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## 25-HYDROXYVITAMIN D LEVELS AND BONE HISTOMORPHOMETRY IN HEMODIALYSIS RENAL OSTEODYSTROPHY

Giorgio Coen<sup>a</sup> et al.  
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**Background:** The importance of 25-hydroxyvitamin D (25-OHD) serum levels in hemodialysis chronic renal failure has not been so far histologically evaluated. Information still lacking relate to the effect of 25-OHD deficiency on serum PTH levels and on bone and its relationship with calcitriol levels.

**Methods:** This retrospective study has been performed on a cohort of 104 patients on hemodialysis from more than 12 months, subjected to transiliac bone biopsy for histologic, histomorphometric and histodynamic evaluation. The patients, M/F,61/43, mean age 52.9±11.7 years, HD age 97.4±61.4 months, were treated with standard hemodialysis and did not receive any vitamin D supplementation. Treatment with calcitriol was not underway at the time of the biopsy. Transiliac bone biopsies were performed after double tetracyclin labels. In addition, serum intact PTH, Alkaline Phosphatase, and 25-OHD were measured. Calcitriol serum levels was also measured in a subset of patients (n=53). The patients were divided according to serum 25-OHD levels in three groups: (A) 0-15 (15 pts), (B)15-30 (38 pts) and (C) >30 ng/ml (51 pts).

**Results:** There was no significant difference in average age, HD-age, serum PTH (490±494 , 670±627 and 489±436 pg/ml respectively [M±SD]), alkaline phosphatase and calcitriol between the three groups. The parameters double-labelled Surface, trabecular Mineralizing Surface, Bone Formation Rate were significantly lower in group A than in the other groups ( p <0.03, <0.03 and <0.02 respectively). Osteoblast Surface and Adjusted Apposition Rate were borderline significantly lower in group A ( p<0.06 and <0.10). There was no statistical difference in the biochemical and bone parameters between groups B and C. A positive significant correlation was found between several bone static and dynamic parameters and 25OHD levels in the range 0-30 ng/ml, showing a vitamin D dependence of bone turnover at these serum levels. However actual evidence of an effect on bone of 25-OHD deficiency was found at serum levels below 20 ng/ml. With increasing 25-OHD levels beyond 40 ng/ml a downslope of parameters of bone turnover was also observed.

**Conclusions:** Since PTH serum levels are equally elevated in low and high 25-OHD patients, while calcitriol levels are constantly low, an effect of 25-OHD deficiency (group A) on bone, consisting of a mineralization and bone formation defect, can be hypotesized. The effect of vitamin D deficiency of bone turnover is found below 20 ng/ml. The optimal level of 25-OHD appears to be in the order of 20-40 ng/ml. Levels of the D metabolite higher than 40 ng/ml are accompanied by a reduction of bone turnover.

## **HISTOMORPHOMETRIC ASSESSMENT OF BONE TURNOVER IN URAEMIC PATIENTS: COMPARISON BETWEEN ACTIVATION FREQUENCY AND BONE FORMATION RATE.**

Ballanti P, Coen G, et al.

Histopathology. 2001 Jun;38(6):571-83.

**AIMS:** The histomorphometric assessment of bone formation rate (BFR/BS) in bone biopsies from uraemic patients is of crucial importance in differentiating low from high turnover types of renal osteodystrophy. However, since BFR/BS relies on osteoblasts, activation frequency (Ac.f), encompassing all remodelling phases, has recently been preferred to BFR/BS. This study was carried out to consider whether estimation of Ac.f is superior, in practical terms, to that of BFR/BS in distinguishing between different rates of bone turnover in uraemic patients.

**METHODS AND RESULTS:** Bone biopsies from 27 patients in predialysis (20 men and seven women; mean age 53 +/- 12 years) and 37 in haemodialysis (22 men and 15 women; mean age 53 +/- 12 years) were examined. The types of renal osteodystrophy were classified on the basis of morphology. Bone formation rate and Ac.f were evaluated according to standardized procedures. The Ac.f was calculated both as a ratio between BFR/BS and wall thickness (W.Th) and as a reciprocal of erosion, formation and quiescent periods (EP, FP and QP). Patients were affected by renal osteodystrophy with predominant hyperparathyroidism (two predialysis and 16 dialysis), predominant osteomalacia (three predialysis and seven dialysis) or that of advanced (nine predialysis and five dialysis) or mild (seven predialysis and four dialysis) mixed type or adynamic type (six predialysis and five dialysis). Activation frequency, which with either formula requires the measurement of W.Th, i.e. the thickness of bone structural units (BSUs), was not calculated in three dialysis patients with severe hyperparathyroidism and in one predialysis and four dialysis patients with severe osteomalacia, because only incomplete BSUs were found. In dialysis, EP was higher in the adynamic than in the other types of osteodystrophy. During both predialysis and dialysis, FP was higher in osteomalacia than in the other forms of osteodystrophy, and in adynamic osteopathy than in hyperparathyroidism or in advanced and mild mixed osteodystrophy. During predialysis and dialysis, QP was higher in the adynamic than in the other forms of osteodystrophy. Correlations were found between BFR/BS and Ac.f, during predialysis ( $r=0.97$ ) and dialysis ( $r=0.95$ ).

**CONCLUSIONS:** The superiority of Ac.f in assessing bone turnover, in comparison to BFR/BS, is conceptual rather than practical. The highest values for FP in osteomalacia and for QP in adynamic bone allow a clearer characterization of these low turnover conditions.

**PTH 1-84 AND PTH "7-84" IN THE NONINVASIVE DIAGNOSIS OF RENAL BONE DISEASE.**

Coen G, Bonucci E, Ballanti P, et al.  
Am J Kidney Dis. 2002 Aug;40(2):348-54.

BACKGROUND: The intact parathyroid hormone (PTH) assay evaluates levels of serum 1-84 PTH and other N-terminally truncated PTH fragments, mainly PTH "7-84." This PTH molecule has been found experimentally to interfere with biological activity of PTH 1-84, perhaps through

its binding to the PTH receptor complex. Therefore, assuming that high levels of PTH 7-84 are a cause of bone resistance to PTH, it has been hypothesized that a decreased 1-84 to 7-84 PTH ratio caused by a relative increase in PTH 7-84 level might help in the noninvasive diagnosis of low-turnover osteodystrophy (LTO).

**METHODS:** This study was performed in 35 patients with chronic renal failure on hemodialysis therapy who underwent bone biopsy for a histological, histomorphometric, and histodynamic study. In addition, blood samples were obtained for intact PTH, 1-84 PTH, and total PTH assays. PTH 7-84 level was obtained from the difference between total and 1-84 PTH assay results.

**RESULTS:** Nine patients had LTO (8 patients, adynamic bone disease; 1 patient, osteomalacia), 12 patients had hyperparathyroidism (HP), and 14 patients had mixed osteodystrophy (MO). On average, 1-84 PTH levels were approximately 60% of mean values for intact PTH. The two assays were strictly correlated. Average 1-84 to 7-84 PTH ratios were  $1.57 \pm 0.85$ ,  $1.73 \pm 1.31$ , and  $1.95 \pm 2.1$  in the three histological groups (LTO, HP, and MO, respectively), with no significant difference.

**CONCLUSION:** Contrary to previous expectations, results do not favor the hypothesis of a role of 7-84 PTH in bone resistance in renal osteodystrophy. The 1-84 to 7-84 PTH ratio is not a marker of LTO and is of no use in noninvasive histological diagnosis.

## **SERUM LEPTIN IN DIALYSIS RENAL OSTEODYSTROPHY**

Giorgio Coen<sup>o</sup> et al.  
AJKD 2003

**Background:** Leptin is a hormone considered to play a role in the prevention of osteoporosis and probably acting on the bone tissue through inhibition of osteoclasia. Its action has been attributed to interference in the OPG/RANKL equilibrium. Contradictory data have also been reported, casting doubts on the positive effect on bone mass of the hormone, at least in males. The relation

between serum leptin levels of dialysis patients and renal osteodystrophy, defined by histomorphometric and histodynamic parameters of bone, so far has not been studied.

**Protocol and methods:** The study has been carried out on 46 HD patients, 32 males and 14 females, aged  $57.2 \pm 11.4$  years. A transiliac bone biopsy after double tetracycline labeling was performed, for histologic, histomorphometric and histodynamic studies. Blood samples were drawn for leptin, iPTH, PTH 1-84, Osteoprotegerin, BoneAP, Ca, P, 25-OHD, and calcitriol. Serum leptin was measured with a RIA (Mediagnost, Germany).

**Results:** 18 patients had mixed osteodystrophy (MO), 17 hyperparathyroidism, 9 adynamic bone disease and 2 osteomalacia. Aluminum histochemistry was positive in one case with ABD and one with MO. A sex difference was found in serum leptin levels,  $48.9 \pm 38$  in women and  $12.2 \pm 13.2$  ng/ml in men ( $p < 0.0002$ ). In the entire population lnleptin was significantly correlated to BMI ( $p < 0.01$ ). SDS leptin (adjusted for BMI, gender and age) was inversely correlated to PTH 1-84, OcS/BS ( $p < 0.05$ ) and borderline to BFR/BS. Correlations between leptin and the other parameters was enhanced in the male population. SDS leptin was inversely correlated to OcS/BS ( $p < 0.01$ ), Noc/BS ( $p < 0.01$ ) and MAR ( $p < 0.01$ ). In addition SDS leptin correlated inversely borderline to ObS/BS ( $p < 0.06$ ) and significantly to Osteoprotegerin ( $p < 0.05$ ). No difference was found in serum leptin levels between the histologic groups.

**Conclusions:** The reported data confirm the finding of a positive relation between serum leptin and BMI and the higher levels in women compared to men. Serum leptin is connected with bone resorption and also bone formation, both inversely related to its serum levels. The decrease in osteoclasia which goes along with increasing serum leptin levels does not seem to be related to an enhanced Osteoprotegerin effect, since it was accompanied by decreased Osteoprotegerin levels. Low turnover bone disease does not appear to be caused by increased serum leptin levels. The nature of the interrelation between serum leptin and PTH 1-84 requires further studies.