Sexual hormone abnormalities in male patients with renal failure

Alice Schmidt¹, Anton Luger² and Walter H. Hörl¹

¹Division of Nephrology and Dialysis and ²Division of Endocrinology, Department of Internal Medicine III, University of Vienna, Vienna, Austria

Introduction

Endocrine abnormalities are a common feature of chronic renal insufficiency [1,2]. Changes of androgen synthesis and metabolism develop early after the onset of renal insufficiency and are likely to be caused by primary hypogonadism and/or disturbances of the hypothalamic–pituitary axis. Uraemic toxins, co-morbidity, and concomitant drug administration are supposed to contribute to the observed changes, yet the exact mechanism remains unclear. Impaired function of the hypothalamic–pituitary–gonadal axis is not reversed by initiation of otherwise effective haemodialysis or peritoneal dialysis therapy. In contrast, renal transplantation was reported to restore endocrine function, but study results are conflicting. A complete normalization as well as persistingly low testosterone levels have been described after transplantation and gonadotrophin levels were also reported to be persistingly high or normal [3,4].

Pathophysiology and pathogenesis

In male patients with renal failure, plasma testosterone levels are decreased or in the low normal range in the face of an increase in the elevated gonadotrophins, LH (luteinizing hormone), and FSH (follicle-stimulating hormone). These changes are likely to be the consequence of a combined abnormality. The pulsatility of hypothalamic GnRH (gonadotrophin releasing hormone) release is known to be essential for adequate pituitary gonadotrophin synthesis [5]. Therefore, it was speculated for a long time that either a decrease of GnRH-pulse frequency or diminished answer of the pituitary gland might be responsible for the abnormalities of androgen synthesis in uraemia. Using ‘deconvolution analysis’ of blood samples of patients with renal insufficiency (obtained at 10-min intervals throughout a period of 24 h), Veldhuis et al. [6] were able to identify abnormalities of the GnRH-pulse generator with a decrease of GnRH-pulse strength but an unaffected GnRH-pulse frequency.

Furthermore, low testosterone levels are not able to induce adequate gonadotrophin synthesis in uraemia, suggesting an additional impaired feedback mechanism at the hypothalamic–pituitary level. On the other hand, peripheral Leydig-cell resistance seems to be responsible for the moderately decreased testosterone production despite mildly elevated gonadotrophin
levels. These changes of the hypothalamic–pituitary–gonadal axis function in renal insufficiency are combined with a decreased metabolic clearance of at least GnRH, LH, FSH and prolactin.

Aetiology

Several aetiologic factors appear to contribute to the described changes. Recently, a circulating LH–receptor inhibitor was suggested, which might contribute to Leydig-cell resistance and impaired feedback mechanisms at the hypothalamic–pituitary level [7]. Furthermore, decreased urinary LH excretion in uraemia causes elevated LH blood levels and LH subtypes. Less acidic and bioactive LH forms might thus contribute to the decrease in testosterone production [8]. Hyperprolactinaemia in renal insufficiency is partially induced by a decreased metabolic clearance but also by autonomic overproduction. At least primary hyperprolactinaemia leads to (secondary) hypogonadism [9]. Co-morbidity, especially critical illness, might further contribute to disturbances of sexual hormone synthesis. For example, malnutrition and obesity lead to a decrease of LH-pulse strength. Critical illness and diabetes mellitus were reported to induce a combination of primary and secondary hypogonadism. Furthermore, an inverse correlation between hypertension and low testosterone levels was described [10]. Hyperparathyroidism stimulates prolactin synthesis and hyperprolactinaemia is, as already mentioned, also associated with secondary hypogonadism. In addition, ageing induces changes of sexual hormone synthesis. The age-related increase in SHBG (sex hormone binding globulin) levels (+1.2%/year) further induces a more distinct fall in free (=active) testosterone (−1.2%/year) than in total (=protein bound and free) testosterone levels (−0.4%/year) [11].

Several drugs are also known to interfere directly with the synthesis of sexual hormones and their effects. Spironolactone and cimetidine block androgen receptors and spironolactone additionally reduces 17α-hydroxylase/C17-20 lyase activity, leading to reduced testosterone biosynthesis. Glucocorticoids decrease testosterone synthesis directly via gonadal steroid receptors and centrally at the hypothalamic–pituitary level. Cyclosporin A and tacrolimus exhibit, at least in animals, a direct toxic effect on Leydig cells and the hypothalamic–pituitary axis. Like spironolactone, ketoconazole leads via enzyme inhibition (17-20 lyase) to a decrease of androgen synthesis. Tricyclic antidepressants, benzodiazepines, and opiates may induce secondary hypogonadism through central mechanisms [10].

Consequences of androgen deficit

Androgen deficit in adults causes changes in body composition comparable with those observed with GH deficiency [12]. Body mass index (BMI) increases via an increment of body fat, while lean body mass is reduced. An androgen deficit is thus associated with reduced muscle mass, osteoporosis, and a higher incidence in bone fractures. In addition to its negative effects on body composition, the androgen deficit also causes impaired libido and sexual function and might lead to depression [11,13].

Therapy

Symptomatic patients with elevated prolactin levels may benefit from a trial with dopamine agonists like bromocriptine. Bromocriptine was shown to improve sexual function, presumably by reducing elevated circulating prolactin levels. Unfortunately, there is a high frequency of side effects. Newer dopamine agonists such as cabergoline have a lower rate of side effects; however, their usefulness in this context is not yet proven [9]. Clomiphene citrate has also been reported to cause a normalization of testosterone levels [14]. Administration of zinc in zinc-deficient patients might be a reasonable therapeutic option [15].

Erythropoietin treatment is known to improve quality of life with an increase in exercise tolerance, life satisfaction and happiness. In addition, it was shown that erythropoietin therapy improves sexual function, normalizes the pituitary–gonadal feedback mechanism with reduction of plasma LH and FSH concentrations and increases plasma testosterone levels in patients with chronic renal failure. Furthermore a reduction in elevated prolactin levels has been described [16–19]. Controlling the severity of secondary hyperparathyroidism might also be of benefit by lowering prolactin levels in some patients [20].

Another therapeutic option may be the substitution of androgens. Prior to the introduction of recombinant human erythropoietin in 1989, transfusions and androgens were the mainstay of treatment of anaemia due to chronic kidney diseases. In addition to its effects on haematopoiesis, androgen therapy is associated with positive nutritional and anabolic effects [21,22].

Side effects of androgen therapy

Careful monitoring of androgen substitution therapy is mandatory because of possible side effects, such as weight gain, the development of oedema, gynaecomastia, and polycythaemia with an increased risk of thrombosis. Furthermore, androgens induce prostate growth, resulting in hypertrophy, and possibly also in the progression of occult microcarcinomas in older men. Additionally, androgens may have negative effects on serum lipids, resulting in higher triglycerides with a reduction in HDL cholesterol, thereby increasing the risk for cardiovascular events [11,21,22]. Conversely, there is increasing evidence in the literature that low levels of androgens are associated
with adverse cardiovascular risk factors, including an atherogenic lipid profile, systolic and diastolic hypertension, obesity, insulin resistance, and raised fibrinogen in humans. The acute intravenous administration of testosterone has been demonstrated to have a marked antiischaemic effect in men with coronary artery disease [23].

**Progression of renal disease by androgens?**

Observations in animals and humans indicate that there is an association between male gender and a more rapid progression of kidney diseases, independent of blood pressure and cholesterol levels.

In ovariectomized rats, for example, testosterone but not oestrogen substitution therapy led to severe histologic changes with proteinuria after a treatment course of 16 weeks [24].

There are also gender-related differences in the morphology and the function of kidneys, resulting in bigger size, higher numbers of nephrons, greater intrarenal blood flow, and higher intrarenal resistance in male rats. These effects are supposed to be mediated partially by intrarenal hormone receptors, which are localized in most parts of the nephron. Androgens, but also to some extent oestrogens, stimulate the proliferation of mesangial cells and matrix accumulation as well as the synthesis of cytokines, vasoactive substances (renin–angiotensin system, endothelins) and growth factors (growth hormone, IGF-1), which may contribute to the progression of kidney diseases. On the other side, oestrogens may also have some protective effects in kidney diseases, by lowering plasma lipids and by antioxidative effects on cell membranes [25].

Gender-related differences have been described concerning also the incidence of several renal diseases. The incidence of Goodpasture’s syndrome and membranous glomerulonephritis for instance is three times higher in men than in women. A recently published meta-analysis showed that the progression of IgA nephropathy and membranous glomerulonephritis as well as of polycystic kidney disease are highly correlated with male gender [26,27].

In conclusion, patients with renal insufficiency show, from the onset of their disease, a pattern of hormonal changes resulting from complex disturbances at the hypothalamic, pituitary, and gonadal level. The causes appear to be multifactorial, with clear contributions of co-morbidities and therapy. This endocrine dysfunction can only partially be influenced by renal replacement therapy, such as haemodialysis or kidney transplantation. The beneficial effects of androgens on erythropoiesis and nutrition are well documented in dialysis patients. However, the value of androgen substitution in patients with impaired renal function not yet on dialysis or in renal transplant patients is not proven and a negative influence on progression of kidney disease cannot be excluded.

**References**


