Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure

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Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure.

Background. Metabolic bone disease might commence early in the course of renal failure. This study therefore examined the frequency and severity of the skeletal changes in predialysis chronic renal failure by measurements of bone mineral density (BMD), biochemical markers of bone turnover (osteocalcin, bone-specific alkaline phosphatase, carboxy terminal propopeptide of type I collagen, and carboxy-terminal telopeptide of type I collagen), parathyroid hormone (PTH), ionized calcium (Ca$^{++}$), phosphate (P), and vitamin D metabolites.

Methods. The study was performed in 113 patients (male/female: 82/31) with chronic renal diseases [mean glomerular filtration rate (GFR) of 37 ml/min] and in 89 matched, normal control subjects. Dividing the patients into quartiles according to GFR revealed that BMD decreased with the gradual decline in renal function at all the measured skeletal sites, but was most pronounced in the femur: 0.63 ± 0.03, 0.74 ± 0.02, 0.77 ± 0.02, and 0.82 ± 0.03 g/cm$^2$ in each quartile from lowest to highest GFR compared with 0.82 ± 0.02 g/cm$^2$ in the control group ($P < 0.0001$). All of the measured bone markers showed increasing plasma levels with the more advanced stages of renal failure. Serum PTH and serum P levels increased, whereas serum Ca$^{++}$ and 1,25-dihydroxyvitamin D decreased. BMD Z-scores of the femur and of the forearm correlated to the biochemical markers and to PTH ($P < 0.05$ to $P < 0.0001$). The biochemical markers all showed strong correlations to PTH, also when corrected for the effect of the decline in GFR ($r = 0.40$ to 0.92, $P < 0.01$ to $P < 0.0001$).

Conclusion. Skeletal changes are initiated at an early stage of chronic renal failure, as estimated from reduced BMD and elevated levels of PTH and from the biochemical markers of both bone formation and bone resorption.

Key words: BMD, biochemical bone markers, parathyroid hormone, metabolic bone disease, skeleton, renal osteodystrophy, osteopenia, dialysis.

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(AP), and the vitamin D status. However, currently, biochemical markers of bone turnover are being evaluated in the diagnosis and monitoring of metabolic bone disease [18]. Among these, osteocalcin, carboxy terminal propeptide of type I collagen (PICP), and bone-specific AP (BAP) reflect bone formation, whereas carboxy-terminal telopeptide of type I collagen (ICTP) reflects bone resorption.

The usefulness of these new potential markers of bone turnover in patients with renal failure has not been clarified, although a few studies have shown a good correlation between some of the bone markers and some of the histomorphometric parameters of bone turnover in patients on maintenance dialysis [19, 20].

This study was designed further to examine the frequency and severity of the skeletal demineralization in patients with predialysis CRF by measurements of the BMD in different skeletal regions (trabecular and cortical bone) and by evaluation of the serum levels of osteocalcin, PICP, BAP, and ICTP in patients with mild to moderate CRF as compared with these measures of bone metabolism in a healthy control group.

METHODS

The study design was cross-sectional. Patients were recruited from the outpatient clinics at three Danish County Hospitals. All hospital records of patients followed at the nephrological departments were evaluated, and patients with a serum creatinine value above 130 \( \mu \text{mol/liter} \) (upper normal range) were invited to participate, unless exclusion criteria were met. Exclusion criteria included: patients with acute renal failure, patients receiving maintenance dialysis, kidney transplanted patients, patients who currently were taking or who within the last five years had been taking medication known to influence bone metabolism [such as corticosteroids, other immunosuppressive agents, hormone replacement therapy (HRT), vitamin D analogs, anticoagulants, or lithium], and bedridden patients. Thus, several patients with glomerulonephritis (immunosuppressive therapy) and several female patients (HRT) had to be omitted. Four hundred hospital records were evaluated. One hundred and fifty patients were contacted, and 128 agreed to participate. Fifteen had to be excluded because of the presence of one or more exclusion criteria, and therefore, 113 patients (31 females of whom 16 were postmenopausal and 82 males), all Caucasian, were included. None of the patients were on a protein-restricted diet, and none received phosphate binders at the time of the investigation.

The demographic data of the patients are presented in Table 1. The patients were stratified into quartiles according to the glomerular filtration rate (GFR) in order to examine the influence of increasing impairment of the renal function on BMD and the biochemical bone markers. Group 1 (GFR 6 to 26 ml/min) represented patients with the most advanced stages of renal failure. Groups 2 (GFR 27 to 47 ml/min) and 3 (GFR 47 to 69 ml/min) represented patients with moderate and mild renal impairment, respectively, whereas group 4 (GFR 71 to 110 ml/min) was established from a group of patients with a serum creatinine level above the upper normal range (130 \( \mu \text{mol/liter} \)), but who had a GFR within the normal range when the creatinine clearance was measured. Group 5 represented the control subjects. The patients in group 1 had a lower body mass index (BMI) of 24 ± 4 kg/m\(^2\) compared with the other patient groups, in which BMI was 27 ± 5 kg/m\(^2\). There was no difference in age between the groups. In groups 1 through 3, females constituted 29, 35, and 35% of the patients, respectively, whereas only 14% of the patients in group 4 were women.

Twenty-two patients with insulin-dependent diabetes were included and equally distributed between groups 1 through 3, whereas there were fewer diabetic patients in group 4.

The control group of healthy subjects (\( N = 89, \) group 5) was chosen to match the patient group with regards to gender, age (within 5 years for women and within 10 years for men), and body weight (±5%) in order to eliminate the effect of these three major determinants on the BMD, which are unrelated to the renal disease [21, 22]. Healthy subjects were recruited among hospital staff along with their relatives and friends. The study was approved by the regional committee of ethics. All participants gave their written informed consent.

Bone density measurements

Bone mineral density of the lumbar spine (L2 through L4) in the anteroposterior projection, the femoral neck, the distal forearm, and the total body were determined by DEXA on a QDR2000 bone densitometer (Hologic Inc., Waltham, MA, USA) expressed as exact values in g/cm\(^2\) and as Z scores, which represent the BMD value normalized for age- and sex-matched mean, or as T scores that refer to the young adult reference mean calculated from the manufacturer’s database of 400 males and 900 females. Coefficients of variation at our clinic are 0.9% at the lumbar spine, 1.9% at the femoral neck, 1.0% at the distal forearm, and 0.8% for the whole-body scan.

Biochemical measurements

Blood samples were drawn after an overnight fast between 8 and 10 a.m. Urine was collected for 24 hours in order to calculate the creatinine clearance rates. Serum samples for determination of biochemical bone markers were stored at \( -80^\circ \text{C} \) until analysis. GFRs were assessed by a 24-hour creatinine clearance value. Serum Ca\(^{++} \) and serum P were measured using routine laboratory
Table 1. Clinical features of patients with chronic renal failure stratified into quartiles by GFR and of the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Gender f/m</td>
<td>10/18</td>
<td>8/20</td>
<td>8/20</td>
<td>4/24</td>
</tr>
<tr>
<td>Age years</td>
<td>59 (14)</td>
<td>55 (13)</td>
<td>54 (12)</td>
<td>53 (13)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>25 (5)</td>
<td>27 (5)</td>
<td>27 (6)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>Mean GFR ml/min</td>
<td>16 (6)</td>
<td>39 (8)</td>
<td>58 (10)</td>
<td>86 (19)</td>
</tr>
</tbody>
</table>

Underlying renal disease

<table>
<thead>
<tr>
<th>IDDM</th>
<th>NIDDM</th>
<th>Glom. neph.</th>
<th>HKD</th>
<th>PKD</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (10)</td>
<td>11 (38)</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td>5 (17)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Abbreviations are: BMI, body mass index; HKD, hypertensive kidney disease; PKD, polycystic kidney disease; Miscellaneous, congenital malformations, Alport syndrome, gout- and drug-induced nephropathy, unknown cause. Values are means ± sd or N (%).

RESULTS

Bone mineral density

Bone mineral density was reduced at all areas of the skeleton examined, when all the patients were compared and the interassay CV was 5.8%.

Serum 25-hydroxyvitamin D was measured by a radioimmunoassay (Incstar Kit 60160; Incstar Corp., Stillwater, MN, USA) after acetonitrile extraction. Intra-assay and interassay CVs were 8 and 15%, respectively. Serum 1,25-dihydroxyvitamin D was extracted by acetonitrile, purified through a C18-OH reverse phase column, and finally measured by a radioimmunoassay (Nichols-Kit 40-6040). The intra-assay and interassay CVs were 6.5 and 13.2%.

Serum cross-linked ICTP was measured by an equilibrium radioimmunoassay from Orion Diagnostics (Espoo, Finland). Intra-assay and interassay CVs were 5 and 6% [23]. The PICP was measured by an equilibrium RIA (Orion Diagnostics), with an intra-assay and interassay CV of 3 and 5%, respectively. Serum AP was measured spectrophotometrically using serum nitrophenylphosphate as the substrate according to recommendations from the Scandinavian Committee on Enzymes [24]. Intra-assay and interassay CVs were 1.8 and 3%, respectively. BAP was measured spectrophotometrically in the supernatant after lectin precipitation. The intra-assay and interassay CVs were 8 and 25%. Serum osteocalcin was determined by a radioimmunoassay using rabbit anti-serum against bovine bone gla protein. The intra-assay and interassay CVs were 5 and 10% [25].

Statistical analysis

Students unpaired t-test was used to evaluate the differences between patients and control subjects. Analysis of variance or the Kruskal–Wallis test was used to test differences between groups. Bivariate correlations were performed in log-transformed data. A forward stepwise regression analysis was used to detect predictors of BMD [26].

Statistical analyses were performed using the software Stat View 4.5 (Abacus Concepts, Berkeley, CA, USA).

RESULTS

Bone mineral density

Bone mineral density was reduced at all areas of the skeleton examined, when all the patients were compared with the matched control group. The difference in BMD at the site of the lumbar spine was −6.3% (0.98 ± 0.04 vs. 1.04 ± 0.02 g/cm², P < 0.05); the femoral neck, −12.1% (0.72 ± 0.01 vs. 0.82 ± 0.02, P < 0.0001); the distal forearm, −5.7% (0.68 ± 0.01 vs. 0.72 ± 0.01, P < 0.05); and the total body, −4.2% (1.08 ± 0.01 vs. 1.12 ± 0.01, P < 0.05).

When the patients were separated into quartiles according to the degree of renal failure, it was found that BMD decreased in relationship to the decrease in GFR at all measured sites, as shown in Figure 1.

The greatest differences between the patient groups and the control group were found at the site of the femur (P < 0.05), as well as between patients and control subjects (P < 0.05), were found. At the levels of the lumbar spine, the distal forearm and the total body significant differences (P < 0.05 to P < 0.001) were identified between the lowest GFR quartile (group 1) and the control group (group 5).

The prevalence of osteoporosis as defined by the World Health Organization (a T score of less than −2.5) was significantly increased (P < 0.0001) in the patient group (30%) as compared with the control group (10%) and even more so in the patients with the more advanced stages of renal failure (Table 2).
The possible impact of the age at onset of CRF on BMD was examined by dividing all the patients into two groups according to the onset of the renal disease before or after the age of 30 years, which is the age of peak bone mass [27]. The results were expressed as Z scores (Fig. 2) in order to account for the differences in current age and sex between the two groups. Patients with an early debut of the renal disease had significantly reduced BMD as compared with patients with a debut of the disease later in life at the sites of the lumbar spine, the femoral neck, and the distal forearm.

When dividing the study group according to whether the patients had insulin-dependent diabetes mellitus (IDDM) or other kidney diseases, it was found that the combination of impaired renal function and IDDM enhanced the risk of low BMD, as illustrated in Figure 3. The BMD Z scores of the femoral neck and of the distal forearm were significantly reduced in the group of patients with IDDM, as compared with patients with different chronic renal diseases, whereas the BMD of the lumbar spine was not significantly reduced.

### Parameters of calcium homeostasis

Patients with predialysis CRF exhibited several abnormal parameters involved in the bone metabolism, as compared with their matched controls.

As shown in Figure 4, serum PTH and P levels increased significantly ($P < 0.05$) with the decline in GFR, whereas serum Ca$^{2+}$ decreased ($P < 0.05$), with the lowest circulating levels found in patients with the most severe degree of renal impairment. The serum levels of 1,25-dihydroxyvitamin D were also reduced ($P < 0.05$) in the advanced stages of CRF.

### Biochemical markers of bone turnover

The mean serum levels of the different biochemical markers of bone formation (osteocalcin, PICP, and BAP), as well as of bone resorption (ICTP), all increased with the more advanced stages of renal impairment. Significantly increased ($P < 0.05$) serum values of osteocalcin, BAP, PICP, and ICTP were found in the group of patients with the most advanced stages of renal failure when compared with the control group (Fig. 5).
Bivariate correlations between the biochemical bone markers and PTH and GFR are shown in Table 3. A strong positive correlation ($P < 0.0001$) was demonstrated between PTH and the bone markers osteocalcin, BAP, and ICTP, whereas the correlation to PICP was not significant. A significant inverse correlation ($P < 0.0001$) was found between PTH and GFR. Each of the measured bone markers was negatively correlated to GFR ($P < 0.05$ to $P < 0.001$). To further examine the relationship between PTH and the bone markers, a partial correlation analysis was performed. The correlation between PTH and the bone markers remained significant after the adjustment for the influence of GFR: osteocalcin, $r = 0.89$, $P < 0.0001$; BAP, $r = 0.69$, $P < 0.0001$; ICTP, $r = 0.64$, $P < 0.0001$; and PICP, $r = 0.27$, $P < 0.05$.

In order to examine the effect of the serum levels of PTH on BMD, patients were divided into three groups according to the degree of secondary hyperparathyroidism: Serum PTH increased to more than two times above normal limits (120 pg/ml), serum PTH between 60 and 120 pg/ml, and serum PTH within normal reference range (<60 pg/ml). A negative association between the degree of secondary hyperparathyroidism and BMD was found at the sites of the lumbar spine, the hip, and the total body, but not in the arm, and the patients who had the most severe degrees of secondary hyperparathyroidism had the most reduced levels of BMD as compared with the patients with PTH levels within the normal reference range (Fig. 6).

To examine the importance of the different risk factors for reduced BMD, a forward stepwise regression analysis was performed with BMD of the hip given in Z scores as the dependent variable and BMI, creatinine clearance rates, serum PTH, and the duration of and age at onset of the renal disease as independent variables. BMI and creatinine clearance rates were the two variables that significantly predicted BMD, accounting for 19% of the variation ($R^2 = 0.19$, $P < 0.001$) in BMD, and each of the

Fig. 3. Bone mineral density (Z-scores) of patients with insulin-dependent diabetes mellitus (IDDM; ■) compared to patients with other chronic renal diseases (□). *$P < 0.05$, by Student’s t-test.

Fig. 4. Parameters of calcium homeostasis in patients with chronic renal failure divided into quartiles according to glomerular filtration rate (GFR) compared to control subjects. Symbols are: (●) group 1, mean GFR 16 ml/min; (▲) group 2, mean GFR 39 ml/min; (■) group 3, mean GFR 58 ml/min; (●) group 4, mean GFR 83 ml/min; (○) group 5, control group, mean GFR 144 ml/min. *$P < 0.05$, Kruskal-Wallis test.
Table 3. Correlations between biochemical bone markers, PTH and GFR

<table>
<thead>
<tr>
<th></th>
<th>logPTH</th>
<th>logBGP</th>
<th>logICTP</th>
<th>logBAP</th>
<th>logPICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>-0.62b</td>
<td>-0.58b</td>
<td>-0.64b</td>
<td>-0.34a</td>
<td>-0.24a</td>
</tr>
<tr>
<td>LogPTH</td>
<td></td>
<td>0.80b</td>
<td>0.67b</td>
<td>0.52b</td>
<td>0.47b</td>
</tr>
<tr>
<td>LogBGP</td>
<td></td>
<td></td>
<td>0.49b</td>
<td>0.35b</td>
<td></td>
</tr>
<tr>
<td>LogICTP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.53b</td>
</tr>
<tr>
<td>LogBAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LogPICP</td>
<td></td>
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</tr>
</tbody>
</table>

* P < 0.05, b P < 0.0001

Fig. 6. Bone mineral density (BMD; Z-scores) in patients with chronic renal failure divided according to the degree of secondary hyperparathyroidism. Patients were divided into three groups: serum parathyroid hormone (PTH) < 60 pg/ml (●); serum PTH between 60 and 120 pg/ml (▲); serum PTH > 120 pg/ml (◆). *P < 0.05, Student’s t-test.

two variables contributed equally [standard coefficients (standard errors) of 0.24 (0.03) and 0.30 (0.006)]. Serum PTH and duration and age at onset of the renal disease were not significant predictors in this type of analysis.

DISCUSSION

In this group of 113 patients with predialysis CRF, BMD was reduced in the axial, as well as in the appendicular skeleton, indicating that both cortical bone and trabecular bone were affected. The prevalence of overt osteoporosis (T-score < −2.5) was found to be increased when compared with healthy sex-, age-, and weight-matched controls. The study included patients ranging from mild to severe degrees of renal failure, and the decrease in BMD was most pronounced in patients with the lowest levels of GFR. Debut of the renal disease before skeletal maturity was reached and diabetic nephropathy further increased the risk of low BMD. In a multivariate analysis, GFR and BMI were the strongest predictors of BMD.

Secondary HPT, reduced levels of serum Ca++ and serum 1,25-dihydroxyvitamin D, and increased serum levels of P were evident in the patients with moderate to severe degrees of renal failure.
The biochemical markers of bone turnover (osteocalcin, ICTP, PICP, and BAP) all exhibited elevated serum levels in the patient groups with the more advanced stages of renal failure corresponding to the degree of secondary HPT. Adjusting the correlation between PTH and the different biochemical bone markers for the influence of GFR did not change the results, indicating that the increased levels of the different biochemical bone markers might indeed represent increased bone turnover caused by the secondary hyperparathyroidism and not just caused by retention of the substances. The presence of advanced secondary HPT (serum PTH > 120 pg/ml) was associated with decreased BMD.

Whether BMD measurement is an appropriate tool in the diagnosis and/or monitoring of renal bone disease is still a matter of debate. DeVita et al concluded from a study comparing histomorphometric results to DEXA results that the sensitivity of BMD measurements was poor [20]. Furthermore, Malluche and Fauergere pointed out that DEXA measurements did not separate the different types of ROD (high turnover, low turnover, and mixed uremic osteodystrophy), which may be essential for the choice of treatment [28]. However, the severity of the symptoms of ROD may not correlate with the histological changes, as some patients have severely abnormal bone histology and no symptoms and vice versa [2]. Patients with reduced bone mass are at great risk of experiencing fractures, the most severe consequence of ROD, and this part of the population at risk can be detected by DEXA measurements. This investigation has shown that even in predialysis stages of CRF, a substantial proportion of the patients, patients who would not be considered for bone biopsies in the daily clinic, showed signs of disturbed bone metabolism as measured by noninvasive methods.

Specific biochemical markers of bone turnover have been studied extensively over the last decade, but the actual concept in the bone research field is that these biochemical markers are of no certain diagnostic use in the single patient, but might be of some use in following the results of clinical trials [29, 30]. The reasons for the limitation in the daily clinical use are a substantial intra-individual variability [31] and a poor correlation between the markers and the rate of bone loss [32].

Only a few publications exist on the use of biochemical bone markers in patients with predialysis CRF. In those, it was concluded that the retention of the bone markers osteocalcin and ICTP caused by the reduced renal clearance [23, 33] introduced an error, which made it difficult to interpret the results. The clearance of PICP and BAP is not by the kidney, but takes place in the liver, which may render these markers more suitable in the evaluation of renal bone disease [34, 35].

The results of this study support the findings from histomorphometric studies [3, 8, 36] that skeletal changes commence at an early stage of renal failure. Bianchi et al reported that patients with predialysis CRF have reduced BMD levels that correlate to the reduction in GFR [16]. However, they concluded that only cortical bone was affected, which is in disagreement with the present results showing that trabecular and cortical bone are equally affected in these uremic patients. Reasons for this discrepancy might be due to different scanning techniques and different patient groups.

It has been proposed that the duration of the renal disease might be an important risk factor for low BMD. In dialysis patients, some studies showed a negative correlation between time on dialysis and BMD [11, 12], whereas others failed to prove such a correlation [8, 9, 37]. In those studies, the duration of the predialysis phase of the renal disease was not considered, which from our investigation seems to be of importance when evaluating renal bone disease. Further support for this argument was supplied by Heaf, Hielsen, and Mogensen, who, in a group of patients followed from predialysis to dialysis stages of their renal disease, found that some of the patients with the lowest BMD at the time when dialysis treatment was commenced actually gained bone mass within one year, perhaps because of the improvement in the uremic state or because of supplementation with 1,25-dihydroxy-vitamin D [8].

Therefore, when considering the initiation and the early stages of ROD, the predialysis period seems as important as the end-stage period.

It has been suggested that the underlying renal disease may have some influence on the severity of the renal bone disease. Cundy et al, in a study on histomorphometric changes in predialysis patients, demonstrated that tubulointerstitial renal diseases affect the skeleton more than glomerulovascular diseases and suggested that this might be due to more pronounced changes of the calcium homeostasis caused by the former group of diseases [38]. This is in opposition to the results of others in which patients with diabetic nephropathy [15, 39] have been found to have increased risk of renal bone disease. It is not clear, however, whether the diabetic state or the renal complication is the most important factor, as others have shown that IDDM by itself is a risk factor for reduced BMD [40, 41], whereas patients with NIDDM have normal or even increased BMD [42]. Furthermore, Moorhead et al found that patients with polycystic kidney disease were less susceptible to bone changes than patients with other renal diseases [43].

In this study, IDDM but not NIDDM was found to be a risk factor for low BMD, whereas the patient groups with other renal diseases each comprised numbers of patients that were too limited to be evaluated separately.

Reduced BMD has been demonstrated in children and adolescents with CRF [44]. This is in accordance with the results of this investigation, where it appears to be of
importance whether chronic renal disease occurs before skeletal maturity is reached, suggesting that patients with a debut of the renal disease before adulthood may not achieve an adequate peak bone mass and, therefore, have an increased risk of developing osteopenia when factors causing accelerated bone loss appear.

The secondary hyperparathyroidism and low serum levels of 1,25-dihydroxyvitamin D, which become evident in end-stage renal failure, have been shown to be initiated at early stages of the renal disease [45, 46], which corroborate with the results of this study.

The elevated levels of the biochemical bone markers found in this study are in accordance with results from a few other studies performed in predialysis patients in which the bone formation markers osteocalcin [47], BAP [48], and PICP [34] have been evaluated. Elevated serum levels of the bone markers have been reported consistently in patients receiving maintenance dialysis [51, 48–52], but in these patients with none or very little remaining kidney function, the accumulation of substances may be pronounced.

The apparent lower serum concentrations of PICP and BAP in the patients with incipient renal failure (group 4) may be coincidental, as there was no significant difference from the values of the control group, or it may be due to the fact that this group consisted almost exclusively of male subjects, who may have lower values of bone markers than female subjects in the age groups mainly represented in this study [18].

The strong correlation demonstrated in this study between the severity of secondary HPT and the serum levels of the measured biochemical bone markers, whether cleared by the kidney or by the liver, persisted when the results were corrected for GFR. This may suggest that the secondary HPT in patients with severely impaired renal function results in an increased bone turnover with increased bone formation as well as increased bone resorption, which has been demonstrated in large population studies by Malluche et al and Hamdy et al [1, 3].

It cannot be excluded that in the terminal stages of CRF, retention of osteocalcin and ICTP is of some importance. However, the state of high bone turnover caused by the secondary HPT seems, from this study, to be a more important determinant of the increased serum levels of osteocalcin and ICTP than the GFR. Thus, the inverse correlation between BMD and PTH and the measured bone markers demonstrated in this study is consistent with the results of Bianchi et al [16] and others [53, 54]. However, neither Heaf, Nielsen, and Mogensen [8] nor Huraib et al [10] found such correlations in dialysis patients. These apparent discrepancies may be explained by the fact that BMD is determined by many factors and reflects both past and current influences [21, 54], whereas the levels of the biochemical bone markers and PTH describe the immediate metabolic state of the skeleton, a state that may or may not have been established long enough to have caused substantial bone loss.

Despite the obvious adverse effects on BMD of the different aspects of CRF that were evaluated in this study, a considerable variation in BMD exists within this group of patients. The contribution of other factors such as heritage, hormonal status, and physical activity is possible. The advantage of a longitudinal study as opposed to the cross-sectional design used in this study is therefore obvious, and long-term prospective studies with skeletal symptoms and fragility fractures as efficacy endpoints are needed to validate the predictive value of these noninvasive methods in relationship to symptomatic bone disease in patients with CRF.

In conclusion, a state of high bone turnover resulting in reduced bone density is present early in the course of CRF (GFR 6 to 70 ml/min), as estimated from reduced BMD levels, elevated serum PTH, reduced 1,25-dihydroxyvitamin D levels, and the elevated levels of biochemical markers of both bone formation (osteocalcin, PICP, BAP) and bone resorption (ICTP). This study further demonstrates that useful information on the bone status can be obtained by using noninvasive methods, such as BMD measurements and biochemical markers of skeletal formation and resorption in patients with predialysis CRF.

ACKNOWLEDGMENTS

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