brain and cerebrospinal fluid of ESRF patients (3, 4). Guanidine is a competitive gamma-amino butyric acid (GABA) receptor antagonist and may counteract GABA inhibition of respiratory muscles (4). In this particular case, gabapentin, a novel amino acid derived by the addition of a cyclohexyl group to the chemical backbone of GABA, may have been effective in treating hiccups for two reasons: it increased endogenous GABA-mediated inhibition of inspiratory muscles (3, 4), or it reduced calcium influx via inhibition of voltage-operated calcium channels in presynaptic terminals of respiratory muscles. Furthermore, gabapentin also increases the levels of serotonin, an important neurotransmitter for the raphe magnus nucleus in the medulla, the most likely source of GABAergic inhibitory inputs to the hiccup reflex arc (5). Indeed, there are several reports of gabapentin being used for the treatment of intractable hiccups in the setting of cancer or gastrointestinal disorders, but not in ESRF (6–8).

Dizziness, somnolence, and peripheral edema are the most frequent side effects of gabapentin. However, in trials where gabapentin was used for treating hiccups (6–8), no side effects were reported. Gabapentin is also advantageous in that it is effective for restless leg syndrome, neuropathic pain, and pruritis in patients with renal failure (9,10). Thus, gabapentin may be useful for ESRF patients with intractable idiopathic hiccups.

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Bone Mineral Density, Vascular Calcifications, and Arterial Stiffness in Peritoneal Dialysis Patients

The objective of this study was to evaluate the correlation of bone mineral density (BMD), evaluated by DXA, with vascular calcifications, arterial stiffness, and vascular disease in patients on peritoneal dialysis. Vascular calcifications were evaluated by vascular calcification score on plain x ray, and arterial stiffness was measured by pulse wave velocity using the Complior device (Artech Medical, Pantin, France). Adjusting for multiple factors, lower BMD at the femoral neck, but not at the lumbar spine, was associated with higher pulse wave velocity (p = 0.037), higher vascular calcium score (p = 0.013), and peripheral artery disease (p = 0.006). These data reinforce the hypothesis of the existence of a link between bone disease and cardiovascular disease in dialysis patients.


KEY WORDS: Bone mineral density; vascular calcifications; arterial stiffness.
peritoneal dialysis patients, the relationship of BMD with vascular calcifications, pulse pressure, pulse wave velocity (PWV), and cardiovascular disease.

PATIENTS

This study was a cross-sectional analysis of a cohort of peritoneal dialysis patients. Seventy patients (37 males, 33 females) without previous parathyroidectomy were enrolled after signing an informed consent form. Mean age was 52 ± 14 years and mean dialysis duration was 46 ± 28 months; 17 patients were diabetic. During the 6 months preceding BMD evaluation, 29 and 33 patients were treated, respectively, with calcium carbonate (1.2 ± 0.45 g/day) and calcitriol (1.6 ± 1.2 µg/week). During this period, dialysate calcium concentrations of 1.25 and 1.75 mmol/L were used, respectively, in 40 and 30 patients. No patient had been previously treated with bisphosphonates or cinacalcet. Coronary artery disease, peripheral artery disease (PAD), and cerebral vascular disease were diagnosed, respectively, in 20, 18, and 8 patients, based on clinical manifestations and diagnostic tests.

METHODS

Bone mineral density was evaluated by dual-energy x-ray absorptiometry (DXA) using the Hologic QDR Discovery scanner (Hologic, Bedford, Massachusetts, USA) in the lumbar spine and the femoral neck, using NHANES III as the database reference (3). DXA parameters are not standardized for dialysis patients and we used the WHO cutoff of a T-score > –1 SD, which defines normal BMD. According to the Osteoporosis Work Group (4), a Z-score ≤ –1 SD, which is adjusted to age, could be more appropriate to diagnose low BMD in dialysis patients. During the first month after BMD evaluation, vascular calcifications were evaluated on plain x-rays of pelvis and hands using a method previously described (5), with the final score ranging from 0 to 8. Arterial stiffness was evaluated by pulse pressure (pulse pressure = systolic blood pressure – diastolic blood pressure) and by carotid–femoral PWV using a noninvasive automated device (Complior; Artech Medical, Pantin, France). Serum levels of the following biochemical parameters were evaluated every month and time averaged for the 6 months preceding the DXA evaluation: calcium, phosphorus, calcium–phosphate product, albumin, alkaline phosphatase, and C-reactive protein. Total intact parathyroid hormone was evaluated every 3 months by immunochemiluminescence using a second-generation assay.

Statistical Analysis: Data are presented as frequencies for categorical variables and as means with SD for continuous variables. Univariate analysis was performed by independent samples t-test, chi-square, Fisher’s exact test, paired-samples t-tests, and Pearson correlation coefficient. The association of DXA parameters with cardiovascular factors was evaluated by linear and logistic regression models adjusting for age, gender, diabetes, and body mass index. Absence of collinearity was checked in all models. Vascular calcification score (VCS) was evaluated as a categorical dependent variable (VCS ≥ 3) based on our previous studies showing an association between VCS ≥ 3 and higher cardiovascular mortality (5). Statistical analyses were performed using the SPSS system 14.0 (SPSS Inc., Chicago, Illinois, USA). A p value < 0.05 was considered statistically significant.

RESULTS

Vascular calcifications were present in 43 patients. A T-score ≤ –1 SD was observed at the lumbar spine in 39 patients and at the femoral neck in 43 patients. A Z-score ≤ –1 SD was present at the lumbar spine in 21 patients and at the femoral neck in 24 patients.

In univariate analysis, lower femoral T-score (Table 1) was associated with higher pulse pressure, higher PWV, higher prevalence of vascular calcification, and higher prevalence of PAD. Lower femoral BMD was associated with higher VCS and higher PWV (Figure 1). Lower femoral BMD was also associated with presence of coronary artery disease (0.66 ± 0.15 vs 0.74 ± 0.13 g/cm², p = 0.03) and PAD (0.64 ± 0.14 vs 0.75 ± 0.13 g/cm², p = 0.006) (Figure 1). Patients with vascular calcifications had a higher lumbar T-score than patients without calcifications (–1.1 ± 1.5 vs –1.7 ± 1.6 SD, p = 0.02). In multivariate analysis, BMD evaluated at the femoral neck was negatively associated with VCS ≥ 3, PAD (Table 2), and PWV (Table 3), adjusting for age, gender, diabetes, and body mass index. In similar models, a lower femoral Z-score, but not T-score, was associated with VCS ≥ 3 [odds ratio (OR) = 0.5, p = 0.030] and PAD (OR = 0.44, p = 0.016).

DISCUSSION

In this group of peritoneal dialysis patients, we have verified that low BMD at the femoral neck, but not at the lumbar spine, is independently associated with VCS on plain x-ray and with arterial stiffness. The association of lower bone mineral mass or density with vascular calcifications or PWV has already been demonstrated in nonrenal and dialysis patients (1,6,7) but, for the first
time, an association between low BMD and plain x-ray vascular calcifications and vascular disease is shown in dialysis patients. Evaluation of vascular calcifications is now required to classify the mineral and bone disorder seen in chronic kidney disease (2), and plain x-ray may be a simple and inexpensive method to do so. One explanation for the association of lower BMD with PWV or vascular disease is their common relationship with vascular calcifications (6,8). The absence of association between lumbar BMD and arterial stiffness or vascular calcifications present in our study has already been described in dialysis patients (7) and may be explained by the presence of vascular calcifications in the aorta possibly contributing to a higher BMD value (7). This can also explain why, in our study, patients with calcifications had a higher lumbar T-score compared with patients without calcifications. The pathogenesis of the association between low BMD parameters and vascular calcifications is not known yet and might be explained by a common etiologic factor. Both hyperparathyroidism and adynamic bone disease may be associated with low bone volume (9) and may also be associated with hyperphosphatemia and hypercalcemia, which are inducers of vascular calcifications (10). Low bone turnover has also been associated with vascular calcifications (11). This study presents, however, some limitations: Vascular score has the advantage of simplicity and low cost but it is a semiquantitative evaluation, and the cross-sectional analysis allows only identification of associations between the variables.

In conclusion, in this group of patients, lower values of bone mineral density, evaluated by DXA, at the femoral neck but not at the lumbar spine were associated with more calcifications, arterial stiffness, and peripheral
artery disease. The mechanisms for this association are not yet identified but these findings reinforce the hypothesis of the existence of a link between bone disease and vascular disease in dialysis patients.

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