Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease

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Abstract

Background. Abnormally low serum testosterone levels were recently associated with an increased mortality risk in male dialysis patients. However, the prevalence of testosterone deficiency in end-stage renal disease (ESRD) is not well defined. We hereby explore the prevalence and correlates of clinical testosterone deficiency in a large cohort of ESRD male patients.

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Methods. Two hundred and sixty ESRD men [median age 59 (25th–75th percentile 48–67) years] were included. Testosterone concentration and testosterone deficiency (<10 nmol/L) were studied in relation to clinically evident cardiovascular disease and markers of inflammation at baseline as well as deaths registered during the following 36 months.

Results. Testosterone deficiency was present in 44% of the patients, while 33% showed testosterone insufficiency (10–14 nmol/L), and only 23% had normal testosterone values (>14 nmol/L). Testosterone was strongly and inversely correlated to inflammatory markers (CRP, IL-6 and fibrinogen), even after correction for age and sex hormone-binding globulin. In a crude spline curve, low testosterone concentrations were associated with worse outcome. A clinical condition of testosterone deficiency was independently associated with cardiovascular co-morbidity [odds ratio (OR) 2.51; 95% confidence interval (CI) 1.32–4.76] and death (OR 2.00; 95% CI 1.01–3.97) in logistic regression analyses.

Conclusions. Testosterone deficiency is a common finding among male ESRD patients, and it is independently associated with inflammation, cardiovascular co-morbidity and outcome. Future studies are needed to determine the potential adverse effects of male hypogonadism in ESRD and the possibility of improving risk profile, quality of life, and ultimately outcome with testosterone supplementation in these patients.

Keywords: endocrine dysfunction; haemodialysis; risk factor; sex hormones

Introduction

Although end-stage renal disease (ESRD) patients have a greatly increased risk of premature death [1], the reasons for this magnified risk are not fully understood. Chronic kidney disease (CKD) per se is associated with a wide range of metabolic alterations, including disorders in the secretion of hormones and the response of target tissues, causing a number of endocrine dysfunctions that may contribute to worse outcomes [2,3]. Among those, male hypogonadism (i.e. testosterone deficiency) is the most common gonadal alteration in men, mainly due to reduced prolactin clearance [4] and uremic inhibition of luteinizing hormone signalling at the level of the Leydig cells [5]. Although certain efforts have been devoted in the past to the consequences of uraemic testosterone deficiency on sexual dysfunction [6] and anaemia [7], little attention has been given to the growing body of evidence suggesting that testosterone deficiency may contribute to the onset, progression or both of cardiovascular disease (CVD) [8].

Recently, low testosterone levels in apparently healthy male populations have been identified as a predisposing risk factor to increased mortality and cardiovascular morbidity [9,10]. We recently reported that abnormally low endogenous testosterone values (defined in that study as below the 33rd percentile of distribution) were associated with increased risk of death in a relatively small cohort (n = 126) of men undergoing haemodialysis [11]. Moreover, recent studies suggest novel links between low testosterone values and bone disorders [12] or endothelial activation [13] in ESRD patients. Despite this, there is limited quantitative evidence regarding the prevalence and consequences of a clinical condition of testosterone deficiency in men with ESRD [6,14,15]. Because a limited sample size may have biased our earlier estimations of the clinical condition of testosterone deficiency [11], the aim of the present analysis was to assess the frequency of hypogonadism (hereby defined as total testosterone <10 nmol/L [16]) in an enlarged screening of ESRD men. At the same time, we studied purported links with well-established risk factors and outcome. We therefore assessed testosterone concentrations in a large cohort of ESRD male patients with a wide age range.

Materials and methods

Subjects and experimental design

This is a post hoc analysis of data arising from the combination of two prospective ESRD patient materials coordinated at the Department of Renal Medicine, Karolinska Institutet, Stockholm, Sweden. These are two cohorts of incident and prevalent dialysis patients, respectively. The incident material is an ongoing prospective cohort study of patients sampled close to the beginning of dialysis at the Karolinska University Hospital Huddinge, Stockholm, Sweden [17]. Patients included in this analysis were recruited between June 1999 and October 2007. Exclusion criteria were liver dysfunction, clinical signs of infection and unwillingness to participate. The prevalent material included haemodialysis patients [18], and because this study aimed at analysing the variability of inflammatory markers over time, an additional exclusion criterion, on top of the aforementioned criteria, was lack of sufficient CRP measurements during a 3-month monitoring period. This patient material was used in our previous report [11], and patient recruitment in this cohort occurred from October 2003 through March 2004. Testosterone levels were measured in all male patients with plasma available (n = 260). Patients were divided

<table>
<thead>
<tr>
<th>n</th>
<th>CKD 5 before start of dialysis</th>
<th>Incident dialysis</th>
<th>Long-term dialysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>55</td>
<td>122</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (48–65)</td>
<td>56 (46–63)</td>
<td>64 (49–73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>48</td>
<td>49</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>41</td>
<td>40</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Wasting (SGA &gt;1), %</td>
<td>20</td>
<td>24</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>s-albumin, g/L</td>
<td>33±6</td>
<td>33±6</td>
<td>34±4</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>4.9 (1.9–12.5)</td>
<td>8.5 (2.5–16.0)</td>
<td>6.8 (3.1–21.0)</td>
<td></td>
</tr>
<tr>
<td>Total testosterone, nmol/L</td>
<td>13.0 (9.6–15.0)</td>
<td>12.0 (8.7–16.0)</td>
<td>9.9 (7.2–12.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Differences across the groups were corrected for age using a mixed model procedure.
according to whether they were (i) CKD stage 5 patients studied just before initiation of dialysis therapy \( n = 83; \) median GFR 7 (5–8) mL/min, median time before dialysis initiation 0.8 (2.9–0.5) months, (ii) incident dialysis \( \leq 90 \) days on dialysis, \( n = 55, \) vintage time 0.2 (0.6–0.7) months and (iii) prevalent dialysis \( >90 \) days on dialysis, \( n = 122, \) vintage time 27 (15–57) months. General characteristics are presented in Table 1. In age-adjusted comparisons, testosterone values did not differ between the groups, and therefore, patients were studied together. Each patient’s medical chart was reviewed to extract data pertaining to the underlying CKD, CVD history, diabetes mellitus and survival. Fatal events were registered from the day of examination and up to 36 months after from medical records. The study protocols were approved by the Ethics Committee of Karolinska Institutet Hospital and Uppsala University Hospital. Signed informed consent was obtained from all patients prior to the inclusion in the study.

**Laboratory analyses and nutritional status**

Blood samples were collected following an overnight fasting (in pre-dialysis patients) or before the dialysis session. Plasma and serum were separated and kept frozen at \(-70^\circ C,\) if not analysed immediately. In pre-dialysis patients, GFR was calculated from the mean of urea and creatinine clearance from a 24-h urine collection. Serum concentrations of interleukin (IL)-6 were quantified by immunometric assays on an Immulite analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) according to the instructions of the manufacturers. High-sensitivity CRP (hsCRP), fibrinogen, s-albumin, s-creatinine and haemoglobin concentrations were analysed using certified methods at the Department of Clinical Chemistry in Karolinska University Hospital or Uppsala Academic Hospital. Serum testosterone concentration and sex hormone-binding globulin (SHBG) were assessed from frozen samples using certified routine methods at the Department of Laboratory Medicine in Karolinska University Hospital. For classification of hypogonadal testosterone, the following classification from the Endocrine Society [16] was used: (i) normal, testosterone >14 nmol/L; (ii) lower normality range (testosterone insufficiency), testosterone 10–14 nmol/L; and (iii) testosterone deficiency, testosterone <10 nmol/L. Interestingly, a cut-off of 10 nmol/L was shown to be the level where symptoms of hypogonadism started to be significantly more prevalent in elderly patients [19]. Free testosterone was calculated from total testosterone, SHBG and s-albumin concentrations using mass action equations [20]. Body mass index (BMI) and dynamometric measurements were determined in fasting conditions on a dialysis day where applicable. Subjective global assessment (SGA) was used to evaluate the overall nutritional status. For the purpose of this study, a state of protein-energy wasting (PEW) was defined as SGA >1.

<table>
<thead>
<tr>
<th></th>
<th>Testosterone deficient ( n = 112 (44%) )</th>
<th>Non-testosterone deficient ( n = 148 (56%) )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone, nmol/L</td>
<td>7.6 (6.0–9.2)</td>
<td>13.5 (12.0–17.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td>23.5 (16.2–33.0)</td>
<td>32.0 (21.5–43.0)</td>
<td></td>
</tr>
<tr>
<td>Free testosterone, nmol/L</td>
<td>0.19 (0.13–0.24)</td>
<td>0.32 (0.26–0.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>65 (56–70)</td>
<td>55 (43–63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>38 (34%)</td>
<td>50 (34%)</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>84 (75%)</td>
<td>65 (44%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wasting (SGA &gt;1), %</td>
<td>46 (42%)</td>
<td>31 (22%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>s-albumin, g/L</td>
<td>33±5</td>
<td>35±5</td>
<td>0.01</td>
</tr>
<tr>
<td>s-creatinine, µmol/L</td>
<td>774±235</td>
<td>848±243</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±4.8</td>
<td>24.4±4.2</td>
<td>ns</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>8.4 (4.0–20.4)</td>
<td>13.1 (4.9–36.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>13.0 (4.3–26.0)</td>
<td>4.5 (1.7–10.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>10.0 (6.9–18.4)</td>
<td>6.3 (3.9–9.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>5.1 (3.8–5.9)</td>
<td>4.4 (3.5–5.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Progesterone, nmol/L</td>
<td>3.4 (2.4–4.4)</td>
<td>3.8 (3.0–5.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Deaths during follow-up, n (%)</td>
<td>41 (37%)</td>
<td>35 (23%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Testosterone deficiency was defined as testosterone levels <10 nmol/L. Data are presented as median (25th–75th percentiles), average ± SD or percentage frequency.
Restricted cubic splines were used to evaluate non-linear relationships between multivariate analysis including the parameter of interest, age and SHBG. Significant correlations were then tested in a Kruskal–Wallis test. Differences among three groups with correction for age were done using a mixed model procedure. Spearman’s rank correlation ($\rho$) was used to determine correlations of testosterone with other variables. In order to test the independence of these associations from the natural process of ageing and SHBG levels, significant correlations were then tested in a multivariate analysis including the parameter of interest, age and SHBG. Restricted cubic splines were used to evaluate non-linear relationships between testosterone levels and mortality [21]. We chose three knots at 6, 10 and 14 nmol/L, corresponding to the round approximation of tertiles, which has been suggested to offer adequate fit of the model, and is a good compromise between flexibility and loss of precision caused by over-fitting a small sample [22]. Logistic regression analyses were used to study the contribution of testosterone deficiency to clinical history of CVD and registered deaths during a 3-year follow-up. Selection of the confounders in these models was performed on the basis of presumed pathophysiological pathways, and all covariates satisfied the proportional odds assumption. To avoid the possibility that the different nature of the patients included in the analysis may influence these results, we included the sampling point (that is, whether the patients had not yet started dialysis, were incident or long-term dialysis) as a fixed effect in the logistic regression models. Since P-values are not adjusted for multiple testing, they have to be considered as descriptive. All statistical analyses were performed using statistical software SAS version 9.2 (SAS Campus Drive, Cary, NC, USA).

**Results**

The male population presented a median age of 59 (25th–75th percentiles 48–67) years. Whereas 83 (33%) of them had diabetes mellitus, 149 (57%) had a clinical history of CVD. Most patients were on antihypertensive medications [\(\beta\)-blockers, \(n = 161\); calcium channel blockers, \(n = 94\); and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), \(n = 132\)], as well as other commonly used drugs in terminal CKD (such as phosphate and potassium binders), and vitamin B, C and D supplementation. Eighty-five patients (34%) were on lipid-lowering medication (statins).

The median level of total testosterone was 11.0 (8.2–14.0) nmol/L. Whereas 112 men (44%) had testosterone deficiency (<10 nmol/L), 88 (33%) presented testosterone insufficiency (10–14 nmol/L), and only 60 (23%) patients had normal testosterone values (Figure 1). No differences in testosterone levels were found between consumers and non-consumers of [\(\beta\)-blockers, Ca blockers or statins, respectively (data not shown). Patients on ACEI/ARB presented slightly higher levels of testosterone (12.0 vs. 11.0 nmol/L, \(n = 128/132\), \(P = 0.05\)), the same being true for estimated free testosterone. These patients also tended to be younger (57 vs. 62 years, \(P = 0.003\), and correction for age made these differences disappear (not shown).

Table 2 illustrates general and clinical characteristics of the men included in the study according to their testosterone status. Men with testosterone deficiency at the time of inclusion proved to be older, with a higher prevalence of clinical CVD, more often wasted (as suggested by a higher SGA score, and lower s-albumin and s-creatinine levels), and with elevated levels of inflammatory markers (as depicted by higher CRP, IL-6 and fibrinogen levels). SHBG and estimated free testosterone also proved to be reduced. The percentage of deaths registered during the 3-year follow-up period was significantly higher in the testosterone-deficient men.

Spearman rank test was used to test univariate correlations between testosterone and selected parameters. As expected, testosterone was negatively associated with age (\(P = -0.36; P < 0.0001\)) and leptin (\(P = -0.17; P < 0.01\)), while positively associated with s-albumin (\(P = 0.18; P < 0.01\)) and s-creatinine (\(P = 0.16; P < 0.05\)). We also observed a negative rather strong association with inflammatory markers such as hsCRP (\(P = -0.38; P < 0.0001\)), IL-6 (\(P = -0.42; P < 0.0001\); Figure 2) and fibrinogen (\(P = -0.29;
P < 0.001). All these associations proved to be independent of age and SHBG in a multivariate model including age, SHBG, and the association of interest (data not shown).

Testosterone-deficient patients had a higher prevalence of clinical CVD at the beginning of the study. A logistic regression analysis (Table 3A) revealed that the odds of presenting with CVD concurrently increased with older age, testosterone deficiency and the presence of diabetes. Deaths were registered during a follow-up period of up to 36 months. Eighty-eight fatal events occurred (34%). Patients who died presented lower median testosterone levels at baseline (9.8 vs. 12.0 nmol/L, P = 0.03; n = 88/172). Spline curves showed that low testosterone concentrations had an impact on mortality prognostication, although this was rather weak (Figure 3). We thereafter studied a condition of testosterone deficiency (<10 nmol/L) on outcome. Logistic regression analysis revealed that mortality was associated with testosterone deficiency, independent of age and the presence of diabetes mellitus or inflammation (Table 3B).

**Discussion**

The occurrence of testosterone deficiency is estimated to vary from 6% to 9.5% in community-dwelling men aged 40–75 years, rising to 15–30% in diabetic or obese men [23,24]. In this study, we report that testosterone deficiency is a much more frequent condition (44%) in ESRD patients, together with a substantial proportion of individuals at risk of deficiency (33%). We also observe that although testosterone values per se significantly predicted clinical outcome, this was a somewhat weak effect. A state of testosterone deficiency, however, proved to be independently associated to the inflammatory status, cardiovascular co-morbidity and 3-year mortality.

This is, to the best of our knowledge, the largest assessment of testosterone deficiency in male ESRD patients available in the literature. Our results demonstrate the commonness of this condition, thereby expanding previous reports in more heterogeneous CKD populations [14,15]. This prevalence is slightly lower than that observed in our previous report in haemodialysis patients, where deficiency, insufficiency and normal testosterone levels were reported in 52%, 32% and 16%, respectively [11]. Differences may be explained, nonetheless, by sample size limitations and also by differences in age, patients being slightly younger in this enlarged material [median age 59 (48–67) years] than in our previous study [63 (49–73) years] [11]. We thus believe that this larger number of patients, probably more representative for the ESRD population, may here provide a better estimation of the frequency of this condition. Because many of the signs and symptoms of hypogonadism are insidious in onset and can accompany normal ageing or CKD, diagnosis of hypogonadism in ESRD patients should be based primarily on laboratory testing in addition to clinical manifestations. Indeed, current guidelines advocate total testosterone assessment for accurate diagnosis of hypogonadism [16,25,26]. However, use of total testosterone concentration for diagnosis of hypogonadism in elderly populations, such as in our study, probably results in under-diagnosis because SHBG increases with age. The value of assessing free or bioavailable testosterone has so far not been established, perhaps because assays for free testosterone are either difficult to perform or unreliable, not being available at present in a routine or commercial manner [25,26]. Also, estimation formulas, like the one used in this study, may not be reliable for diagnostic purposes [25,26].

The pathophysiological mechanisms causing the high prevalence of male hypogonadism in CKD are not com-

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**Fig. 3.** Spline curve showing log-transformed hazard ratios and 95% confidence intervals (dashed line) for all-cause mortality associated with serum testosterone values in 260 ESRD male patients. The model is plotted as restricted cubic splines with three knots (P for linearity = 0.37).
Testosterone deficiency in ESRD

Testosterone deficiency is a common condition in chronic kidney disease (CKD) [4-6]. Indeed, our study showed that after age adjustment, no difference in serum testosterone concentration upon dialysis initiation was observed, agreeing with previous evidence that testosterone is not substantially cleared from circulation by dialysis [27,28], and altogether indirectly supporting the notion that reduced production is the major cause of this abnormality in CKD patients. Co-morbid conditions commonly encountered in CKD patients, such as protein-energy wasting, obesity, diabetes mellitus and hypertension, have all been associated with low testosterone levels [29]. In addition, a variety of medications could impact on gonadal function and need to be carefully evaluated in CKD patients, who frequently are subject to polypharmacy. In this regard, DeLong et al. [30] reported in a small study that ACEI/ARB associated with reduced free testosterone levels in HD men, proposing synergistic effects of reduced endogenous testosterone to ACEI/ARB-induced erythropoietin resistance. Agreeing with our previous report [11], we cannot confirm this observation, as this larger material shows a crude opposite direction for this association, which disappeared after correction for age. On the other hand, it is also possible that persistent inflammation may constitute another cause of testosterone deficiency, as hypogonadism is common in chronic diseases with an inflammatory component such as chronic lung obstructive disease [31] and heart failure [32]. Interestingly, testosterone replacement in hypogonadal men with diabetes or coronary disease shifts the cytokine balance to a state of reduced inflammation and vice versa [33,34]. Supporting this hypothesis, our results show a strong negative association between testosterone concentrations and serum inflammatory biomarkers.

CKD and CVD share many similarities. In both, there is a clear anabolic-catabolic imbalance with an excess of catabolic hormones and a deficiency of many anabolic hormones [8,35]. This aberration has, until recently, relatively been ignored, yet it is plausible that this hormonal derangement is a poor prognostic sign in both conditions and contributes to significant symptoms, as it has been proposed for chronic heart failure [36]. Indeed, an abundance of evidence relates testosterone deficiency with atherosclerotic complications, CVD and increased mortality risk in various pathologies [8-10,37]. Possible mechanisms include inhibition of the synthesis of endothelial progenitor cells involved in tissue repair [38,39], impaired vasodilation through decreased NO release or direct Ca\(^{2+}\) antagonism in vascular endothelial and smooth muscle cells [8], or aggravation of the perfusion capacity in the myocardium [40]. To relate, at least in part, the high prevalence of testosterone deficiency with the increased cardiovascular risk of ESRD patients is a tempting idea as treatment options are ready available. In our study, testosterone deficiency was associated to the presence of CVD and 3-year mortality in logistic regression analyses, irrespective of age and other confounders. Interestingly, in male haemodialysis patients, testosterone deficiency was linked with increased carotid artery intima-media thickness, atherosclerotic plaque occurrence and reduced flow-mediated dilatation [13]. Thus, these observations add to our previous report [11], and suggest altogether a novel link between reduced testosterone concentrations, CVD risk and mortality in this patient population.

Several limitations of the present study should be noted. Firstly, because it is a cross-sectional design, the present analysis is limited in its ability to establish causal relationships. Secondly, since this study combines two existing patient materials with different designs, selection bias may exist. However, to minimize this effect, the sampling phase was included as a covariate in regression analyses. Finally, because our analysis relies solely on testosterone values, it may have led to some misclassification; in particular, we do not have information on clinical signs of hypogonadism or current use of testosterone therapy. However, as discussed earlier, such medication is currently rare in ESRD clinical practice, and symptoms of hypogonadism have low specificity and coincide with those inherent to CKD, making its identification inaccurate. In any case, this limitation may result in underestimation of the true prevalence of male hypogonadism, and it rather reinforces the clinical implications of our results. Notwithstanding these possible limitations, our analysis has several strengths. Firstly, our clinical laboratory used uniform methods to collect data on serum testosterone concentrations. Secondly, testosterone deficiency was diagnosed according to widely accepted diagnostic criteria in this relatively large population of male ESRD patients. Finally, the availability of extensive and complete data on a wide range of important risk factors and end points, including inflammatory biomarkers, co-morbidities and deaths, allowed us to ensure a more unbiased estimate for these relations.

In conclusion, hypogonadism is a common endocrine dysfunction in male ESRD patients that shares links with important pathways (inflammation and cardiovascular morbidity) of the elevated mortality risk of this patient population. The possible adverse effects of testosterone deficiency on cardiovascular risk associated with CKD are presently unknown, and future clinical and experimental studies should explore causal mechanisms linking testosterone deficiency with uraemic-related derangements. Whether restoration of testosterone levels or supraphysiologic administration would diminish cardiovascular risk or improve nutritional status requires further investigation. Indeed, androgen therapy in uraemic patients has resulted in significant amelioration of muscle mass, nutritional status [41,42] and anaemia [7], pathways all of which could indirectly improve patient’s cardiovascular risk and ameliorate survival [43]. In any case, improvements at these levels are likely to improve quality of life and reduce disability in this patient population.

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Conflict of interest statement. None declared.

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