Mineral Bone Disorder in Hemodialysis Patients – a New Face of an Old Concept

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Aim: We studied in a hemodialysis (HD) population the correlations between bone metabolism markers measured by DEXA compared with other bone markers: serum calcium, serum phosphate, serum iPTH level and the inflammatory status, known as high risk for morbidity in HD patients which has not been studied yet.

Method: Twenty-seven patients from a hemodialysis unit were included in the study. The following parameters were measured: serum calcium (Ca), serum phosphate (P), total alkaline phosphatase (AP), intact parathormon level (iPTH) as bone metabolism markers and fibrinogen and C reactive protein (CRP) as inflammatory markers. Osteodensitometry was measured with DEXA technique and T-score was recorded. Statistical data were analyzed with the program Excel 2007 and mean, SD, Pearson's correlation coefficient r and χ^2-test were calculated.

Results: Significant correlations were found between serum Ca levels and P (p=0.002), AP (p=0.002) and T-score (p=0.0003). Also there was a correlation between CRP and phosphate (p=0.029) and CRP and fibrinogen (p=0.037). Calculating the correlation coefficient r, the significant correlation threshold was relevant to Ca and AP (r=0.33, p <0.05), Ca and BMD (r=0.31, p <0.05), P and BMD (0.30, p <0.05), P and fibrinogen (r=0.6, p <0.01).

Conclusions: In HD patients, CRP is correlated with bone metabolism, in the absence of infection. Serum phosphate is the only marker correlated with bone markers, inflammatory markers and T-score for osteodystrophy, being an important tool for the future prognostic of these patients.

Keywords: dialysis, osteoporosis, calcium, phosphate

Introduction

The development of chronic kidney disease-mineral bone disorder (CKD-MBD) is a common entity well known and studied in the last years, related to phosphate and calcium disturbances in chronic kidney disease patients. The pathologic cascade of these disturbances starts with calcitriol deficiency and continues with hypocalcaemia, hyperphosphatemia and secondary hyperparathyroidism (HPTS) [1].

In the End Stage Renal Disease (ESRD) patients usually have an accelerated bone loss due to abnormal bone turnover that leads to a high prevalence of bone health problems, e.g. osteopenia and osteoporosis. Secondary hyperparathyroidism, osteomalacia and adynamic bone disease, the main bone problems in chronic renal failure, may all be responsible for a reduction in bone mineral density (BMD). Dual-Energy X-ray Absorptiometry (DEXA) is the most accurate and non-invasive way to measure BMD, although bone biopsy is the most reliable but invasive method. Osteoporosis is defined as a metabolic bone disease characterized by low bone mass and micro architectural deterioration of bony tissue leading to enhanced bone fragility and a consequent increase in fracture risk [2].

The World Health Organization's (WHO) definition of osteoporosis is applicable to Bone Mineral Density measurements using DXA (Dual X-ray Absorptiometry). BMD measured by DXA is expressed as absolute BMD (g/cm²) and may be designated by the number of standard deviations (SD) from the young normal mean (T score). The WHO developed guidelines for their use in the clinical diagnosis of osteoporosis and is based on the T score, with a T score of less than -1.0 being defined as osteopenic and a T score less than -2.5 being referred as osteoporotic [3].

The purpose of our study was to compare the bone turn-over markers with DEXA findings and with the inflammatory markers, which are well known to induce cardiovascular morbidity and mortality in HD patients. Correlation between bone markers and inflammatory markers were less studied lately in HD patients.

Methods

Twenty-seven patients (17men and 9 women) from a hemodialysis unit were included in the study after written informed consent and anthropometric and biochemical data were recorded. Inclusion criteria were: at least one month of maintenance hemodialysis, no vascular access infection or other clinical signs of infection (pharyngeal and nasal cultures, urine probes-negative for infection), no bone fractures and pre mid-week dialysis probes were taken from venous line of the HD machine. The biochemical data were included in three categories: bone serum markers, DEXA results and inflammatory markers. The bone markers were: serum calcium (mg/dl), serum phosphate (mmol/l), serum alkaline phosphatase AP (U/l), intact parathormon iPTH (pg/ml); the inflammatory markers were: C reactive protein (CRP-mg/l) and fibrinogen (mg/dl).

A certified technician measured BMD at the femoral neck and the lumbar spine (L2 to L4) using a DEXA densitometer. WHO criteria were used for categorizing the respondents based on DEXA results. The DEXA results were recorded as lumbar spine BMD (g/cm²), femoral neck BMD (g/cm²) and T-score (SD from normal). Bone den-

Table I. Parameters in the study group

Biochemical data	Mean±SD	Range	Normal range
Serum calcium(mg/dl)	9.36±0.65	8.14–11.3	8.8–10.3
Serum phosphate(mmol/l)	1.86±0.5	0.89–2.6	0.7–1.4
Total alkaline phosphatase(U/l)	101.4±85.4	56.5–510	40–129
Intact PTH (pg/ml)	491±487	98–1900	<350
Fibrinogen (mg/dl)	477±139	327–775.4	250–450
CRP(mg/l)	18.8±24	1–97.9	0–5
Spine BMD	1.02±0.2	0.5–1.41	
Femoral neck BMD	0.8±0.15	0.6–1.13	
T score	–1.34	0.1–4.4	< 1SD

Fig. 1. Linear regression trendlines for Ca, AP, P and i-PTH

sity (or bone mineral density) is a term normally referring to the amount of mineral matter per square centimeter of bones. Bone density is used in clinical medicine as an indirect indicator of osteoporosis and fracture risk. The T-score was noted, representing the number of standard deviations above or below the mean for a healthy 30 year-old adult of the same sex and ethnicity as the patient.

The statistical analysis included descriptive statistics to rule out the association between bone markers, inflammatory markers and DEXA scan results. The statistical tests used in this study were: mean, SD, t-test, chi-square test and logistic regression. The variables considered were bone parameters, DEXA parameters and inflammatory markers mentioned above. The difference between the subjects was considered significant if the P value were less than 0.05. The correlation threshold for the number of subjects was r=0.30.

Results

The characteristics and clinical variables of the subjects are presented in Table I.

To be noted that Ca had a low level trend, only one case had a high level of serum Ca compared with P, which had higher levels. P levels are an important issue in HD unit related mainly with the diet. Repartition on sexes and age groups are as follows: 9 women (35%) and 19 men (65%), mean age 55 years (SD 11 years). Mean time in dialysis was 2.5 years, with a 3 times per week/4 hours prescription.

We used chi-test to compare the serum values of Ca, P, AP and i-PTH. The following results were found: a significant correlation between Ca and P (p=0.002), as these two parameters describe the metabolic equilibrium of bone

metabolism better. Comparing Ca and AP we found also a significant correlation (p=0.002), patients with low Ca levels having high levels of AP. In the same correlation was Ca with the T-score (p=0.0003), Ca with BMD at the spine level (p=0.0003), CRP with the P levels (p=0.0029). There was no correlation between Ca and inflammatory markers, AP and inflammatory markers and T-score and other bone markers such as Ca, AP and i-PTH.

Using WHO criteria as a cutoff point, 16 subjects (63%) had a T-score lower than -1, of them 11 subjects (41%) had osteopenia and 6 subjects (22%) had osteoporosis.

The correlations between three groups of bone and inflammatory markers were calculated using Pearson's coefficient. The signification threshold was 0.30, and there was

Table II. Correlation coefficient (r) between the studied parameters

	Ca	P	AP	iPTH	Spine	Femoral neck	T-score	Fibrinogen	CRP
Ca	–	0,0238	0,3361	0,0296	-0,0867	0,1371	0,3177	0,1425	0,1340
P		–	0,1656	0,0231	0,2301	0,3065	0,2907	0,3573	0,1222
AP			–	0,0046	0,2013	0,1765	-0,132	0,1181	0,0578
iPTH				–	-0,1449	0,1483	-0,0550	0,0229	0,1810
Spine					–	0,6571	0,6252	-0,0719	-0,1781
Femoral neck						–	0,7154	-0,1469	-0,1296
T-score							–	-0,0423	-0,2206
Fibrinogen								–	0,3771
CRP									–

a strong correlation between Ca-AP (r=0.33, p <0.05), P and femoral neck BMD (r=0.30, p <0.05), Ca and T-score (r=0.31, p <0.05), P and fibrinogen (r=0.36, p <0.01). These results were concordant with the correlations found at the chi-test. There was also a strong correlation between bone densities measured to the spine and femoral neck with the T-score, and between inflammatory markers. The correlations are presented in Table II.

The regression trend line was linear analyzing Ca and AP and P and i-PTH. Figure 1 reveals the trend lines of these parameters.

Discussions

Patients with impaired kidney function have bone and mineral disturbances leading to extra skeletal calcifications and complex changes in bone turnover that predispose them to increased fracture risk and vascular calcifications [4,5]. Reduced synthesis of active vitamin D contributes to secondary hyperparathyroidism. Therefore, this condition is managed with activated vitamin D. However, hypercalcaemia and hyperphosphatemia limit the use of activated vitamin D. Secondary hyperparathyroidism is a common feature in patients with chronic kidney disease. Its serious clinical consequences include renal osteodystrophy, calcific uremic arteriolopathy and valvular calcifications, factors well known to increase morbidity and mortality. Renal osteodystrophy may result in considerable morbidity for patients with end-stage renal disease. Secondary hyperparathyroidism, adynamic bone disease and osteomalacia, the main bone problems in chronic renal failure, may all be responsible for a reduction in bone mineral density (BMD) [6,7].

Mineral bone metabolism is significantly modified in HD patients, due to the absence of active vitamin D, secondary hyperparathyroidism and lack of phosphate elimination due to kidney failure. Bone metabolism is influenced by Ca, P, AP and i-PTH but also by other factors which have been extensively studied. There is a strong evidence that low Ca levels stimulate increased secretion of iPTH, but also the P level influences the vascular calcifications in HD patients [8]. We found a significant correlation between Ca levels and P, AP. Low Ca levels had a linear trend line with i-PTH, as it usually happens [9]. As we wanted to compare the bone markers with inflammatory markers, we found that the CRP levels are correlated to phosphorus, very few data existing in the literature on this regard. It is well known that vascular calcifications are increased by inflammation, extensive studies indicated the role of CRP and other mediators of inflammation. As the inflammation is a stimulator for atherosclerosis, there are two groups of biochemical inflammatory markers that are increasing the cardio-vascular risk to this category of patients. Therefore lowering the inflammation is another important tool to dialyzed patients which is hard to obtain because of many complications that can occur during dialysis: infections, dialysis membrane incompatibility, tubes,

hyperparathyroidism, uncontrolled hypertension [10,11].

Regarding hyperphosphatemia, a common disturbance in HD patients, we found a correlation with hypocalcaemia, hyperparathyroidism, fibrinogen and CRP levels. This can reveal that P can be an important parameter associated to inflammation. There are studies concerning the relationship of high P level and infection related events [12]. Hyperphosphatemia was also correlated with i-PTH levels, and no statistical difference was noted regarding hypocalcaemia. This can be motivated through increased diet intake of P, rather than Ca and iPTH levels, leading to hyperphosphatemia. Diet intake of P can easily be modified, an intense medical and psychological counseling being necessary. Unfortunately, hypophosphatemic diet is hard to obtain [12,13].

Bone metabolism, known as a main target for disturbances in dialysis patients is related mainly to iPTH levels, other markers being actively involved [14,15]. In our study, the DEXA findings correlated well with Ca levels, indicating that hypocalcaemia must be corrected in order to obtain a good bone health.

Osteoporosis is a predictor for bone fractures, affecting the quality of life, but the most important consequence of it are the vascular calcifications, further aggravated by inflammatory biomarkers.

Conclusions

Mineral bone disorder is a very important problem in chronic kidney disease patients, involving many physiological changes. High phosphate levels may be associated with increased inflammation, as showed by CRP values, contributing further to the rationale for aggressive management of hyperphosphatemia in these patients.

Hyperphosphatemia is better correlated with iPTH level than hypocalcaemia. Instead, hypocalcaemia is correlated better with bone density changes. The relationship of Ca and AP indicates that a normal serum calcium level must be on objective for HD patients, as it is the iPTH level. These biochemical markers can be adjusted by complex nutritional and medical strategies.

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