ORIGINAL ARTICLE

Prevalence of hypogonadism in male patients with renal failure

F Albaaj, M Sivalingham, P Haynes, G McKinnon, R N Foley, S Waldek, D J O'Donoghue, P A Kalra

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See end of article for authors' affiliations

Correspondence to: P A Kalra, Department of Renal Medicine, Hope Hospital, Stott Lane, Salford M6 8HD, UK; philip.kalra@srlt.nhs.uk

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Background: Hypogonadism in men may be secondary to renal failure and is well recognised in patients with end-stage renal disease. It is thought to contribute to the sexual dysfunction and osteoporosis experienced by these patients. However, the association between hypogonadism and lesser degrees of renal dysfunction is not well characterised.

Methods: The gonadal status of 214 male patients (mean age 56 (SD 18) years) attending a renal centre was studied; 62 of them were receiving haemodialysis and 22 continuous ambulatory peritoneal dialysis for end-stage renal disease, whereas 34 patients had functioning renal transplants and 96 patients were in the low-clearance phase. Non-fasting plasma was analysed for testosterone, follicle-stimulating hormone, luteinising hormone, sex hormone-binding globulin, parathyroid hormone and haemoglobin. Creatinine clearance was estimated in patients not on dialysis, and Kt/V and urea reduction ratio were assessed in patients on dialysis. Testosterone concentrations were classified as normal (>14 nmol/l), low-normal (10–14 nmol/l) or low (<10 nmol/l).

Results: 56 (26.2%) patients had significantly low testosterone levels and another 65 (30.3%) had low-normal levels. No significant changes were seen in sex hormone-binding globulin or gonadotrophin levels. Gonadal status was not correlated with haemoglobin level, parathyroid hormone level, creatinine clearance, or dialysis duration or adequacy.

Conclusion: Over half of patients with renal failure, even in the pre-dialysis phase, have low or low-normal levels of testosterone, which may be a potentially reversible risk factor for osteoporosis and sexual dysfunction. These patients may be candidates for testosterone-replacement therapy, which has been shown to improve bone mineral-density and libido in men with low and low-normal testosterone levels.

Male patients with reduced renal function are at risk of impaired reproductive health due to abnormal spermatogenesis, steroidogenesis and sexual function. Depending on the time of onset, hypothalamo-pituitary-testicular dysfunction in uraemia manifests clinically as delayed growth and puberty, sexual dysfunction, androgen deficiency, impaired spermatogenesis and infertility.¹ Deteriorating quality of life in some patients with uraemia is also thought to contribute to sexual dysfunction.^{2–3} Erectile dysfunction, decreased libido and infertility are prominent clinical features in men with uraemia; these abnormalities are often apparent before the need for dialysis and they rarely normalise with the initiation of dialysis. In fact, they often deteriorate, so that as many as 56% of male patients receiving dialysis become impotent.⁴ Although normal sexual activity may be restored with a well-functioning renal transplant, hypogonadism may persist in many people.²

Hypogonadism is widely regarded as an important risk factor for osteoporosis in the male population.^{5–8} People with current or previous renal failure may be at increased risk of developing osteoporosis and fractures due to several factors, including hyperparathyroidism, osteomalacia, aluminium bone disease, β_2 microglobulin depositions, use of steroids and immunosuppressive agents, myopathy and acidosis.⁹ Most previous studies investigating hypogonadism and renal disease have concentrated on patients with end-stage renal disease (ESRD), and little is known about the prevalence of the problem in patients in the low-clearance (pre-dialysis) phase. We therefore conducted a single-centre study to characterise the gonadal status of male patients with a range of renal dysfunction.

MATERIAL AND METHODS

Patient population

We carried out a cross-sectional study that included 214 of our male patients (aged >18 years) who had advanced chronic kidney disease (CKD) or ESRD. No exclusion criteria were applied. All the male patients receiving maintenance haemodialysis at this centre were studied. When patients for study were recruited from clinics, they were randomly selected from the following sources:

- Male patients attending two consecutive continuous ambulatory peritoneal dialysis (CAPD) clinics
- Male patients attending two consecutive transplant clinics
- Male patients with CKD attending four consecutive low-clearance clinics.

The patients' previous exposure to systemic corticosteroids (particularly relevant to the transplant population) was carefully noted, and other clinical parameters such as age, primary renal disease and, in those receiving renal replacement therapy, the total duration of dialysis treatment, were recorded. All patients gave informed consent to be included in the study. At the time of data collection, the local ethics committee recommended that a formal ethical application was unnecessary because the study effectively constituted an audit.

Abbreviations: BMD, bone mineral density; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; eGFR, estimate of glomerular filtration rate; ESRD, end-stage renal disease; FSH, follicle-stimulating hormone; PTH, parathyroid hormone; SHBG, sex hormone-binding globulin; URR, urea reduction ratio

Figure 1 Percentage of testosterone distribution in all patient groups. LC, low clearance; Tx, transplant.

Hormonal assessment

Gonadal status was assessed by obtaining non-fasting early-morning plasma samples. Testosterone, follicle-stimulating hormone (FSH) and luteinising hormone were measured in all patients; sex hormone-binding globulin (SHBG) was also measured in a proportion of patients, as part of a pilot study. Testosterone levels were measured by using the in-house extracted radioimmunoassay and SHBG, FSH and luteinising hormone levels by using Wallace Delfia (two-site immunometric assay, using time-resolved fluorescence). Normal values for testosterone are 10–30 nmol/l, but it is well recognised that testosterone levels decline with ageing (by 0.4–0.8% per year) so that on average the concentration is likely to be around 3.5 nmol/l lower in an 80-year-old than in a 20-year-old.¹⁰ However, as the patients who were studied had a very wide age range, with many in the young age groups, and because patients with testosterone levels within the low-normal range may also be functionally hypogonadal,¹¹ the following classification was used:

- Normal: testosterone >14 nmol/l
- Low normal: testosterone 10–14 nmol/l
- Low: testosterone <10 nmol/l.

Other laboratory analyses

Estimates of glomerular filtration rate (eGFR) were obtained using the Cockcroft and Gault formula^{11–12} for creatinine clearance calculation in patients with low clearance and those who underwent transplants. In patients with CAPD, Kt/V was analysed as a measure of dialysis adequacy according to the Gotch and Sargent method.¹³ Urea reduction ratio (URR) was used to evaluate the adequacy of haemodialysis treatment.¹⁴ Parathyroid hormone (PTH) and haemoglobin were also measured in all patients.

Statistical analyses

Parametric data are presented as mean (standard deviation (SD)) and median. Variables were compared using analysis of variance. Categorical data were compared using χ^2 tests. Correlation regression was used to test the relationships between testosterone levels and eGFR (for patients not on dialysis), dialysis adequacy and duration (for patients on dialysis), PTH and haemoglobin.

RESULTS

Clinical and biochemical demography

Of the 214 male patients studied, 96 were from low-clearance clinics, 84 were receiving dialysis (62 haemodialysis and 22 CAPD) and 34 had functioning renal transplants. The mean (SD) age of all patients was 56 (18) (median 61, range 16–94) years. The patients undergoing transplants were younger (44.6 (16.0), median 38.5 years; $p < 0.01$) than those receiving

dialysis (55.7 (18.7), median 58 years) and those with low clearance (60.6 (15.3), median 63 years). Table 1 summarises the primary renal diagnoses of patients. In all, 40 (18.7%) patients had diabetes. Corticosteroids had been given to 32 patients, which included the majority (64.7%) of patients who had received a transplant as part of their immunosuppressive regimen or for pulsed-steroid treatment of acute rejection; 10 other patients had received steroids as treatment for their primary renal disease ($n = 8$) or for asthma ($n = 2$). The mean (SD) eGFR of all patients with low clearance and with transplants grouped together was 26.0 (19.6) (range 5.5–89.6) ml/min; the eGFR of the patients with low clearance was 18.7 (13.2) (5.5–30.8) ml/min and that of the patients with transplants 35.6 (19.6) (range 19.6–89.6) ml/min. The mean (SD) URR of the patients receiving haemodialysis was 67% (6.8%) (range 50.9–76.8%), and the mean (SD) Kt/V of the patients with CAPD was 2.2 (0.7) (range 1.62–3.44). A total of 23.8% of the patients receiving dialysis was classified as receiving “inadequate” dialysis (URR < 65% for haemodialysis and Kt/V < 2.0 for patients with CAPD); mean duration of dialysis treatment was 41.2 months (range 1–180 months). The mean (SD) haemoglobin and PTH of all the patients was 105 (19) (range 83–127) g/l and 273 (118) (range 5–2500) pg/ml, respectively.

Results of hormonal assays

The mean (SD) testosterone concentration for all patients was 13.9 (6.5) (median 13.2; range 0.5–37.0) nmol/l. Mean (SD) testosterone concentrations were 15.5 (5.1) (range 5.7–27.1 nmol/l) in the transplant group; 13.0 (6.9) (range 0.5–35.5 nmol/l) in the dialysis group; and 14.2 (6.4) (range 0.6–37 nmol/l) in the low-clearance group. Low testosterone was evident in 56 (26.2%) patients, whereas another 65 (30.3%) patients had low-normal levels; only 96 (43.5%) patients had normal testosterone values. Patients with normal gonadal function were younger (mean 52.7 (SD 13.2) years; $p < 0.01$) than patients with low or low-normal testosterone levels (58.1 (16.4) and 59.4 (18.6) years, respectively). Figure 1 shows patients grouped according to modality of renal replacement therapy and the proportion of patients in each gonadal function category. It is important to note that as many as 14.5% and 23.3% of the patients with transplants and 22.9% and 31.2% of the patients with low clearance had low and low-normal testosterone levels, respectively.

SHBG was assayed in the first 91 patients enrolled into the study. As no marked changes between patients were noted during this pilot phase (table 2), it was decided to discontinue the measurement of SHBG in later patients. Table 2 also presents the data for FSH and luteinising hormone; no significant differences were noted between patient groups, and there seemed to be no relationship with gonadal status.

Relationship between gonadal status and clinical parameters

Figure 2 shows a weak negative correlation between age and serum testosterone ($p < 0.001$; $r^2 = 0.052$; adjusted $r^2 = 0.047$). In the 84 patients receiving dialysis, there was no correlation between testosterone levels and URR ($r = 0.089$), Kt/V ($r = 0.242$), and certainly no correlation with inadequate dialysis, or with dialysis duration ($r = 0.044$). In the 130 patients not receiving dialysis, there was no correlation between serum testosterone and either creatinine ($r = 0.030$) or eGFR ($r = 0.019$). There was no correlation between testosterone and haemoglobin ($r = 0.028$) or PTH ($r = 0.044$) in all patients.

DISCUSSION

In this cross-sectional study from one renal centre, more than half of the investigated male patients with renal failure had

Figure 2 Relationships between testosterone levels and ages. There was a weak negative correlation between age and serum testosterone ($p < 0.001$; $r^2 = 0.052$; adjusted $r^2 = 0.047$).

biochemical hypogonadism (low or low-normal testosterone), which is a potentially reversible risk factor for sexual dysfunction and osteoporosis. Hypogonadism was not only highly prevalent in patients receiving dialysis (only 33.4% had normal gonadal status), which has been shown in previous studies,^{15–17} but also evident in a large proportion of patients with low clearance (54.1%) and those with a functioning renal transplant (37.8%). Our patients showed a relationship between increasing age and declining serum testosterone (consistent in patients with low clearance, dialysis and transplant), and this has been variably shown in non-renal patients.^{18–19} The three subject groups were of differing age; although it may have been beneficial to compare subgroups of age-matched patients from within these groups, this was not undertaken because of limited patient numbers (particularly transplants). In the pilot study, no differences in FSH, luteinising hormone or SHBG were identified between the different clinical groups, and there was no correlation between these and the testosterone level.

Our findings in patients with transplants are comparable to those of Shane and Epstein,²⁰ who showed that, although there is a trend to normalisation of testosterone levels by 6–12 months after transplantation,^{21–22} approximately 25% of the men evaluated 1–2 years after transplantation had biochemical evidence of hypogonadism.²⁰ Although as a group these patients tend to be younger, their risk of complications from biochemical hypogonadism is increased by the immunosuppressant drugs that they receive.

In this study, we did not attempt to assess the relationship of biochemical hypogonadism with possible clinical consequences such as sexual dysfunction or osteoporosis and fractures. Sexual dysfunction is common in patients with CKD, and prevalence estimates range from 9% in patients with low clearance to 60–70% in those receiving dialysis,²³ with as many as 56% of male patients receiving dialysis

Table 2 Mean (SD) levels of gonadotrophins and sex hormone-binding globulin

	FSH (U/l)	LH (U/l)	SHBG (nmol/l)
Low clearance	18.7 (3.2)	16.03 (4.5)	37.13 (8.7)
Dialysis	13.21 (3.1)	12.78 (4.4)	44.72 (9.3)
Transplantation	15.42 (4.2)	17.3 (4.7)	36.27 (8.3)

FSH, follicle-stimulating hormone; LH, luteinising hormone; SHBG, sex hormone-binding globulin.

becoming impotent.⁴ Erectile dysfunction, decreased libido, and infertility are prominent in men with uraemia. These problems can be corrected by testosterone treatment,²³ which highlights the importance of biochemical hypogonadism in pathogenesis. Low testosterone levels are found in up to 20% of men with symptomatic vertebral fractures and in 50% of elderly men with hip fractures.^{7–21} Bone disease is almost universal in patients with renal transplants and in those receiving dialysis.²² The problem is not insignificant, as one third of the patients receiving haemodialysis may have a history of previous fracture.²⁴ It has been shown that bone-mineral density (BMD) was less than the fracture threshold in the vertebral region and femoral neck in 23–41% and 10.5% of renal transplant recipients, respectively. Fractures are more frequent after renal transplantation; a recent study on transplant recipients showed that non-vertebral fractures are fivefold more common in adult men, and 18-fold or 34-fold more common in women aged 25–44 and 45–64 years, respectively, than in the healthy population.²⁵

None of our patients had been considered for testosterone treatment, but such a replacement therapy has been shown to increase BMD in hypogonadal and eugonadal men, and to improve symptoms of sexual dysfunction. Testosterone treatment in hypogonadal men rapidly increases 1,25-dihydroxy vitamin D levels and corrects calcium malabsorption, leading to an improvement in calcium balance and an increase in bone formation.²⁶ It has also been shown to markedly increase forearm bone density and spinal BMD in hypogonadal men, regardless of age, over periods of 3 months to at least 1 year.^{27–28} However, all these benefits were extrapolated from results of treatment in other populations, such as healthy older hypogonadal men. Unfortunately, research on the ESRD populations lags behind that on other patient populations. Indeed, there are other potential benefits of testosterone replacement treatment in patients with uraemia with cardiac dysfunction. Treatment may improve cardiac and vascular function, perhaps by adjusting the catabolic-anabolic imbalance and suppressing cytokine activation. It seems that testosterone preparations can be used in patients with ESRD without dose adjustment and with similar safety considerations as in healthy elderly men.²⁹

Table 1 Causes of renal failure in the study patients

	Low clearance		Dialysis		Transplantation	
	n	%	n	%	n	%
Diabetic nephropathy	25	26	10	11.9	5	14.7
Glomerulonephritis	13	13.5	18	21.4	8	23.5
Renovascular disease	16	16.7	10	11.9	0	0
Urological disorders	8	8.3	7	8.3	8	23.5
Reflux and chronic pyelonephritis	2	2.1	11	13.1	7	20.6
Unknown	19	19.8	17	20.2	3	8.8
Others	13	13.5	11	13.1	3	8.8

CONCLUSIONS

We conclude that more than half of our male patients with renal failure have biochemical hypogonadism, which is a potentially reversible risk factor for sexual dysfunction and osteoporosis. We now plan to study the correlation between both BMD (using dual energy x ray absorptiometry scan) and sexual dysfunction (using a directed questionnaire) and gonadal status in patients, and also the effects of testosterone replacement treatment on these parameters in an intervention study.

Authors' affiliations

F Albaaj, M Sivalingham, R N Foley, S Waldek, D J O'Donoghue, P A Kalra, Department of Renal Medicine, Hope Hospital, Salford, UK
G McKinnon, Department of Endocrine Biochemistry, Hope Hospital, UK
P Haynes, Department of Rheumatology, Royal Oldham Hospital, Oldham, UK

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