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Quantitative computed tomography for spinal bone mineral measurements in chronic renal failure

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Abstract

The aim of this study was to assess non-invasively the status of spinal trabecular bone in patients with chronic renal failure and the influence of the disease stage. Single energy quantitative computed tomography (CT) was used in 89 patients with chronic renal failure to measure spinal trabecular bone equivalent density. 23 patients were independent of dialysis and 66 were receiving long-term haemodialysis. Spinal trabecular bone density of the patients was compared with locally determined normal ranges. Although trabecular bone mineral density (BMD) was lower (9% on average) in the patients who were not dependent on dialysis compared with the predicted mean normal values (BMD_p) for age- and sex-matched normal subjects, the difference was not statistically significant. A statistically significant reduction was found in patients on dialysis (BMD/BMD_p 0.75 ± 0.16, Z-score -1.3). Osteosclerosis was found in 11 patients and they were excluded from the study. Longitudinal measurements in 42 patients on dialysis without osteosclerosis showed a 2.9% mean reduction in BMD/BMD_p over a period of 8 months. All but one of the 16 haemodialysis patients with osteopenic spinal fractures had trabecular BMD values lower than the fracture threshold determined by our technique. In conclusion, end-stage chronic renal failure was associated with reduction in the spinal trabecular bone density.

Renal osteodystrophy is a common complication of chronic renal failure. Bone biopsy is considered the only accurate diagnostic tool for both the type and severity of the bone disease in patients with chronic renal failure [1, 2]. However, this invasive method is not well tolerated by the patients, its reproducibility is questionable, and iliac crest specimens may not reflect the bone status of the entire body. Therefore, precise non-invasive methods of evaluating and following bone mineral changes in patients with chronic renal failure are of great clinical importance. The amount and elemental composition of bone minerals at primarily cortical sites in the upper extremities of chronic renal failure patients were studied in a previous investigation [3]. Although the resorptive effects of secondary hyperparathyroidism in renal osteodystrophy are striking in the cortical bone tissue of the extremities, trabecular resorption may also occur. In this study, single energy quantitative computed tomography (CT) was used to evaluate spinal trabecular bone in patients with chronic renal failure and the influence of the disease stage.

Materials and methods

Subjects

Patients. 89 patients (range 26–70-years-old; mean 55 years) with chronic renal failure were studied. Among them, 23 patients were not on dialysis (mean serum creatinine level of 530 mmol l^{-1}, range 190–840 mmol l^{-1}) and 66 patients were on long-term haemodialysis for a mean period of 4.0 years (range 0.3–12 years) in our dialysis unit. Bone mineral status was reassessed 8 months after the initial measurement in 42 dialysis patients (27 men and 15 women). Renal failure was attributed to chronic glomerulonephritis in 58, polycystic kidney disease in 20, obstructive nephropathy in seven and diabetes mellitus in three and one being anephric. None of the patients had undergone either parathyroidectomy or renal transplantation. Patients with diseases, conditions, or medications unrelated to the renal disease that might alter bone mineral metabolism were excluded from the study. All patients were in good physical condition and received phosphorus binding agents orally, as well as multivitamin preparations and hypertensive drugs when indicated.

Normal control subjects. A group of 206 healthy subjects (30–69-years-old) provided the database for the mathematical model derived for the prediction of the trabecular bone mineral density. These subjects were volunteers with no history or symptoms of any condition related to bone disease. The subjects in the control group showed a linear reduction of spinal trabecular bone density with increasing age, with an average annual loss of 2.3 mg cm^{-3} for men and 2.9 mg cm^{-3} for women [4].

Techniques

Radiographic morphometry. Lateral radiographs of the thoracic and lumbar spine were obtained to exclude

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individual vertebrae from the CT measurements. Osteopenia was identified by at least two atraumatic vertebral deformities: wedge fracture (anterior height 20% smaller than the posterior height), biconcavity (middling height 15% smaller than the anterior) or apparent vertebral collapse [5]. By subjective criteria, a homogeneous or "rugger jersey" like increase of the radiographic density in the spine was defined as renal osteosclerosis.

Quantitative CT. A modified version of the Cann–Genant [6] single energy quantitative CT technique was used to measure bone mineral density (BMD) in spinal trabecular bone with a Somatom DR2-G CT scanner (Siemens, Erlangen, Germany). A lateral digital radiograph starting from the xiphoid level was used to position the gantry for 8 mm thick scans through the midportion of the vertebral bodies T12, L1, L2, and L3. The following scan technique was used for the axial scans: 125 KVp, 60 mAs, 240° tube rotation. A region of interest, as large as possible, was drawn manually, excluding the posterior venous complex defect and the cortical rim. The average CT attenuation value was determined in these regions of interest. In cases of vertebral deformities between T12 and L3, the measurements excluded the involved vertebral bodies. Trabecular BMD was expressed as the density of a K_2HPO_4 solution exhibiting a linear attenuation coefficient identical to that of the trabecular bone for the particular photon spectrum. Reference solutions of K_2HPO_4, with concentrations 0, 50, 100, 150, and 200 mg cm^{-3} in Plexiglas tubes positioned under the subject's back, were used for calibration. A linear relationship was found between the CT attenuation values and the concentration of the reference solutions. A correction factor for field non-uniformity was experimentally determined and applied to the measurements [4], no correction was applied for the inhomogeneity of the non-mineral content in the trabecular bone, that is the influence of fat and collagen. The *in vivo* precision in the short term and during a 3 year long period was assessed to be 2.75 mg cm^{-3} and 3.35 mg cm^{-3}, respectively [7], which corresponds to a relative precision of 2.0% and 2.45% in healthy men, 55 years of age. The energy imparted by the examination is 9 mJ and the effective dose is 180 μSv, almost an order of magnitude lower than that of a routine lateral radiograph of the lumbar spine [4, 7].

Statistical analysis. The patient data were expressed both as the ratio of the measured BMD value to the predicted mean value of age- and sex-matched normal controls (BMD_p), and the standard deviations of the appropriate normal mean value (*Z*-score). Patients who had renal osteosclerosis in the radiographs of the spine, and/or exhibited either BMD/BMD_p higher than 1.50, or marked heterogeneity in areas of complete trabecular resorption in CT (Figure 1), were excluded from the mathematical analysis. The significance of differences between groups was tested by unpaired Student's *t*-tests. Linear regression analysis was used to estimate the rate of BMD loss with dialysis duration.

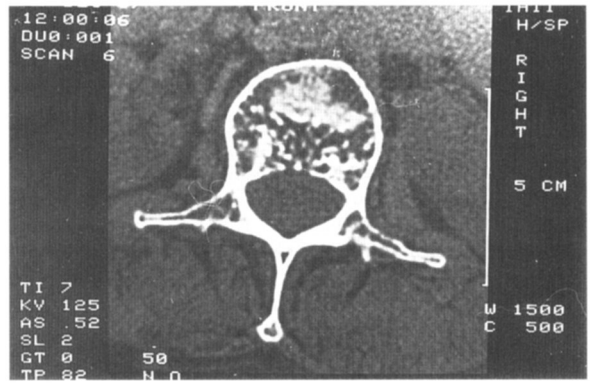

Figure 1. 50-year-old woman with renal osteosclerosis (rugger jersey spine). CT scan shows inhomogeneous trabecular bone with areas of sclerosis and absorption.

Results

Lateral radiographs of the spine revealed biconcavity and wedge-shaped deformity or compression fractures in 16 patients. Trabecular BMD values of 78 chronic renal failure subjects, expressed relative to those of sex- and age-matched control subjects are shown in Figure 2 and Table I. BMD data on the remaining 11 patients (four not dependent on dialysis and seven on long-term haemodialysis) with osteosclerosis are not included in Table I. These patients had extremely high BMD values (up to 370 mg cm^{-3}), as well as remarkable inhomogeneity in the vertebral trabecular bone area (Figure 1).

Patients not dependent on dialysis showed a minor reduction in the mean BMD/BMD_p and *Z*-score values (0.911 ± 0.225 and -0.36, respectively), but this reduction was not statistically significant ($p = 0.06$, Table I). Patients on dialysis showed a mean BMD/BMD_p value 0.747 ± 0.163 and a mean *Z*-score equal to -1.29 (Table I). Therefore, these patients exhibited a statistically significant reduced mean BMD relative to both matched normal controls ($p < 0.001$) and patients

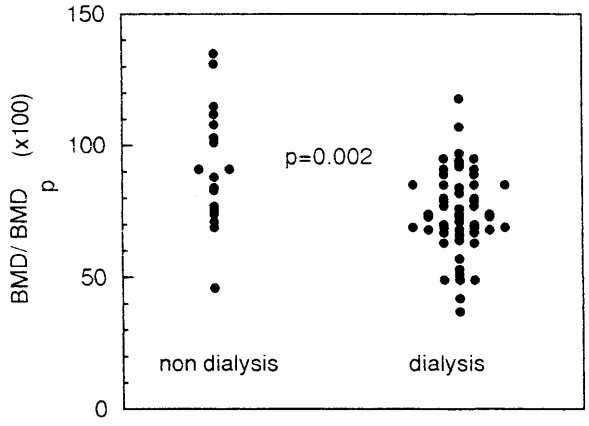

Figure 2. Spinal trabecular bone mineral density (BMD) in uraemic patients relative to bone mineral density in matched normal controls (BMD_p).

Table I. Spinal trabecular bone density relative to age- and sex-matched normal controls in non-dialysed chronic renal failure patients and in patients receiving long term dialysis

Group	n	Age		BMD/BMD_p		
		Mean	Standard deviation	Mean	Standard error of the mean	Coefficient of variation
Not in dialysis	19	59.5	7.1	0.911	0.052	25%
In dialysis	59	54.3	9.2	0.747[a]	0.021	22%

[a] $p<0.001$.

not on dialysis ($p<0.001$). The mean degrees of osteopenia was similar in the two sexes ($p=0.98$).

Sequential BMD measurements in 42 patients on dialysis with no signs of osteosclerosis showed a statistically significant mean reduction of BMD (7.5 mg cm^{-3}) within the study period. Moreover, the mean BMD/BMD_p in the second measurement was decreased by 2.9% relative to the first ($p=<0.001$). The mean of BMD/BMD_p change in men did not differ from that in women ($p=0.3$). The rate of BMD/BMD_p change was found to be larger in younger patients ($p=0.004$, Figure 3). Linear regression analysis failed to demonstrate any statistically significant dependence of the rate of BMD/BMD_p change on the duration of dialysis ($p=0.12$). Moreover, the rate of change of BMD/BMD_p in patients on dialysis due to chronic glomerulonephritis ($n=25$) did not differ statistically ($p=0.6$) from that of patients with polycystic kidney disease ($n=10$).

Discussion

The main findings of this study are the reduced spinal trabecular BMD values in haemodialysis patients relative to both normal subjects and patients not on dialysis. It is well known that even asymptomatic patients with chronic renal failure show histological evidence of renal osteodystrophy at an early stage of their disease [1]. Osteitis fibrosa, osteomalacia, adynamic disease, osteosclerosis and osteoporosis may occur either exclusively, or concurrently, in the same patient. However, these lesions do not appear to the same extent in various parts of the skeleton. Therefore, iliac crest biopsies are not expected to reflect the whole-body bone mineral status. This invasive technique is not well tolerated by the patients and thus has a questionable reproducibility. Another approach for studying renal osteodystrophy can be based on the use of non-invasive techniques.

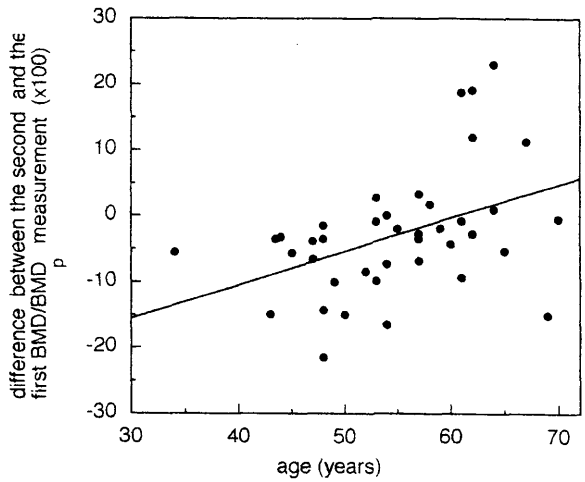

Figure 3. Difference between the second and the first assessment of the ratios of the measured spinal trabecular bone mineral density in patients on dialysis (BMD) to that mean value in age- and sex-matched normal subjects (BMD_p).

Radiogrammetry [3, 8, 9], photon absorptiometry [3, 10–19] and neutron activation analysis [3, 20–23] are among the non-invasive techniques used to study renal osteodystrophy. These techniques are used to assess either regional or total body bone mineral status. Bones with high trabecular content, such as the spine, are appropriate skeletal sites for such measurements because the spine is a skeletal region where its earliest and most severe manifestations of osteopenia may occur. Both quantitative CT and dual energy photon absorptiometry have been accepted as clinically applicable methods for spinal studies. Gabay et al [18], applying dual photon absorptiometry reported reduced spinal BMD ($Z=-0.64$) in whole vertebrae in 76 patients on extrarenal dialysis for at least 1 year, irrespective of the dialysis technique. However, Chan et al [17], measuring spinal BMD in 10 patients in maintenance dialysis with dual energy X-ray absorptiometry reported normal mean values ($p=0.90$). The non-tomographic absorptiometric techniques used by Gabay et al and Chan et al lack the advantage of measuring pure trabecular bone, and the anticipated high prevalence of posterior arch osteoarthritis as well as the pre-existing spinal fractures could introduce significant errors [24].

In the current study, data on patients with osteosclerosis (12% of the patients) were not included in the mathematical analysis because: (a) the hypodense areas in the rugger jersey vertebral bodies exhibited negative values in up to 50% of the pixels in the region of interest, and (b) some patients with very high density mean values (more than 150% of the controls) had vertebral fractures at the same time. High mean CT attenuation values do not always reflect the adequate mechanical characteristics of the vertebral body [25]. Two patterns of renal osteosclerosis were observed: (a) inhomogeneous

trabecular bone with areas of sclerosis and absorption, which corresponds to the well known rugger jersey spine (Figure 1), and (b) homogeneously increased density (CT attenuation values) with a diminished distinction between cortical and trabecular areas. Therefore, a bias towards either normal or increased mean BMD/BMD_p values could be induced in the analysis. In addition, neither the rugger jersey spine nor the diffusely sclerotic vertebrae are sensitive radiological criteria for evaluating progression or remission of renal osteodystrophy [26]. Increased BMD values in osteosclerosis cannot be interpreted in terms of the underlying histological pattern, as both osteomalacia and osteitis fibrosa have been reported in situations of normal, decreased, or increased mass of spinal bone [13].

Patients not treated with dialysis showed a small, but not statistically significant, decrease in BMD/BMD_p. In the same group of patients, similar results were found with partial body neutron activation analysis of phosphorus levels in the bones of the hand [3]. Gabay et al [18] who measured spinal BMD of whole vertebrae in 11 patients a few days to 4 months before the initiation of dialysis treatment, reported a negative mean Z-score (-0.49 ± 1.72). The findings by Gabay et al [18] and the current study are in accordance with biopsy findings by Dahl et al [27] who reported that bone resorption, osteoid formation and mineralization remain in balance even in patients with advanced chronic renal failure. However, taking into account the marginal p value in the t-test between normal subjects and patients not dependent on dialysis ($p=0.06$, $1-\beta=0.52$) further investigations involving larger number of patients without osteosclerosis are needed.

Only a few reports address the *in vivo* assessment of pure trabecular bone tissue in chronic renal failure. Sakurai et al [14] used single energy quantitative CT in the distal femur and found CT attenuation values to be within the normal limits in 47 non-dialysis patients and reduced mean values in 28 patients on dialysis relative to healthy control subjects. Conversely, Torres et al [10, 13] found that uraemic patients show normal or even high CT attenuation values in the spinal trabecular bone. However, the technique by Torres et al does not use reference solutions for calibration and measures only the fourth lumbar vertebra. In addition, the control group used was rather limited. In another study, Boling et al [28] found only a minor mean spinal BMD reduction relative to matched controls (4% on average) in a group of 27 patients on dialysis. The findings by these studies differ from those of the current study because patients with spinal osteosclerosis were excluded from the present evaluation.

Fracture threshold has been defined as the trabecular bone equivalent density value of 110 mg cm^{-3} [29] or the trabecular BMD value that corresponds to the fifth percentile of 45-year-old healthy women [30] which in our control group was 108 mg cm^{-3}. In a previous study, applying our quantitative CT technique in women with post-menopausal osteoporosis (aged 38–67 years), we found that 92% exhibited BMD values below the fracture threshold and their mean BMD/BMD_p was equal to 0.70 [4]. In the present study 52% of the patients on dialysis without osteosclerosis exhibited BMD values below the fracture threshold. All but one of the patients with fractures had BMD values lower than the fracture threshold determined by our technique. In addition, one woman reported an atraumatic fracture of the clavicle. Therefore, the criteria applied for post-menopausal osteoporotic women are also valid for patients on dialysis.

Sequential BMD measurements in patients receiving dialysis showed that the BMD/BMD_p in the second measurement was decreased by 2.9% on average relative to the first. This finding is in accordance with $\sim 16\%$ lower mean BMD/BMD_p values in patients receiving dialysis for an average of 4 years relative to that of patients not on dialysis. In summary, our findings reflect the complexity of bone tissue alterations associated with chronic renal failure. Although quantitative CT has no predictive value for the histological appearance of the underlying bone (Torres et al [13]), trabecular BMD data could offer valuable information on bone status in terms of fracture prediction [6, 29–32]. In conclusion, quantitative CT technique showed that patients on long-term dialysis are prone to spinal fractures due to reduced trabecular bone mineral density.

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