end-stage renal disease [9], our estimated prevalence of 14% is lower because it is based on non-dialysis individuals with mild kidney dysfunction from the general population. Alternatively or in addition, our applied age-specific cutoff for the definition of low TT may help to explain the different prevalence estimates. Recent guidelines recommended cutoffs between 9.8 and 10.4 nmol/l (280 and 300 ng/dl, respectively) to define the lower limit of normal TT concentrations for healthy young men, but lacked consensus on the TT threshold in older men [25]. In contrast to fixed cutoffs, age-specific percentile cutoffs may reflect the existence of different serum TT concentration thresholds below which metabolic changes related to low TT may occur [26]. Furthermore, our sensitivity analyses with alternative cutoffs for the definition of low TT showed comparable associations with all-cause mortality in men with kidney dysfunction, proving the validity of our findings.

Using TT concentrations to refine mortality risk stratification, we identified men with kidney dysfunction and low TT concentrations as high-risk individuals with a more than 2-fold increased risk of all-cause mortality. We also found an age-related attenuation in the combined risk profile in men aged 29–69 years. With regard to albuminuria and CKD, mortality risk stratification by TT status did not reveal any significant risk profiles. Recent data suggest that TT may be a 'biomarker of good health' [27]. TT concentrations have been shown to fall in association with various different conditions such as obesity, metabolic syndrome, or dyslipidemia, and change over time as well as in response to changing health status [28]. Thus, it seems plausible that low TT concentrations are related to increased morbidity. Along this line, there is growing evidence showing that low TT concentrations are associated with the development of metabolic syndrome [12], dyslipidemia [29], and increased health care utilization [30]. Independent associations of low TT concentrations with increased mortality risk were previously reported from different prospective cohort studies including ours [8, 31–33]. Overall, our finding that low TT concentrations show an additive effect on the association of kidney dysfunction with all-cause mortality is not surprising, since multisystemic disorders (that are widely prevalent in the aging male) such as CKD, metabolic syndrome, or sarcopenia are likely to be associated with hormonal dysregulation. But according to a cross-sectional study among 1,470 men from the general US population, low TT concentrations are not directly associated with CKD [34]. This study suggests low TT is a surrogate parameter of disease severity rather than a causal CKD risk factor.

Experimental results suggest that TT may promote decline in renal function [35, 36]. Castration in male rats for example, completely prevents reductions in GFR and glomerular injury [35], whereas the acute infusion of testosterone causes renal vasodilation with increases in GFR [36]. The recently stopped TOM (Testosterone in Older Men with Mobility Limitations) trial among elderly men (mean age 74 years) reported that testosterone treatment was associated with an increased risk of adverse cardiovascular events [37]. For the interpretation of these results, it must be mentioned that the starting doses in the TOM trial were higher than those recommended by the

manufacturer, and the treatment goal (34.7 nmol/l) was considerably higher than that recommended by the Endocrine Society in these patients (13.9–17.4 nmol/l) [37]. Against this background, the high rate of adverse cardiovascular events in the TOM trial is suggestive of oversupplementation. However, there is a lack of rigorous clinical trials examining the effects of chronic testosterone on cardiovascular-renal disease risk [36]. It may still be possible that exogenous testosterone affects CKD progression and related symptoms, although there are insufficient data to support this hypothesis at present. Accordingly, a recent review of 51 testosterone trials with various outcomes concluded that the current evidence about the safety of testosterone treatment in men is of low quality and limited by short follow-up times [38].

To evaluate the predictive utility of low TT concentrations, we included continuously distributed TT concentrations into the multivariable model predicting mortality from CKD but failed to meaningfully alter the predictive ability of the multivariable model, as evidenced by small changes in the area under the ROC curve, C statistic, and IDI. A reasonable finding, given the powerful traditional risk factors including age, smoking, hypertension, dyslipidemia, and diabetes mellitus that were already in the model [23]. Further sensitivity analyses excluding first-year deaths yielded similar estimates, suggesting that the association between kidney dysfunction, low TT, and all-cause mortality was not simply due to acute illness and increased levels of systemic inflammation.

Given the revealed associations of kidney dysfunction and low TT concentrations with increased mortality risk, we assumed a synergistic relationship such that the presence of low TT enhances the risk of mortality attributable to kidney dysfunction. When we investigated this hypothesis by analyzing a parsimonious model including terms for low TT, eGFR, and their interaction, the interaction term was statistically significant, even after age adjustment. But the interaction term lost statistical significance in the multivariable model, suggesting that while low TT and kidney dysfunction are both associated with increased mortality risk, they are primarily additive rather than synergistic and may even share some similar risk factor profiles. Accordingly, we detected this additive effect in combined risk stratification analyses, showing that the subgroup of men with kidney dysfunction and low TT concentrations had the highest mortality risk, even after adjustment for major confounders.

Potential limitations of the present investigation may arise from the single spot measurement of TT and urinary albumin. Because of the variability in urinary albumin excretion, at least two specimens collected within a 3- to 6-month period would have been desirable to quantify urinary albumin excretion more accurately. In the absence of repeated measurements, it is generally recommended to use the UACR [39]. Furthermore, single measurements of eGFR [40] and TT concentrations [41] have been shown to be of prognostic value in previous epidemiological studies. The major strength of our study is the large population-based sample of men with a broad age range from 20 to 79 years, enabling refined risk stratification based on TT status. Furthermore, we were able to comprehensively evaluate the independent and combined associations of reduced eGFR and albuminuria with all-cause as well as cardiovascular mortality.

Our findings suggest that the combined assessment of measures of impaired kidney function together with TT concentrations might help to detect increased mortality risk associated with CKD, even in the general population. Based on our main finding that the combined risk profiles considerably improved mortality risk stratification, our results offer the potential to facilitate the appropriate recognition and screening of high-risk individuals for the application of individualized treatment plans. However, further research is necessary to prove whether TT replacement therapy indeed reduces progression of CKD or protects against CKD-related mortality risk.

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