The vulnerable man: impact of testosterone deficiency on the uraemic phenotype

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Abstract
Testosterone deficiency or hypogonadism is a common finding in men undergoing dialysis, to a great extent a consequence of the failing kidney per se. Testosterone restoration in hypogonadism is common practice among endocrinologists. However, there is currently little awareness of this condition among both uremic patients and nephrologists, and in many cases, testosterone deficiency remains unscreened and untreated. This review article summarizes our current understanding of the role of testosterone deficiency at the crossroad of cardiometabolic complications of patients with chronic kidney disease. Pathways discussed include, among others, the plausible role of testosterone deficiency in the development of anaemia and ESA hyporesponsiveness, muscle catabolism, endothelial dysfunction, cognitive dysfunction, decreased libido, cardiovascular disease and mortality. As there are limited sources to guide decision-making, we also review existing testosterone replacement therapy studies in the context of CKD as well as considerations for side and adverse effects. This review makes a case for consideration of screening and better management of hypogonadism in men undergoing dialysis.

Keywords: anaemia; androgen; haemodialysis; hormone; men

A clinical example
A 59-year-old overweight man [body mass index (BMI) 28.6 kg/m²] and Type-2 diabetes was undergoing haemodialysis (HD) thrice weekly for 2 years due to chronic kidney disease (CKD). He reported a loss of 4–6 kg of body weight in the previous 3 months due to decreased appetite. In addition, he had felt depressed and fatigued for more than 6 months and was receiving relatively high doses of erythropoietin-stimulating agents (ESAs) (127 IU/kg/week) on top of the usual angiotensin-convverting enzyme inhibitor (ACEI), statins, phosphate binders, β- and Calcium (Ca) blockers. On a direct question from the nephrologist, he admitted that his libido had diminished and that he suffered from erectile dysfunction for quite some time. Laboratory values showed elevated C-reactive protein (7.8 mg/L), low serum albumin (33 g/L), low serum ferritin (50 µg/L) and low cholesterol (3.2 mmol/L) levels. DEXA examination revealed a t-score of −1.4 indicating osteopenia/osteoporosis. Most would agree that this man sadly stereotypes a large proportion of dialysis patients. As his nephrologist had read a review about testosterone deficiency, he ordered the analysis, and found low testosterone values of 7.6 nmol/L (normal 10.4–34.7 nmol/L).

Hypogonadism: the essence of the problem?
At a community level, testosterone deficiency or hypogonadism is present in ~17–30% of men aged 40–79 years, and its prevalence is clearly associated with ageing 1, 2]. Clinical symptoms of hypogonadism may be subtle but often include fatigue, decreased libido, erectile dysfunction, increased sleepiness, decreased energy and negative mood states [3]. Hypogonadism is also associated with changes in body composition, including decreased lean body mass, increased fat mass and decreased bone mineral density [4]. A higher risk of testosterone deficiency is observed in common medical conditions, such as Type-2 diabetes mellitus, obesity, depression, rheumatoid flares, hypertension and the metabolic syndrome [5–8]. As discussed in this review, testosterone deficiency is also a common feature of the failing kidney.

Whereas treatment of hypogonadism has been initiated primarily for relief of sexual symptoms, there is now increasing interest among endocrinologists in addressing the potential adverse metabolic and general health issues associated with hypogonadism. Indeed, testosterone has many functions other than its effect as a virilization agent; it is a potent anabolic hormone that associates with pathophysiological mechanisms involved in sarcopenia, anaemia, atherosclerosis, cardiovascular disease (CVD) and premature mortality. This review
article summarizes our current understanding of the role of testosterone deficiency at the crossroad of cardiometabolic complications in the general population and contextualizes this evidence using scarce data in CKD patients. However, there are limited sources to guide decision-making in commonly seen cases where testosterone replacement therapy may be considered, such as in the aforementioned clinical example. For that reason, we will also review existing testosterone replacement therapy studies in the context of CKD and considerations for adverse effects.

Physiology and natural course of endogenous testosterone during lifespan

Testosterone blood levels peak early in the morning and fade during the day. In blood, 70% of total testosterone is bound to the sex hormone-binding protein (SHBG) and the remainder is loosely bound to albumin, with only 1–3% present as free testosterone. The biologically active component of total testosterone comprises both free testosterone and that loosely bound to albumin. Although testosterone levels decline with ageing [2], this decline is progressive throughout life and there is no setting point as in women (menopause). Total testosterone declines with an absolute rate of ∼0.12 nmol/L per year (0.5–1% per year) [9]. Because SHBG increases with age, the rate of decline in the free testosterone fraction is faster [10]. For this reason, clinical cut-off for deficient endogenous testosterone usually does not take into consideration the individuals’ age. Although testosterone production from the testis is under the control of pituitary hormones, its degradation is influenced by the enzyme aromatase in adipose tissue cells, which converts it to oestrogen. Low blood testosterone level is much more common in obese individuals and those with metabolic syndrome. This is why some obese men appear to have some degree of feminization and a reduction in secondary sex characteristics. From an evolutionary perspective, testosterone is thought to increase in challenging situations relevant for reproduction [11] such as when competitors are confronted with a challenging opponent [12]. Indeed, a recent study described increasing testosterone levels in Spanish Soccer fans as they prepared for defence and/or enhancement of their social status during the 2010 World Cup Final [13].

Since testosterone synthesis is partially suppressed by multiple causes linked to a failing kidney, it is possible that the ‘normal’ progressive reduction in renal function with age contributes, at least in part, to this natural decline. No studies, to our knowledge, have, however, addressed this issue. The community-based PREVEND cohort suggested that risk factors such as age, BMI and plasma glucose contributed to exacerbating the male progression to ESRD to a greater extent than for comparable women [14]. It may not be coincidence that also ageing, diabetes and increased BMI are also associated with lower testosterone levels [4].

Testosterone deficiency in CKD: signs, symptoms and prevalence

Hypogonadism is the most common gonadal alteration in men with CKD due to the inhibition of luteinizing hormone signalling [15] and reduced prolactin clearance by the kidneys [16, 17]. Comorbid conditions commonly encountered in CKD patients, such as obesity, diabetes mellitus and hypertension, may further contribute to decreased testosterone levels [4–6]. Because nephrotic male rats develop hypogonadotropic hypogonadism secondary to an increased sensitivity of the pituitary to the negative feedback effects of testosterone [18], it is tempting to theorize that major urinary protein losses may also impact on free testosterone levels. Lastly, a variety of medications commonly prescribed to CKD patients such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), spironolactone, ketoconazole and glucocorticoids have been reported to interfere directly with the synthesis of sex hormones [16, 19]. Statin therapy may also contribute to decreased testosterone levels in non-renal populations [20, 21]. Finally, it has been reported that Cinacalcet decreased median total testosterone concentrations by 16% in dialysis patients (http://pi.amgen.com/united_states/sensipar/sensipar_pi_hcp_english.pdf). Proper assessment of hypogonadism relies critically on accurate evaluation of serum testosterone, and to a lesser extent, on medical history or patient self-report. This is particularly true in aged individuals and in CKD patients, where many of the signs and symptoms of hypogonadism are insidious in onset and accompany the progression of the disease. On the basis of laboratory testings, recent reports (Table 1) estimate an ∼40–60% prevalence of hypogonadism in men undergoing dialysis (Figure 1). Although insufficient information exists regarding the prevalence of this syndrome in CKD patients not requiring dialysis, it seems proportional to the reduction in renal function [22]. The use of total testosterone concentration for diagnosis of hypogonadism in generally elderly populations (Table 1) probably results in underdiagnosis, because SHBG increases with age and albumin decreases as acute-phase reactant. In fact, the study of Yilmaz et al. [22] reports a considerably higher prevalence of hypogonadism when the definition is based on free testosterone levels. Finally, the value of salivary testosterone for diagnosis of androgen deficiency in CKD was recently discussed [23].

Testosterone deficiency and renal anaemia: is suppression of hepcidin the link?

Anaemia and hyporesponsiveness to ESA are commonly observed in CKD patients and is associated with increased morbidity, mortality and a high healthcare economic burden [24]. Although many reasons for ESA resistance exist, low testosterone levels have not been well discussed. A well-known side effect of testosterone therapy in non-renal populations is polycythaemia. As the
anti-anaemic effect of testosterone supplementation seems to be of clinical significance [25], it may not be surprising that orchiectomy causes a decrease in haemoglobin levels of ~12 g/L [26]. Likewise, hypogonadal ESA-naïve CKD patients were more likely to be anaemic, despite adjustment for important anaemia risk factors [27]. In addition, hypogonadal ESA-treated dialysis patients were more likely to have high ESA dosages [27]. Thus, male hypogonadism may represent a contributing factor to renal anaemia.

Although the exact mechanism(s) by which testosterone stimulates erythropoiesis are not evident, it seems that testosterone does stimulate erythropoietin production and erythroid progenitor cells [28]. Nevertheless, Coviello et al. [29] showed that although testosterone was associated with an increase in haemoglobin, erythropoietin levels did not change. Recent evidence demonstrates that testosterone acts instead on iron metabolism via inhibition of hepcidin [30]. Indirectly supporting this hypothesis, an association between low testosterone levels and high levels of hypochromic red blood cells was reported in male dialysis patients [27]. As hepcidin synthesis in the liver is up-regulated by persistent inflammation [31, 32] and testosterone supplementation suppresses inflammatory biomarkers [33], testosterone may also suppress hepcidin synthesis indirectly via inflammatory signals.

Testosterone has not been well discussed in the renal literature, since the ‘pre-ESA period’ during the 1970–80s when androgens were used to treat renal anaemia [34]. Because hypogonadal CKD men are a subgroup of patients predisposed to anaemia and ESA hyporesponsiveness, it is plausible that restoration of testosterone levels in these patients may translate into better haemoglobin values and better ESA responsiveness. A number of past studies have addressed androgen supplementation in dialysis patients (both men and women) as a means to improve erythropoiesis [34, 35]. Some [36–38], but not all [39], studies suggest that the combined use of ESA and androgens elicit higher haematocrit than ESA alone. There are, however, no studies that have tested the implications of testosterone restoration in uremic hypogonadism on ESA resistance. In support of this possibility, a small retrospective study showed that nandrolone decanoate administration increased lean body mass in nine malnourished non-hypogonadal HD patients [40]. In addition, haematocrit increased and this translated into reduced ESA dosages for half of the patients.

**Testosterone deficiency and muscle stores in the pro-catabolic uraemic environment**

Muscle mass, muscle strength and exercise capacity are major determinants of physical function that decline with ageing, particularly in the uraemic milieu. This contributes to the high incidence of frailty and disability observed in the risk of adverse outcomes [41], and in the accumulation of body fat and development of insulin resistance. Muscle synthesis and muscle adaptation to exercise is strongly influenced by anabolic endocrine hormones and local load-sensitive autocrine/paracrine growth factors. Among those, GH, insulin-like growth factor (IGF)-I and testosterone are directly involved in the process as they promote muscle protein synthesis.

Epidemiological evidence in non-renal populations supports the relationship between age-related testosterone decline with the deterioration in muscle mass, strength and functional status [42, 43]. Hypogonadal men present lower lean body mass, appendicular body mass or impaired myofibrillar protein synthesis in several cross-sectional population-based studies [44–47]. Recent observational studies have also shown a positive association between low testosterone levels and the decline in physical function, mobility and occurrence of falls in older

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**Table 1. Prevalence of hypogonadism in men with CKD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Origin</th>
<th>Patients considered</th>
<th>Age</th>
<th>Definition of deficiency (nmol/L)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albaaj et al.</td>
<td>UK</td>
<td>214 predialysis, dialysis and Tx</td>
<td>M 52</td>
<td>TT &lt; 10</td>
<td>26%</td>
</tr>
<tr>
<td>Karakitsos et al.</td>
<td>Greece</td>
<td>100 non-diabetic HD patients</td>
<td>A 48</td>
<td>TT &lt; 10</td>
<td>50%</td>
</tr>
<tr>
<td>Carrero et al.</td>
<td>Sweden</td>
<td>126 HD patients</td>
<td>M 63</td>
<td>TT &lt; 10</td>
<td>52%</td>
</tr>
<tr>
<td>Gungor et al.</td>
<td>Turkey</td>
<td>420 HD patients</td>
<td>A 54</td>
<td>TT &lt; 10</td>
<td>66%</td>
</tr>
<tr>
<td>Kyriazis et al.</td>
<td>Greece</td>
<td>111 HD patients</td>
<td>A 65</td>
<td>TT &lt; 8</td>
<td>44%</td>
</tr>
<tr>
<td>Yilmaz et al.</td>
<td>Turkey</td>
<td>239 CKD 1–5 patients</td>
<td>A 54</td>
<td>TT &lt; 10</td>
<td>33%, in Stage 5 = 57%</td>
</tr>
<tr>
<td>Carrero et al.</td>
<td>Sweden</td>
<td>262 CKD 5 patients</td>
<td>M 59</td>
<td>TT &lt; 10</td>
<td>44%</td>
</tr>
</tbody>
</table>

Tx, renal transplant patients; HD, haemodialysis; M, median; A, average; TT, total testosterone; T, testosterone.
men [48, 49]. Based on this evidence, hypogonadism or testosterone deficiency in men with CKD may be an additional risk factor contributing to muscle wasting. Interestingly, markers of muscle mass were significantly reduced and predicted outcome in men starting dialysis, but not in women [50, 51]. In support of this hypothesis, we observed that adjustment for creatinine levels (as a reflection of muscle stores in patients with minimal or no residual function) abrogated the association between hypogonadism and mortality in male dialysis patients [52].

Testosterone is an anabolic hormone that plays an important role in inducing skeletal muscle hypertrophy by promoting nitrogen retention, stimulating fractional muscle protein synthesis, inducing myoblast differentiation and augmenting the efficiency of amino acid reuse by the skeletal muscle [42]. Testosterone suppresses myostatin expression [53], inhibits apoptosis [54], induces muscle mRNA IGF-I expression [55] and mediates body compositional changes by affecting the differentiation of mesenchymal-derived pluripotent stem cells [42]. These stem cells, which are present in both muscle and fat tissue, are committed to the myogenic lineage and inhibited from the adipogenic lineage with testosterone usage [42]. Thus, androgen supplementation translates into reciprocal body composition changes in muscle mass gain and fat mass loss [56, 57].

In frail men exhibiting low or diminished testosterone levels, testosterone replacement therapy improved muscle strength and indicators of physical function [58, 59]. Johansen et al. [56, 57] demonstrated that androgen supplementation can also improve muscle mass and strength in non-hypogonadal malnourished male and female CKD patients. This effect was, however, not observed in a controlled study of hypogonadal CKD male patients treated with placebo or transdermal testosterone gel for 6 months [60]. Not only compliance issues but also the analysis of secondary outcomes and the lower bioavailability of transdermal administration may have influenced at this level [60]. Thus, further studies are necessary to assess if uremic hypogonadism cures with low muscle mass and strength, and if restoration of testosterone levels to normal can ameliorate muscle stores in this wasted patient population.

Testosterone and the GH/IGF-1 axis represent different anabolic pathways. Existing convincing evidence that these two hormones stimulate each other’s productions and potentiate their respective anabolic effects [55, 61]. Recent studies have reported that the combined administration of GH and testosterone resulted in greater anabolic efficacy than either hormone alone [62, 63]. Curiously, elite athletes seem to have come to this conclusion much earlier than scientists; quoting Giannoulis et al. [61], ‘Ben Johnson won a gold medal in the 100 meters in the 1988 Olympic Games in Seoul. It was soon rescinded when he tested positive for anabolic steroids. He subsequently admitted under oath that he took human GH in addition to the anabolic steroids. The first peer-reviewed papers on the effects of GH given to adults did not appear until 1989. Given the positive anabolic effects that GH and androgens have per se in uremic patients, this combined approach could certainly be an interesting and yet unexplored therapy for combating the wasting/sarcopenia of CKD.

**Testosterone deficiency, sexual function, mood and cognitive function**

Sexual dysfunction remains a problem in male dialysis patients. Whereas studies in non-renal patients show that testosterone supplementation consistently improve libido, the effect on erectile dysfunction appears to be more doubtful [64]. A small study in dialysis patients observed that correction of biochemical hypogonadism with testosterone rarely restores sexual function to normal [65]. Although a meta-analysis by Zarrouf et al. [66] showed some beneficial effects of testosterone on depression scores in the general population, the effects of testosterone replacement on mood and quality of life have not been consistent across trials and current evidence does not support testosterone supplementation as an antidepressant. In the general population, the effects of testosterone on memory and measures of cognitive function have shown mixed results, probably as a result of the low sample sizes and short-term follow-up [64]. In most studies, an improvement in spatial memory was reported. As male CKD patients are at increased risk of both cognitive dysfunction [67] and depression [68], it would be interesting to test if restoration of testosterone deficiency positively impacts on mood and cognitive function.

**Testosterone deficiency and bone health**

Testosterone plays an important role in bone mineral density by increasing osteoblastic activity and reducing osteoclastic activity [45] and in ageing men, there is a strong association between low testosterone and bone loss [69]. Conversely, the osteoblast-derived hormone osteocalcin, in addition to its endocrine role as a regulator of energy homeostasis, favours male fertility by promoting testosterone synthesis by Leydig cells in the testes [70]. Although no intervention study has yet been large enough (neither in sample size nor study duration) to demonstrate a reduction in fracture risk with testosterone supplementation, a meta-analysis suggested that testosterone replacement positively affects bone density and reduces bone loss [71]. A small study of men undergoing HD reported that testosterone correlated negatively with sRANKL concentrations, and the authors proposed that RANKL might mediate the effect of testosterone on bone metabolism in these patients [72]. No studies have addressed the impact of testosterone deficiency on uraemic bone status.

Meng et al. [73] reported an unexpected inverse association between testosterone levels and serum phosphate in two large, independent community-based cohorts of older men, even after adjustment for eGFR and oestradiol. The authors speculated that this association may reflect enhanced deposition of phosphate in the bone, reduced bone resorption or unrecognized effects of testosterone on gastrointestinal absorption or renal phosphate excretion. However, a subsequent analysis in CKD patients could not confirm this finding, and the association between testosterone and phosphate was largely dependent on PTH [74]. Perhaps, bone mineral disorders in uraemia may
override the associations of endogenous testosterone and phosphate observed at a community level. A final mechanism by which testosterone may be of further interest pertains to recent reports on an association between 25(OH)-D-vitamin and testosterone levels in community-dwelling men [75–77]. Pilz et al. [78] recently demonstrated that daily vitamin D supplementation increased testosterone levels in men without renal disease. Further studies are needed to understand the links between these pathways and to test if supplementation with native D-vitamin can normalize testosterone levels in CKD or vice versa.

Testosterone deficiency and cardiovascular risk

Men are between two and three times more likely to die prematurely from CVD than women. Likewise, in dialysis patients, death due to CVD is higher in men when compared with women [79]. Why male gender is such a strong cardiovascular risk factor is not completely understood. From an evolutionary perspective, the ‘antagonistic pleiotropy hypothesis proposes that hyperactivation of m-TOR by testosterone renders robust men at young reproductive ages at the cost of an accelerated ageing process [80]. Hypothesis apart, the explanation of this gender difference has largely been based on the supposition that sex hormones are cardioprotective in women and have adverse actions in men. There is, however, little medical evidence to support the premise that testosterone is ‘bad for the heart’. On the contrary, recent evidence points that low testosterone is more likely to be associated with atherosclerosis development than gender per se.

The majority of cross-sectional epidemiological studies report low testosterone in CKD patients with CVD [81]. In the meta-analysis of Corona et al. [82] in healthy men, low testosterone consistently associated with the presence of CVD. In dialysis patients, those with the history of CVD also displayed lower testosterone levels than their counterparts, even when age and other potential confounders were taken into account [52, 83, 84]. Testosterone negatively correlates with in vivo surrogate markers of atherosclerosis in non-renal populations, including intima media thickness (IMT) of the carotid artery wall and the degree of aortic calcification [85, 86]. Likewise, testosterone was inversely associated with flow-mediated dilatation in non-dialysed CKD patients [74] and directly linked with increased IMT, atherosclerotic plaques [87] and pulse wave velocity [84] in men undergoing HD. The recent report of Zhang et al. [88] showed in two independent population-based cohorts that high testosterone levels were associated with shortened QT-interval duration, which could indirectly explain the differences in cardiovascular risk between men and women earlier alluded to, as well as the increased susceptibility to arrhythmias in ageing men. Consequently, experimental models and animal studies demonstrate that testosterone administration shortens QT-interval duration [89, 90]. Although mean decreases are small and unlikely to affect risks of arrhythmic events in patients receiving Q-T prolonging medications, the implication of this finding in the pro-arrhythmic uraemic milieu need consideration.

Low testosterone levels are predictors of future cardiovascular events, independently of age. In 239 non-dialysed CKD patients, Yilmaz et al. [74] reported that the risk of cardiovascular events (fatal and non-fatal) was reduced by 22% for each nanomole per litre increment of total testosterone. Low testosterone levels were also found to predict CVD death in two dialysis populations [52, 84]. This evidence agrees with most large population-based prospective studies and studies in individuals with pre-existing CVD or diabetes [91–97]. Both Ruige et al. [98] and Corona et al. [82] concluded in their meta-analyses that endogenous testosterone in healthy men do associate with reduced risk of cardiovascular events. However, and although independent from other risk factors, these associations were in general weak and more prominent among individuals above 70 years of age. It has been proposed that testosterone may just be a marker of health and reflect underlying CVD. In a prospective population-based cohort study with 2416 men (aged 69–81 years), those in the highest quartile of testosterone had a 30% lower risk of CV events [99]. Because this association was not materially changed in analyses excluding men with pre-existing CVD, this study supports the hypothesis that testosterone per se may be linked to this risk over and above underlying CVD. Data from basic and interventional studies discussed below suggest different mechanisms of action by which the gonads may in fact influence heart and vasculature.

When the gonads talk to the heart: potential mechanisms of action

Testosterone may indirectly relate to cardiovascular complications by its association with risk factors such as dyslipidaemia, obesity, diabetes, metabolic syndrome or old age, which may contribute to endothelial dysfunction and atherosclerosis. Nevertheless, testosterone seems to play a role per se in lipid metabolism by affecting lipoprotein lipase and lipolysis, and in several disease populations, testosterone supplementation has resulted in modest reductions of both total and LDL cholesterol without affecting triglycerides [64]. A recent meta-analysis reported a small, but significant, decrease in HDL cholesterol as well [25]. Hypogonadism may also indirectly impact on cardiovascular health via insulin sensitivity, which seems improved after testosterone supplementation in Type-2 diabetic patients [64].

Furthermore, testosterone may have direct actions in the cardiovascular system. An atheroprotective effect of testosterone was demonstrated by Nettleship et al. [100], in which a high-fat diet was given to a naturally testosterone-deficient mouse model, inducing lipid deposition in the aortic root (fatty streak). Testosterone therapy in such model importantly ameliorated this lipid streak formation. Because of aromatization to oestradiol, testosterone is considered a pro-hormone and oestrogen has cardiovascular properties as well that can link to the effects hereby observed. The authors pharmacologically blocked the oestradiol and aromatase pathways, and the mouse model
was deficient in androgen receptors, suggesting that the mechanisms of testosterone on the endothelium are different and independent of these pathways.

Transdermal testosterone therapy improved exercise-induced myocardial ischaemia during an exercise stress test in men with stable angina [101]. These vasodilatory effects of testosterone on coronary and other vasculature were confirmed by the findings that men with prostate cancer undergoing androgen-deprivation therapy experience an increase in central arterial pressure [102]. Just to mention a few, animal experiments also suggest inhibitory effects of testosterone supplementation on neointimal plaque development [103]. Other mechanisms of action of testosterone include stimulation of endothelial progenitor cells [104], increasing nitric oxide release from vascular endothelial cells [105], or perfusion enhancement in the myocardium [106, 107].

Finally, uraemia is a pro-inflammatory condition, and inflammation is an established promoter of atherosclerosis [108, 109]. The hypothalamic-pituitary-testicular axis is suppressed by inflammatory cytokines [110, 111], and therefore, any inflammatory disease may induce testosterone deficiency. Thus, low testosterone could be considered a biomarker of this illness. In support of this, studies depict a strong inverse association between endogenous testosterone and surrogates of inflammation in various CKD populations [52, 83, 84, 87] (Figure 2). However, it is also possible that testosterone has immunomodulatory actions per se, as suggested by the suppression of cytokine production in hypogonadal men with diabetes, coronary heart disease and metabolic syndrome after supplementation with testosterone [33, 112, 113].

Testosterone deficiency and mortality risk: causal effect or just an epiphenomenon?

At a general population level and in specific pathologies, epidemiological evidence relates testosterone deficiency with increased mortality risk. The largest of these studies is the report from Khaw et al. [92], who examined the relationship between testosterone and mortality in a nested case–control study, including 11,606 men aged 40–79 years. The authors showed that testosterone was inversely related to all-cause and CVD mortality. Similar associations have also been reported by us in HD patients [52] (Figure 3), results subsequently confirmed in other patient populations [83, 84]. These studies are limited by a relatively low sample size and in some cases, categorization of the variables of interest. A Turkish study observed a rather strong impact of testosterone on the mortality of HD patients, but this was largely dependent on age [114]. In another study, the presence of kidney dysfunction (CKD stage 3–5) and low testosterone levels was additive mortality risk factors [115]. The inability of these observational studies to denote causality leave us, in any case, with the uncertainty of whether we are facing a novel risk factor in uraemia or a risk marker of unmeasured confounders and/or underlying complications.

A meta-analysis including community-based studies of generally healthy men recently assessed this issue addressing the association between testosterone levels and mortality [116]. This analysis included 11 studies with more than 16,000 individuals and showed that low endogenous testosterone levels are associated with increased risk of

![Fig. 2. Univariate associations between serum testosterone and IL-6 among 260 ESRD men. Reproduced from Carrero et al. [83].](image)

![Fig. 3. Kaplan-Meier survival analysis for (A) all-cause and (B) CVD-related mortality in prevalent men undergoing HD according to testosterone levels. Low testosterone levels were defined below the 33rd percentile of testosterone distribution (8 nmol/L). Reproduced from Carrero et al. [52].](image)
all-cause and CVD death in community-based studies of men. However, the authors report considerable between-study heterogeneity, which limits somehow the validity of these summary estimates. Based on these results, one plausible conclusion is that a low testosterone level at a general population level is due to pre-existing diseases and therefore simply a marker for general health. This hypothesis is supported by the fact that acute as well as chronic diseases, such as CKD, lower testosterone production is due to decreased synthesis in the testis. Another possible explanation is that low testosterone levels caused by pre-existing diseases might contribute to other diseases resulting in an increased risk of fatal events. This is supported by experimental evidence previously discussed, suggesting a role of testosterone per se in atherosclerosis, cardiac failure or muscle synthesis. If this is the case, restoration of uraemic hypogonadism is likely to positively impact on various physiological pathways that may directly and indirectly impinge upon both the prognosis and quality of life of uraemic patients.

The paradox of kidney disease progression in men

The progression rate of renal disease is in general faster for men than for women [117, 118]. To explain faster progression in men, animal models of kidney injury have shown that orchidectomy in male rats attenuated the development of glomerular and tubular damage, kidney fibrosis as well as proteinuria [119, 120]. Other animal studies [121–123] point towards pro-inflammatory, pro-apoptotic and pro-fibrotic effects for testosterone during acute and chronic kidney injury. Androgens may also increase tubular sodium and water reabsorption activating both the renin–angiotensin and endothelin systems [124]. However, it is difficult to extrapolate such experimental findings into clinical observations, given that testosterone levels are diminished with reduced kidney function and that both CKD and progression to ESRD occur mainly in the elderly, which should at the same time present lower testosterone levels. On the basis of these animal studies, it can be theorized that testosterone supplementation may damage the kidney and accelerate the progression of CKD. Doublier et al. [125] showed that testosterone supplementation induced podocyte apoptosis in female oestrogen receptor knockout mice. However, a study in male STZ-induced diabetic rats demonstrated that it is not the absolute levels of testosterone that renders male sex as a risk factor, but rather, a relative imbalance of testosterone to oestradiol and progesterone [126]. Again, we do not know if this is true in the clinic, and no study has to date showed any increased risk of renal injury after testosterone supplementation in any patient population. In a small interventional study, 29 non-dialysed patients with CKD (GFR 5–30 mL/min) and malnutrition were randomly assigned to nandrolone decanoate or placebo during 3 months [127]. The authors reported anabolic effects without altering renal function. Nevertheless, regular monitoring of renal function should be advocated if testosterone supplementation is given to CKD patients.

Safety concerns with testosterone replacement

Several reviews at a general population level have gathered data regarding adverse events associated with testosterone supplementation in men (Table 2), but have not provided solid evidence regarding the safety of testosterone treatment [25, 128, 129]. The imprecision, high heterogeneity of the trials contemplated to date and their methodological limitations may nevertheless explain the inconsistent findings across the reported studies. In particular, the brief duration of most testosterone trials limits inferences about the long-term safety of this treatment.

The greatest concern of physicians with regard to testosterone therapy is the possibility of stimulating prostate cancer [130]. This concern derives from the use of androgen deprivation for the treatment of advanced prostate cancer [131]. Testosterone supplementation has been contraindicated in men with prostate cancer because these tumours are androgen sensitive. However, and despite decades of research, available data fail to demonstrate a causative role for testosterone in this association [132]: a large international study of men with prostate cancer and age-matched controls found no links between prostate cancer risk and serum concentrations of total or free testosterone [133, 134]. In addition, a meta-analysis of adverse events from 19 randomized controlled studies in hypogonadal men found no differences in the risk of prostate cancer among patients receiving testosterone therapy or placebo [135]. Several studies have shown that testosterone administration in healthy older men can increase PSA levels significantly compared with placebo [61]. The increments observed, however, do not render PSA levels above the normal upper limit nor did the incidence of prostate-related events differ [61]. Nevertheless, caution is necessary when administering this treatment and regular PSA monitoring is required both prior and during testosterone treatment [136].

Androgen therapy has been linked to atherosclerosis, erythrocytosis, dyslipidaemia, ventricular hypertrophy and cardiac dysfunction [25, 137]. In particular, a recent
meta-analysis described a small decrease in HDL cholesterol associated with testosterone therapy [25]. Some of these potential associations stem from anecdotal observations in cases when testosterone was administered at supraphysiological levels, namely among users of anabolic steroids. Instead, when administered at physiological levels, decreased ventricular mass and increased cardiac indices have been reported [138]. The erythropoietic-stimulating effects of testosterone are regarded as an adverse event at a general population level, but it may represent an indirect asset in the treatment of renal anemia. Although believed uncommon, pharmacological dosages of testosterone may induce or worsen sleep apnoea [139]. Finally, an increase in blood pressure and clinically significant oedema may seldom occur after testosterone administration in healthy older men [25, 128, 129]. In male HD patients treated with testosterone, fluid retention has been reported as an adverse event [65], and because of that there is a general warning in labels of testosterone products about precautions in CKD patients. Finally, some possible formulation-specific adverse effects may occur, in particular in the case of intramuscular injection pain and bleeding may be present in uraemic patients on anticoagulants [128]. Recently, Basaria et al. [140] reported an increase in cardiovascular events after application of supraphysiological dosages of a testosterone gel in older men with frailty, limitations in mobility and a high prevalence of chronic disease. This is not what has been seen in the other testosterone replacement therapy trials in populations of men with vascular disease. Nevertheless, it highlights the need for more large-scale randomized controlled trials of testosterone therapy. It is possible that frailty and limited mobility are conditions that would limit and perhaps negate the purported benefits of this anabolic treatment. Considering these relatively prevalent conditions in uraemia, stringent vigilance and caution during testosterone restoration in CKD patients is recommended.

In conclusion, testosterone administration in healthy older men in near physiological doses and aiming to restore deficiency does not appear to incur serious adverse events, although long-term safety has not been established and regular monitoring of PSA is required. As a consequence ‘The Endocrine Society Task Force’ [136] currently recommends testosterone therapy in androgen-deficient men. Target testosterone levels should be within normal to mid-normal physiological ranges. Testosterone treatment is considered contraindicated in patients with prostate cancer, a palpable prostate nodule, prostate-specific antigen levels above 4 ng/mL or above or equal to 3 ng/mL in men at a high risk for prostate cancer, haematocrit above 50%, untreated severe obstructive sleep apnoea, severe lower urinary tract symptoms due to prostatic hypertrophy or poorly controlled heart failure.

Testosterone replacement therapy in hypogonadal uraemic men: should we?

The patient presented in this review is at increased risk for metabolic disorders/complications and is likely to die from premature CVD. The presence of low-serum testosterone concentrations provides an opportunity not only to treat his symptoms of fatigue and sexual dysfunction, but also to reverse or improve, at least in part, some of these metabolic and nutritional complications while decreasing his cardiovascular risk.

Surprisingly, few studies have tested the consequences of restoring testosterone deficiency in the CKD patient over and above mere sexual function. One of the challenges of uraemia is that kidney failure virtually affects every organ and pathophysiological pathway in the body. Unable to solve all arising complications, nephrologists by necessity must focus on the most crucial and direct risks. To date, most nephrologists may have relegated testosterone deficiency to that box of ‘innocent uraemic bystanders’ that can sometimes be buried in oblivion. In an increasingly old dialysis population, we may rightfully say that ‘libido issues’ are less urgent that bone-mineral or wasting disorders. Ignorance on the topic, reluctance to use hormonal therapy or therapeutic nihilism due to the large number of negative randomized controlled trials in dialysis patients may also contribute. However, the information collected throughout this review suggests, conversely, that besides sexual desire, testosterone deficiency may contribute to the uraemic phenotype, rendering males more vulnerable to uraemia. There is no or little debate among endocrinologists about replacing testosterone in hypogonadism, as there are major physical and psychological benefits and, potentially, a survival advantage. Replacement of hormones to normal physiological levels is routine in endocrinological practice. Today, testosterone can be effectively replaced to the normal physiological range through various routes of administration. Information in this review may make a case for consideration of screening and better management of this syndrome in the male dialysis population. The renal community is in need of sustained evidence on the purported benefits of correction uraemic hypogonadism. Finally, because low testosterone levels are also predictors of cardiovascular events in postmenopausal women [141], studies that examine the clinical outcomes associated with low testosterone levels in uraemic women should follow.

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Resistant hypertension and the neglected antihypertensive: sodium restriction

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Abstract

Resistant hypertension is defined as blood pressure (BP) that remains above goal (such as 140/90 mmHg or more) in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts. Prevalent among 15% of the treated hypertensives, the risk factors for resistant hypertension include older age, chronic kidney disease (CKD), obesity and diabetes mellitus. Causes of resistant hypertension can be classified into four groups: poor adherence, biological–behavioral factors, CKD and secondary causes, and drugs or exogenous substances. However, before labeling the diagnosis of resistant hypertension, it is important to exclude pseudo-resistant hypertension using home BP monitoring in most patients and ambulatory BP monitoring in a few. Before thinking about the next antihypertensive drug, it is important to restrict dietary sodium. Educating the patient on how to interpret the food label and providing feedback by assessing sodium intake with 24 h urine collection are effective sodium restriction strategies. Sodium restriction can lower BP and among patients with proteinuria can even enhance the anti-proteinuric effects of drugs that block the renin–angiotensin system. Sodium restriction is therefore a valuable but a neglected antihypertensive.

Keywords: dietary intake; hypertension; resistant hypertension; sodium

Resistant hypertension: definitions and epidemiology

According to the definition endorsed by the American Heart Association, resistant hypertension is defined as