Peritoneal dialysis *per se* is a risk factor for sclerostin-associated adynamic bone disease

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Chronic kidney disease—mineral bone disorder (CKD-MBD) is a complex syndrome influenced by various factors, such as age, CKD etiology, uremic toxins, and dialysis modality. Although extensively studied in hemodialysis (HD) patients, only a few studies exist for peritoneal dialysis (PD) patients. Since most of these older studies contain no bone biopsy data, we studied the pattern of renal osteodystrophy in 41 prevalent PD patients. The most common presentation was adynamic bone disease (49%). There was a significant inverse association between serum sclerostin (a Wnt/β-catenin pathway inhibitor that decreases osteoblast action and bone formation) and the bone formation rate. Bone alkaline phosphatase had the best sensitivity and specificity to detect both high- and low-turnover diseases. The comparison between nondiabetic PD and HD patients, matched by age, gender, parathyroid hormone level, and length of dialysis, revealed low 25-hydroxyvitamin D levels, worse bone mineralization, and low bone turnover in the nondiabetic PD group. Thus, adynamic bone disease was the most frequent type of renal osteodystrophy in PD patients. Sclerostin seems to participate in the pathophysiology of adynamic bone disease and bone alkaline phosphatase was the best serum marker of bone turnover in these patients.

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Chronic kidney disease—mineral bone disorder (CKD-MBD) is a complex syndrome influenced by various factors, such as age, race, CKD etiology, hormonal derangements, uremic toxins, dialysis modality, and length of treatment. CKD-MBD profiles have been extensively studied in hemodialysis (HD) patients. However, for peritoneal dialysis (PD), only few, older studies exist, most of which contain no bone biopsy data. There is a large difference between current and past clinical practice and patient characteristics regarding PD treatment. Most notably, aluminum- and calcium-based phosphate (P) binders were largely used previously. PD was considered to be a second-rate treatment indicated particularly for the elderly and for patients without vascular access for HD. Furthermore, previous studies did not exclude patients who had previously undergone HD or parathyroidectomy.[1–4]

In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on CKD-MBD were based on the main studies published on this issue and compiled bone biopsy findings. According to these guidelines, the most frequent pattern of renal osteodystrophy (ROD) in PD was adynamic bone disease (ABD; 50%), followed by mild disease (20%), osteitis fibrosa (OF; 18%), mixed bone disease (5%), and osteomalacia (5%); 2% of the patients had normal bone histology.[5] These findings strengthened the worldwide belief that PD is an important risk factor for ABD development. Furthermore, KDIGO proposed the use of the TMV (turnover, mineralization, volume) classification to standardize bone biopsy analysis.[5] Turnover is considered the most important parameter for guiding ROD management. Studies have suggested that at both extremes of ROD (i.e., high- or low-turnover bone disease) there is a loss of bone buffering capacity that may prevent mineral influx to bone and favor mineral efflux from bone. In both situations, bone quality is compromised, and the risk of vascular calcification (VC) and bone fracture seems to be increased.[6,7]

Bone biopsy remains the gold standard for diagnosing ROD. Nevertheless, the invasive nature of the procedure, its cost, and its overall complexity have precluded the use of this

tool in clinical practice. Instead, serum markers of bone turnover have been used to evaluate bone turnover in CKD patients. The reliability of parathyroid hormone (PTH), which is the most commonly used marker, has been questioned.[8,9] Total alkaline phosphatase (tAP) and bone alkaline phosphatase (BAP), both markers of bone formation, and deoxypyridinoline, a marker of bone resorption, have been identified as good options, even in the CKD setting.[10,11]

Recently, another regulator of bone physiology, sclerostin, has been discovered. Sclerostin inhibits the Wnt/β-catenin pathway and consequently decreases osteoblast action and bone formation. Sclerostin is still understudied in CKD patients,[12,13] and, to our knowledge, there has not yet been a study that analyzed sclerostin in adult PD patients.

The present study sought to achieve the following: (a) characterize CKD-MBD in a cohort of PD patients; (b) analyze the role of sclerostin in ROD in these patients; (c) compare the performance of sclerostin with traditional bone turnover serum markers, namely PTH, tAP, BAP, and deoxypyridinoline, to make the diagnosis of high or low bone turnover disease in PD patients; and (d) compare the CKD-MBD profiles between PD and HD patients.

RESULTS

Clinical and laboratory characteristics

Patients had been receiving an adequate dialysis dosage, according to a weekly KT/V.[14] Most of them used a dialysate with a high calcium concentration (1.75 mmol/l), and approximately one-third used calcitriol because of high intact PTH (iPTH) levels. Sevelamer hydrochloride was the main P binder prescribed (90.3%), and only 4.8% of patients received calcium-based P binders. No patient was using aluminum-based P binder. P and iPTH levels were in agreement with the K/DOQI recommendations in 46.3% and 65.9% of patients, respectively.[15] Ionized calcium (iCa) was within the normal range in 70.7% of patients, and 100% of patients had a low level of 25(OH) vitamin D. Table 1 shows the main clinical and laboratory characteristics of patients.

Almost half of the patients were diabetic, and when we analyzed diabetic and nondiabetic patients separately, we found that phosphate, albumin, iPTH, and 25(OH) vitamin D levels were lower in the first group (4.3 ± 1.7 vs. 5.6 ± 1.4, $P = 0.001$; 3.27 ± 0.56 vs. 3.64 ± 0.49, $P = 0.05$; 269 (196–397) vs. 430 (256–1111), $P = 0.05$; and 9.08 ± 3.4 vs. 15.5 ± 6.7, $P = 0.003$, respectively). Calcitriol use was similar between diabetic and nondiabetic patients (26.1% vs. 33.3%, $P = 0.87$).

Vascular calcification

VC was observed in 24.3% of patients. VC was associated with diabetes mellitus (9.5 vs. 43.7%; $P = 0.02$), but not with high or low bone turnover (16.6% vs. 31.6%, $P = 0.29$). There was no association between VC and any other clinical, biochemical and mineral metabolism biomarkers (iCa, P, BAP, iPTH and sclerostin), dialysate calcium concentration or histomorphometric parameters.

Table 1 | General patient characteristics

$n = 41$	Results	Reference range
Age (years)	50.3 ± 10.2	—
Male (%)	56.1	—
Diabetes (%)	43.9	—
Caucasian (%)	22	—
PD length (months)	10 (7–24)	—
d [Ca] 1.75 mmol/l (%)	84.2	—
d [Ca] 1.25 mmol/l (%)	15.8	—
Phosphate binder (%)		—
Calcium based	4.8	—
Aluminum based	0.0	—
Sevelamer	90.3	—
Diuresis (ml/24 h)	1015 ± 669	—
Calcitriol (%)	29.2	—
KT/V (weekly)	2.43 ± 0.75	>1.7
Urinary	0.80 ± 0.72	
Peritoneal	1.63 ± 0.21	
Cr Clearance (weekly)	60.8 ± 44.0	>60
Urinary (L/week/1.73 m^2)	72.2 ± 59.9	
Peritoneal (L/week/1.73 m^2)	49.3 ± 15.4	
iCa (mg/dl)	4.64 ± 0.69	(4.6–5.3)
P (mg/dl)	5.09 ± 1.72	(2.7–4.5)
Albumin (g/dl)	3.49 ± 0.54	(3.4–4.8)
iPTH (pg/ml)	363 (236–686)	(16–87)
tAP	113.5 ± 50.9	(40–129)
BAP (U/l)	52.9 ± 16.1	(11.6–42.7)
Sclerostin (ng/ml)	2.00 ± 1.03	(0.42–0.80)
DPD (nmol/l)	22.2 ± 16.1	(2.59–3.91)
25(OH) vitamin D (ng/dl)	12.6 ± 6.3	(30–100)
VC (%)	24.3	0

Abbreviations: BAP, bone alkaline phosphatase; Cr, creatinine; d[Ca], dialysate calcium concentration; DPD, deoxypyridinoline; iCa, ionized calcium; iPTH, intact parathyroid hormone; P, phosphate; PD, peritoneal dialysis; tAP, total alkaline phosphatase; VC, vascular calcification.

Serum sclerostin and bone-expressed sclerostin

Sclerostin was increased in the serum (2.0 ng/dl) and trabecular bone surface (9.45 %) of PD patients, and both were negatively correlated with bone formation rate (BFR/BS; $r = -0.31$, $P = 0.04$ and $r = -0.34$, $P = 0.02$, respectively) and BAP ($r = -0.48$, $P = 0.001$ and $r = -0.39$ and $P = 0.01$, respectively). In addition, serum sclerostin negatively correlated with other bone formation parameters, namely osteoblast surface (ObS/BS;$r = -0.35$, $P = 0.02$), osteoid volume (OV/BV; $r = -0.31$, $P = 0.04$), and osteoid thickness (O.Th; $r = -0.44$, $P = 0.003$), and resorption parameters, namely eroded surface (ES/BS; $r = -0.40$, $P = 0.01$) and osteoclast surface (OcS/BS; $r = -0.38$, $P = 0.01$). There was no correlation with structural parameters or iPTH.

When we separately analyzed diabetic and nondiabetic patients, serum (2.46 ± 0.97 vs. 1.64 ± 0.92, $P = 0.002$) and bone-expressed sclerostin (11.94 ± 7.45 vs. 8.72 ± 6.67, $P = 0.003$) were found to be increased in the diabetic group.

With regard to the bone expression of sclerostin, we found a distinct pattern of distribution in bone samples from high- or low-turnover patients. In bone specimens from patients with high turnover, the expression of sclerostin was observed