

Renal Osteodystrophy in Hemodialysis Patients

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ABSTRACT

Patterns of bone loss in the axial and appendicular skeleton were studied in 88 chronic hemodialysis patients (59 males and 29 females) and 60 normal volunteers (30 males and 30 females). The hemodialysis patients were properly medicated with phosphate binders and 1α -OH D₃ where necessary. The metacarpal index (MCI), Σ gray scale / diameter (Σ GS/D) and bone mineral content (BMC) were measured as bone mass indices, and the relationship investigated between clinical factors [age, duration of hemodialysis, serum phosphate (P), calcium (Ca), carboxy-terminal fragments of parathyroid hormone (C-PTH), osteocalcin (OC), alkaline phosphate (ALP) and Ca \times P]. The bone loss in the hemodialysis patients was greater than that in the normal controls and was accelerated after menopause in women. However, the bone mass indices in a few of the hemodialysis patients of advanced age (over 60) showed higher values than those of the controls. The bone mass indices in male hemodialysis patients showed a negative correlation with the hemodialysis duration, C-PTH and OC, as did those in female patients with hemodialysis duration. On the other hand, BMC in female hemodialysis patients showed a negative correlation with P, C-PTH and Ca \times P. In conclusion, age and the duration of hemodialysis are the most essential factors in skeletal and trabecular bone loss in male and female hemodialysis patients. Subsequent factors responsible for skeletal bone loss in male patients are C-PTH and OC, and those for trabecular bone loss in female patients are P, C-PTH and Ca \times P. Control of the levels of C-PTH, OC, P and Ca \times P is recommended for prevention of bone loss in hemodialysis patients.

Key words: *Microdensitometry, MCI, Σ GS/D, Quantitative computed tomography with phantom*

Renal osteodystrophy (ROD) in long-term hemodialysis patients is characterized by osteitis fibrosa, osteosclerosis, osteomalacia, aluminium-associated bone disease and osteoporosis^{5,7,16,32}. These changes result from the disturbance of vitamin D activation, imbalance of serum phosphate (P) and calcium (Ca), and interference with the parathyroid hormone metabolism⁷. To assess the degree of bone atrophy in ROD precisely, every hemodialysis patient should be required to undergo bone histomorphometry. However, it may be impossible to perform bone biopsy for all hemodialysis patients. In order to diminish the burden on body and soul, several non-invasive methods for determining the bone mass of patients have recently been developed. These are: single photon absorptiometry^{2,13,34}, dual photon absorptiometry^{9,20,37}, microdensitometry (MD)²⁴, neutron activation analysis^{14,26}, quantitative computed tomography (QCT)^{11,25,36}, QCT with phantom^{4,6,17,19} and dual-energy X-ray absorptiometry^{8,30}. Among these, MD and QCT with phantom are valuable for reflecting bone mass *in*

vivo^{24,27}. The former is for cortical, and the latter for trabecular bone. To determine the degree of ROD, the second metacarpal bone was measured by MD and the third lumbar vertebra by QCT with phantom. This work was undertaken to investigate the relationship between the clinical factors and deterioration of ROD.

MATERIALS AND METHODS

Subjects

The subjects were 88 hemodialysis patients (59 males and 29 females) and 60 normal controls (30 males and 30 females). Diabetic nephrosclerosis and renal amyloidosis patients, and those with a bone fracture at the third lumbar vertebra were excluded. All the patients were undergoing chronic hemodialysis with softened water (bicarbonate, Ca²⁺ 3.5 mEq/liter) three times weekly, and the dializer membranes were cuprophan, cellulose, ethylvinylalcohol, polymethylmethacrylate for 50, 31, 4, 3 cases respectively. Most of the patients were taking phosphate binders (precipi-

tated calcium carbonate) 1.0–3.0 g daily and/or 1 α -hydroxyvitamin D₃ (1 α -OH D₃) 0.25–1.0 μ g daily. Use of medications, such as diphenylhydantoin or corticosteroids was a criterion for exclusion. The normal controls were healthy volunteers with no history of chronic illness and no recognized disorders of the calcium metabolism.

The ages of the hemodialysis patients were as follows: male, 24–78 (mean \pm SD, 50.3 \pm 13.6) years; female, 31–79 (mean \pm SD, 50.9 \pm 13.5) years. The duration of hemodialysis ranged from 1–203 (mean \pm SD, 50.6 \pm 41.1) months for the male and 1–147 (mean \pm SD, 55.5 \pm 44.7) months for the female patients. The ages of the normal controls were as follows: male, 22–75 (mean \pm SD, 49.0 \pm 16.6) years; female, 21–79 (mean \pm SD, 49.1 \pm 17.9) years. There was no significant difference between the male and female hemodialysis patients either in age or the duration of hemodialysis. There was also no significant difference between the hemodialysis patients and normal controls in age for both sexes. Male and female controls were opted 5 persons for every decade.

Measurement of bone mass

MD was applied to measure the density at the middle of the second metacarpal bone on X-ray pictures taken with an aluminium step-wedge. Then the metacarpal index (MCI) and Σ gray scale / diameter (Σ GS/D) were calculated as described by Inoue²⁴. MCI is the ratio of cortex to medulla in length, and is considered to represent the cortical bone metabolism. Σ GS is a value computed by integrating the area which is estimated by a densitometer, and converting the optical density into the number of the aluminium step-wedge. Thus, Σ GS/D is obtained dividing Σ GS by D (Fig. 1).

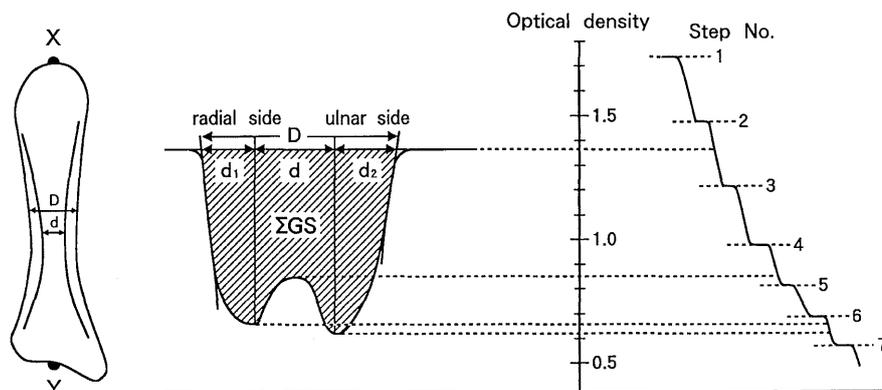


Fig. 1 Microdensitometry (MD)

Bone density is measured at the middle of the second metacarpal bone (mid-point of X–Y). MCI = $(d_1 + d_2) / D$

$$\Sigma \text{ GS} / D = \frac{\Sigma \text{ GS}}{D}$$

QCT with phantom was carried out to measure the bone mineral content (BMC) of the third lumbar vertebra by means of Shimadzu SCT-2000T. The patients and the normal controls were placed on a calibration phantom containing compartments packed with varying densities of solid CaCO₃. The CT numbers from sections obtained from the trabecular portions of the vertebral center were compared with those in the calibration phantom and thereby converted into the equivalent BMC.

Blood examination

Blood samples were obtained from all patients before dialysis. Serum P, Ca, carboxy-terminal fragments of parathyroid hormone (C-PTH), osteocalcin (OC), alkaline phosphatase (ALP) and Ca \times P were measured. P and Ca were measured by the colorimetric method, and radioimmunoassay was applied to assay C-PTH (C-terminal PTH RIA kit, Immuno Nuclear Corporation) and OC (Osteocalcin I¹²⁵ kit, CISD Corporation). In addition to these values, age and the duration of hemodialysis were chosen as the clinical factors regarding deterioration of ROD.

Data analysis

The normal data of bone mass for males and females were analyzed using regression analysis. The significance of difference in the fit of the curves was determined by the *t*-test, using the residual variance of the fit for multiple order regressions.

Bone mass in the hemodialysis patients was compared to the mean values in age-matched normal controls to determine if there were any differences. Moreover, the relationship between delta (Δ) bone mass indices (Δ MCI, Δ Σ GS/D, Δ BMC) and the clinical factors was analyzed. The percentage of Δ bone mass indices (Δ bone

mass indices %) was calculated as follows:

$$\frac{(\text{Bone mass in normal controls}) - (\text{Bone mass in hemodialysis patients})}{(\text{Bone mass in normal controls})} \times 100(\%)$$

RESULTS

MCI, Σ GS/D and BMC against age for normal males and females are shown in Figure 2-7. The statistically best fits to the data are shown with 95% confidence intervals. For all indices of bone mass, cubic regression, rather than a linear regression, significantly improved the quality of the fit data.

MCI and Σ GS/D of normal males showed a peak value during the mid-thirties followed by a

slow decline at the rate of 7.0% / decade (MCI) and 4.7% / decade (Σ GS/D), but MCI again increased after age 65. Those of normal pre-menopausal females also reduced with aging at the rate of 5.6% / decade (MCI) and 4.1% / decade (Σ GS/D). These changes were accelerated after menopause at the rate of 9.4% / decade (MCI) and 7.9% / decade (Σ GS/D).

BMC in normal males and females likewise decreased with aging. The rate of the diminution of

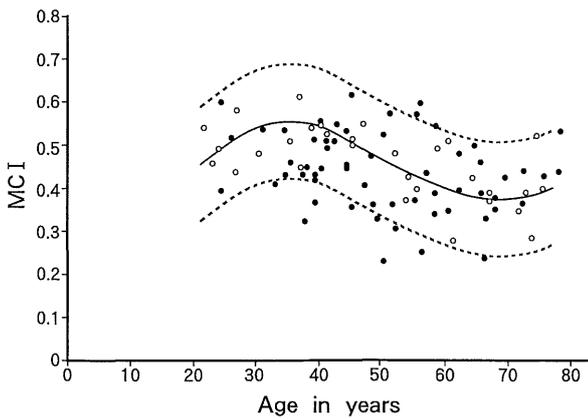


Fig. 2. MCI of normal males measured by MD are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of male hemodialysis patients are expressed as closed circles.

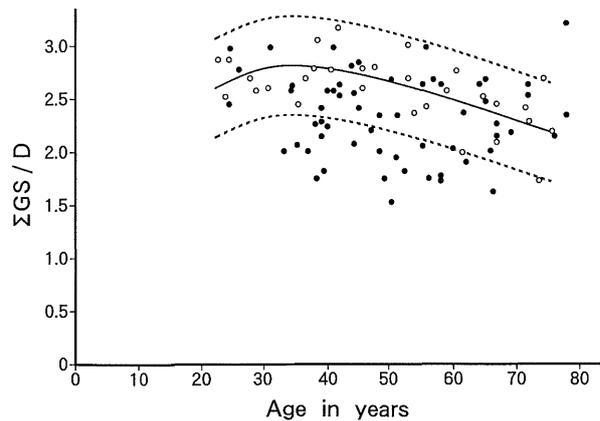


Fig. 4. Σ GS/D of normal males measured by MD are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of male hemodialysis patients are expressed as closed circles.

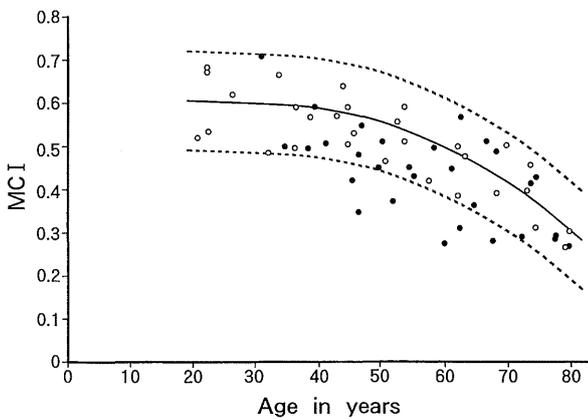


Fig. 3. MCI of normal females measured by MD are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of female hemodialysis patients are expressed as closed circles.

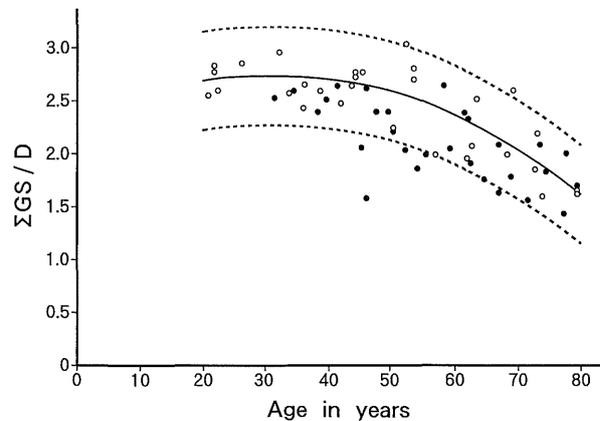


Fig. 5. Σ GS/D of normal females measured by MD are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of female hemodialysis patients are expressed as closed circles.

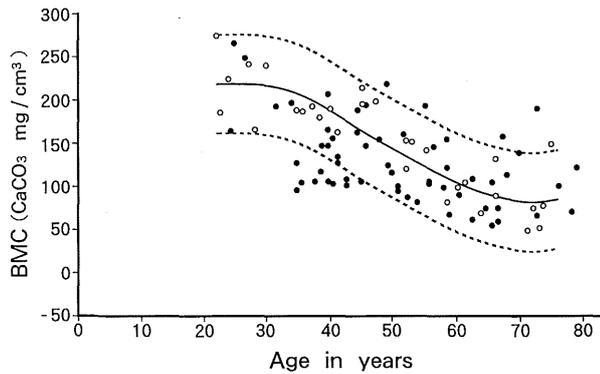


Fig. 6. BMC of normal males measured at the third lumbar vertebra by QCT with phantom are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of male hemodialysis patients are expressed as closed circles.

BMC was 14.6% / decade in males and 13.7% / decade in pre-menopausal females, but accelerated bone loss was demonstrated after menopause (25.9% / decade). In both sexes, the slopes of the cubic regression curves showed little bone loss after 70 years of age.

MCI, Σ GS/D and BMC against age for chronic hemodialysis patients are superimposed on the mean and the 95% confidence intervals for normals (Fig. 2–7). In patients of both sexes, from the thirties to the fifties, bone mass indices showed a tendency toward levels below the mean values of normal controls. However, a few patients of both sexes in the sixties and seventies had higher values for the indices of bone mass over 95% confidence intervals.

The relationship among Δ MCI%, $\Delta \Sigma$ GS/D%, Δ BMC% and clinical factors are demonstrated in Table 1. In the male hemodialysis patients, Δ MCI(%) was related to age, duration, C-PTH and OS; $\Delta \Sigma$ GS/D% was related to age, duration, Ca, C-PTH and OC, and Δ BMC% was related to age. The age revealed a positive correlation with Δ bone mass whereas the other clinical factors revealed a negative correlation. In the female hemodialysis patients, $\Delta \Sigma$ GS/D% was related to duration, and Δ BMC% was related to age, P, C-PTH and Ca \times P. Here again, age showed a positive correlation with Δ bone mass while the other clinical factors showed a negative correlation.

DISCUSSION

The measurement of bone mass of chronic hemodialysis patients is usually carried out to provide a predictive index for ROD or a quantitative evaluation of the degree of ROD which may be dependent on multiple clinical factors³²). The measurement of metacarpal bone by MD and that of a lumbar vertebra by QCT with phantom have been shown to be accurate and reproduc-

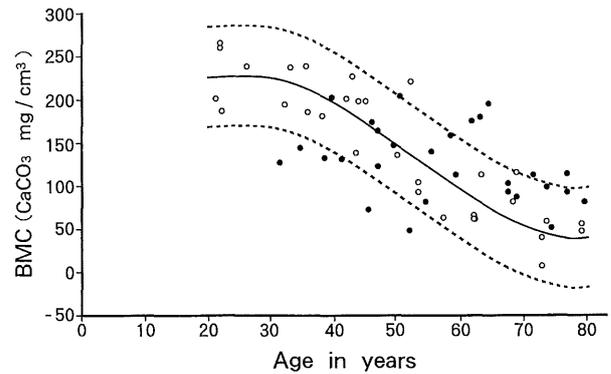


Fig. 7. BMC of normal females measured at the third lumbar vertebra by QCT with phantom are expressed as open circles and plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The data of female hemodialysis patients are expressed as closed circles.

ible^{17,21,24,29}). Further more, there is a linear relationship between CT numbers and the Ca content of the vertebra¹¹). Therefore, instead of bone biopsy, MD and QCT with phantom are very beneficial for evaluating the ROD of hemodialysis patients.

It has been demonstrated that the measurement of the appendicular skeleton, rather than that of the axial skeleton, provides a more sensitive indication of changes in bone mass caused by aging³⁷). It is accepted that MCI and Σ GS/D reflect the cortical bone metabolism²⁴). The pattern of peripheral bone diminution obtained through this study was almost identical with that obtained from appendicular skeleton using other measurement techniques^{12,24}). The values of MCI and Σ GS/D in the hemodialysis patients were lower than those in the normal controls, indicating that the impairment of cortical bone metabolism advances earlier in hemodialysis patients than in normal controls.

Spinal measurement is considered the best method to discriminate the distinguishing characteristics of osteoporosis in the axial skeleton¹⁸). BMC in the third lumbar vertebra of the normal controls showed similar values to those previously described²⁰). Preceding investigators have demonstrated that the bone mass in normal controls is also related to body weight¹⁰), race²⁸) and exercise³¹). In addition to these factors, the bone mass of hemodialysis patients is affected by chronic hemodialysis. The impairment of bone mineral metabolism brought about by final stage renal failure and repeated hemodialysis precipitates changes in the bone of hemodialysis patients.

Characteristic of ROD are as follows: secondary hyperparathyroidism, which results in osteitis fibrosa; the disturbance of vitamin D activation, which brings about osteomalacia^{7,16}); mixed ure-

Table 1. Relationship among Δ MCI%, $\Delta \Sigma$ GS/D% determined by MD, Δ BMC% determined by QCT with phantom and bone related items in chronic hemodialysis patients

	Age	Duration	Ca	P	C-PTH	O.C.	ALP	Ca \times P
Male Δ MCI%	$\gamma=0.258^*$	$\gamma=-0.480^{**}$	N.S.	N.S.	$\gamma=-0.369^{**}$	$\gamma=-0.352^{**}$	N.S.	N.S.
Male $\Delta \Sigma$ GS/D%	$\gamma=0.292^*$	$\gamma=-0.586^{**}$	$\gamma=-0.316^*$	N.S.	$\gamma=-0.343^{**}$	$\gamma=-0.298^*$	N.S.	N.S.
Male Δ BCM%	$\gamma=0.413^{**}$	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Female Δ MCI%	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Female $\Delta \Sigma$ GS/D%	N.S.	$\gamma=-0.375^*$	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Female Δ BMC%	$\gamma=0.743^{**}$	N.S.	N.S.	$\gamma=-0.453^*$	$\gamma=-0.370^*$	N.S.	N.S.	$\gamma=-0.392^*$

Δ MCI%: delta metacarpal index %, $\Delta \Sigma$ GS/D%: delta Σ gray scale/D%, Δ BMC%: delta bone mineral content %, QCT: quantitative computed tomography, Ca: calcium, P: phosphate, C-PTH: carboxyl-terminal parathyroid hormone, OC: osteocalcin, ALP: alkaline phosphate, N.S.: not significant, *: $p < 0.05$, **: $p < 0.01$.

mic osteodystrophy which has the characteristics of both osteitis fibrosa and osteomalacia²³); aluminium deposition into the bone, which induces aluminium-associated low turnover bone disease^{5,32}), and adynamic bone³³). Osteosclerosis results from the deposition of amorphous phosphocalcium which disturbs the maturation into hydroxyapatite and is common in long-term hemodialysis patients¹⁶). The values of bone mass indices do not define what kinds of bone changes are occurring in hemodialysis patients. However, they do give a clear manifestation of bone loss. Therefore, patients with ROD should be treated with appropriate medication in order that their condition does not deteriorate.

The bone mass indices in a few of the hemodialysis patients of advanced age (over 60 years of age) showed higher values than those of the normal controls. It is considered that this change is due to osteosclerosis in long-term hemodialysis, and it was found to be predominant in trabecular bone rather than cortical bone. However, the possibility exists that this change is brought about by the positive Ca, P and C-PTH control yielded by medication with phosphate binders and 1α -OH D_3 ^{1,3,15,22,35}). Nevertheless, since the problem of aluminium-associated low turnover bone disease can be serious in all hemodialysis patients, medication with aluminium-containing antacids should be avoided.

The indices of cortical bone metabolism in the male hemodialysis patients showed a negative correlation with duration, C-PTH and OC. However, no clinical factor except duration correlated with the indices in the female hemodialysis patients. On the other hand, those of trabecular bone in female hemodialysis patients correlated with P, C-PTH and Ca \times P, while those in males showed no significant correlation with clinical factors. From these results, it is clear that periodic examination of Ca, C-PTH and OC for male cortical, and P, C-PTH and Ca \times P for female trabecular bone metabolism is indispensable so that bone mass can be maintained by appropriate me-

dications.

In conclusion, age and the duration of hemodialysis are the most essential factors in skeletal and trabecular bone loss in male and female hemodialysis patients. Subsequent factors responsible for skeletal bone loss in male patients are C-PTH and OC, where those for trabecular bone loss in female patients are P, C-PTH and Ca \times P. Control of the levels of C-PTH, OC, P and Ca \times P is recommended for the prevention of bone loss in hemodialysis patients.

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