Sex hormone–binding globulin is a biomarker associated with nonvertebral fracture in men on dialysis therapy

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Gonadal hormones impact bone health and higher values of sex hormone–binding globulin (SHBG) have been independently associated with fracture risk in men without chronic kidney disease. People with chronic kidney disease have a greatly increased fracture risk, and gonadal dysfunction is common in men receiving dialysis treatment. Nevertheless, in these men the effect of gonadal steroids and SHBG on bone mineral density (BMD) and fracture risk is unknown. Here we investigate relationships between gonadal steroids, SHBG, BMD and fracture in men on long-term dialysis therapy, awaiting kidney or simultaneous pancreas kidney transplantation. Results of serum biochemistry, SHBG, gonadal steroids (total testosterone, calculated free testosterone and estradiol), BMD by dual-energy X-ray absorptiometry and thoracolumbar X-rays were obtained. Multivariable regression models were used to examine associations between SHBG, gonadal steroids, BMD and fracture of 321 men with a mean age of 47 years. Diabetes mellitus was present in 45% and their median dialysis vintage was 24 months. Prior fractures occurred in 42%, 18% had vertebral fracture on lateral spine X-ray, 17% had non-vertebral fragility fracture within 10 years and 7% had both. After adjustment for age, body mass index and dialysis vintage, higher SHBG levels were significantly associated with nonvertebral fractures [odds ratio 1.81 (1.30-2.53)] and remained significant after adjustment for BMD. Calculated free testosterone and estradiol values were not associated with fracture. Prevalent fracture rates were high in relatively young men on dialysis awaiting transplantation. Thus, SHBG is a novel biomarker associated with fracture, which warrants investigation in prospective studies.

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Chronic kidney disease–mineral and bone disorder (CKD-MBD) comprises abnormalities of mineral metabolism that result in a high risk for cardiovascular events, fracture, and mortality. Abnormalities of bone turnover, mineralization and volume are pivotal components of CKD-MBD. They constitute the disparate features of renal osteodystrophy and contribute to the reduction in bone strength that increases fracture risk.[1] Fractures are common, occurring in as many as 50% of patients receiving maintenance dialysis, and morbidity and mortality following fracture is up to 60% greater than for people without CKD.[1,2] Recognized risk factors for fracture in CKD include those shared with the general population such as advancing age, low values of serum 25-hydroxyvitamin D [25(OH)D], and the presence of diabetes mellitus (DM), plus factors specific to patients with CKD including suppressed or elevated levels of parathyroid hormone (PTH), dialysis vintage, and low values of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D].[3,4]

In men without CKD, hypogonadism is associated with reduced bone mineral density (BMD) and an increased fracture risk, and appropriate testosterone replacement to achieve eugonadal status is associated with improvements in BMD. In men with CKD, disturbances in gonadal hormones are a frequent finding, being reported in one-third to one-half of men with CKD stages G3 to 5,[5,6] increasing to 50% to 75% of men undergoing dialysis.[7–9] In these patients, low total testosterone and/or free testosterone levels likely result from a combination of primary testicular failure and secondary hypothalamic-pituitary dysfunction.[10] The pathogenesis includes inhibition of luteinizing hormone (LH) signaling as a direct consequence of kidney failure,[11] increased prolactin production, and reduced renal prolactin clearance.[10,12] In addition, comorbid conditions such as obesity, DM, and hypertension contribute to decreased testosterone levels as can a number of prescribed medications.[13–15]

Although testosterone is the hallmark sex steroid in adult males, both *in vivo* and *in vitro* studies have demonstrated

that estradiol, through aromatization of testosterone, is the predominate sex hormone regulating bone health.[16,17] Estradiol levels in healthy men are comparable to those in premenopausal women during the early follicular phase of the menstrual cycle.[17] Hypogonadal men in the general population have lower estradiol levels as a consequence of reduced substrate availability for aromatase activity,[17] and testosterone replacement produces a concurrent rise in estradiol levels.[18] It is unknown how CKD affects circulating estradiol levels in men and whether this is independent of serum testosterone. In previous studies of men with CKD, the presence of elevated LH levels with normal or low testosterone was associated with higher estradiol levels, whereas other studies have shown normal or low estradiol levels in the presence of elevated LH levels.[10,19,20]

Circulating testosterone and estradiol are tightly bound to the liver-derived glycoprotein sex hormone–binding globulin (SHBG). As described by the "free hormone hypothesis,"[21] serum SHBG levels influence the concentration of free hormone available for receptor interactions and biological actions. In community-dwelling males, higher SHBG levels, independent of the levels of testosterone and estradiol, have been positively associated with vertebral and nonvertebral fractures.[22–25] The effect of CKD on SHBG concentrations is not widely reported, but levels appear to be unaltered by the uremic milieu and dialysis.[20,26,27]

Although the Kidney Disease Improving Global Outcomes (KDIGO) work group recognized the potential impact of altered gonadal hormones on bone quality in patients with CKD-MBD,[28] no published studies have delineated the contribution of gonadal hormone disturbances on bone outcomes in CKD.[29] Given the effects of hypogonadism on bone health and the association of SHBG with fractures in men without CKD, this study aimed to investigate the relationships between gonadal steroids, SHBG, CKD-MBD, and fracture in men with CKD receiving dialysis.

RESULTS

Baseline characteristics

The study included 321 men receiving dialysis, 78% of whom were Caucasian, with a mean age of 47 ± 12 years. The most common causes of CKD were DM (40%) and glomerulonephritis (29%), and the median dialysis vintage was 24 months. Demographic and anthropometric characteristics of the patients are presented in Table 1.

Table 1 | Baseline demographic and anthropometric characteristics of men on dialysis and according to fracture status (combined nonvertebral and vertebral)

Demographic	All patients (N = 321)	Patients with fracture (N = 134)	Patients without fracture (N = 187)
Age (yr)	47 ± 12	49 ± 12	46 ± 12
Body mass index (kg/m^2)	26.3 ± 4.2	25.8 ± 3.9	26.7 ± 4.5
Parathyroidectomy	29 (9%)	16 (12%)	13 (7%)
Dialysis vintage (mo)	24 (9, 60)	24 (10, 66)	28 (9, 60)
Smoking			
Never	144 (45%)	60 (45%)	88 (47%)
Current/former	150 (47%)	64 (46%)	86 (45%)
Unknown	27 (8%)	12 (9%)	15 (8%)
Diabetes mellitus			
Type 1	94 (29%)	50 (37%)	44 (24%)
Type 2	50 (16%)	18 (13%)	32 (17%)
Medication use			
Calcium	161 (50%)	68 (51%)	93 (50%)
Calcitriol	111 (35%)	48 (36%)	63 (34%)
Cinacalcet	31 (10%)	21 (16%)	10 (5%)
Bisphosphonates	11 (3%)	8 (6%)	3 (2%)
Glucocorticoids >3 mo	21 (7%)	7 (5%)	14 (7%)

Biochemistry, sex hormone, and SHBG values

Table 2 indicates values (mean ± SD or median and 25th and 75th percentile values) for biochemical and sex hormone levels. Calcium, magnesium, 25(OH)D, and alkaline phosphatase levels were within the normal range. Serum phosphate levels were elevated, and median PTH levels were within the recommended KDIGO guidelines of 2 to 9 times the upper limit of the assay reference range.[29] Bone turnover markers N-terminal propeptide of type I procollagen (P1NP) and the beta carboxy-terminal cross-linking telopeptide of type I collagen (β-CTx) values were significantly increased but are known to accumulate in patients with CKD.

Median total testosterone levels were within the normal range (11.7 nmol/l); however, one-third of patients had values below the reference value (<9.1 nmol/l). The median calculated free testosterone level was low at 168 pmol/l, and 50% of patients had values below the reference range (<170 pmol/l). Estradiol values were below the detectable limit of the assay (<100 pmol/l) in 28% of patients, and of those with detectable values (N = 230), the median value was 136 pmol/l.

SHBG levels were within the normal range (median, 30.4 nmol/l; 25th, 75th percentile, 21.8, 44). Higher body mass index (BMI) was associated with lower SHBG levels ($\beta = -0.192$, $P < 0.001$). Patients with type 2 DM (N = 50) had lower SHBG levels compared with those without type 2 DM (30.4 vs. 35.8 nmol/l, $P = 0.008$), and longer dialysis vintage also correlated to lower SHBG levels ($\beta = -0.144$, $P = 0.042$). Higher SHBG values significantly correlated with higher total testosterone ($\beta = 0.389$, $P < 0.001$) and free testosterone ($\beta = 0.217$, $P < 0.001$) levels and to estradiol ($\beta = 0.113$, $P = 0.008$) (Figure 1). SHBG levels did not correlate with the use of calcitriol or values of serum 25(OH) D, 1,25 $(OH)_2$D, PTH, alkaline phosphatase, N-terminal P1NP, or β-CTx.

Bone mineral density

BMD data by dual-energy X-ray absorptiometry (DXA) (Norland, XR-36; software 3.9.4/2.0.0) was available for 251 patients. Median BMD values, T-scores, and Z-scores are shown in Table 3. At the lumbar spine, 1% of patients had T-scores in the osteoporotic range (≤−2.5) compared with 28% at the total hip and 30% at the femoral neck. At the one-third radius and ulna and ultradistal radius and ulna, T-scores