A Quantitative CT System Applied to the Femoral Shaft and Lateral Condyle for Evaluating Bone Loss in Patients with Secondary Hyperparathyroidism

Kiyoko Sakurai, Takashi Matsubayashi* and Yusuke Tsukamoto**

Department of Medical Engineering and Technology, Kitasato University School of Allied Health Sciences
*Department of Radiology, ** Department of Medicine, Kitasato University School of Medicine

2次性副甲状腺機能亢進症における骨脱灰化評価のための大腿骨骨幹部および外顆部のQCTシステム

桜井　清子　　松林　　隆*　　塚本　雄介**

腎性骨異栄養症患者の骨脱灰化評価を目的として以前に開発·報告したQCT法を改良したので報告する．今回の方法では，大腿骨骨幹部皮質の3種類のCT値，すなわち，平均CT値(BOCT)，ピークCT値(PKCT)，最大CT値(MXCT)および大腿骨外顆部海綿骨の骨塩量(BMD：LC)と第3腰椎椎体海綿骨の骨塩量(BMD：L3)を測定した．これらのパラメータはすべて通常のCTスキャナ上で容易に得られるようになっている点が前回(ミニコンピュータHP-1000を使用)とは異なる点である．対象は二次性副甲状腺機能亢進症(2HPT)37例，健常ボランティア87例である．患者は通常用量の1,25(OH)$_2$D$_3$を連続投与されている群(CNV群)および症状が進んで1,25(OH)$_2$D$_3$のパルス療法または副甲状腺摘除術が必要となった群(PLS/PTX群)に分けた．BMD：LCとBOCTはCNV群において健常群より有意に低く，透析期間とよく相関した．BOCT, PKCT, MXCTはPLS/PTX群において著明に低値を示した．BMD：LCは初期の2HPTの骨脱灰化評価に有用であること，また，PKCTは，通常量の1,25(OH)$_2$D$_3$では維持できなくなり，パルス療法または副甲状腺摘除術が必要となりつつある移行期を示す有用な指標となり得ることが示唆された．MXCTは進行した症例の骨脱灰化評価のための信頼性の高いパラメータとなり得ることが期待された．BOCTは本症の全段階を通じて徐々に低下していくが，進行した症例においては，PKCTやMXCTの方が感度が良く信頼性も高い．BMD：L3は本症の骨脱灰化評価には有効でないことが判明した．以上の結果より，4つの大腿骨パラメータを含む改良された今回のQCT法は2HPTの骨脱灰化評価にきわめて有用であると結論された．

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北里大学医療衛生学部医療工学科
＊北里大学医学部放射線科，＊＊同内科

INTRODUCTION

It is well known that the spongiosa has a bone turnover rate about eight times as high as that of the cortex[1),2)]. Because of this higher turnover rate, the spongiosa is thought to be a preferable site for detection of early bone loss. However, a review of the literature[3)-7)] reveals that the bone resorption is more predominant in the cortical bone in many patients with chronic renal failure, leading us to consider that the bone mineral measurement of the cortex might be as effective as that of the spongiosa for assessing the bone status of patients under hemodialysis.

Recently, quantitative computed tomography (QCT), dual-energy X-ray absorptiometry (DXA), single-energy X-ray absorptiometry (SXA) and ultrasound methods have been used to assess the bone status. DXA is superior to the others because it has good precision and offers many measurement sites including the whole body. The equipment for SXA or ultrasound methods is compact and easy to use. However, QCT has the great advantage of providing separate sets of information for the cortex and for the spongiosa.

For more than 10 years, we have been studying and issuing reports regarding a new QCT method[8)-10)] applied to the cortex of the femoral shaft as well as to the spongiosa in the femoral lateral condyle. The spongiosa of the condyle shows considerably higher bone mineral density (BMD) than that of the vertebral body. In one paper[10)], we reported that the demineralization of the cortex was much less marked than that of the spongiosa as long as the BMD of the spongiosa remained higher than a critical value, but that the demineralization of the cortex surpassed that of the spongiosa once the BMD of the spongiosa declined to below this value. This set of results suggested that it was necessary to measure both the cortex and the spongiosa in order to completely assess bone loss. This conclusion accords with some other recent papers[11)-13)].

We have improved the QCT method in an effort to make it more convenient to use in clinical settings. In this study, we

Table 1 Subjects

	Number of patients	Age (years)	Duration of dialysis (months)
Healthy volunteers	87		
male	50	40～70	—
female	37	40～70	—
Patients with secondary hyperparathyroidism	37		
male	26	33～67	17～232
female	11	32～67	70～205

used the functions of image analysis installed into a commercially available CT scanner in place of a mini-computer (HP-1000) and a program system developed by ourselves to obtain the parametric values for the cortex and the spongiosa from the CT images. Then, we could obtain the parametric values more easily. Further, we used a commercially available standard phantom with composition highly resembling the constituent elements of bone.

The purpose of our study is to evaluate the utility of this QCT system in assessing the bone status of patients under hemodialysis. In this paper, we describe the improved QCT method and its application in patients with secondary hyperparathyroidism, and we discuss its potential clinical advantages.

MATERIALS AND METHODS

The subject groups are summerized in Table 1. The 87 healthy volunteers had visited our institution for a health check-up. The hemodialysis patients with serum parathyroid hormone (PTH) level above 10 ng/ml (measured by 'Highly sensitive PTH kit', Yamasa, Tokyo) were diagnosed as having secondary hyperparathyroidism (2HPT). These were 37 patients of 2 HPT, who were devided into two groups according to the treatment strategies. Every patient was treated with calcium carbonate to maintain the serum phosphate level below 6 mg/dl. Seventeen patients were treated with daily oral doses ($0.25\mu g$ or $0.5\mu g$) of $1,25(OH)_2D_3$ (the conventional therapy group, CNV group). In patients in whom the conventional therapy did not prevent the development of osteitis fibrosa with increased serum alkaline phosphatase level, parathyroidectomy was indicated before 1986, but oral pulse therapy[14] prior to parathyroidectomy has been indicated since 1986 (the PLS/PTX group; 20 patients). Parathyroidectomy had been performed 3.5-6 years before the present study, and oral pulse therapy had been continued intermittently for 4-5 years.

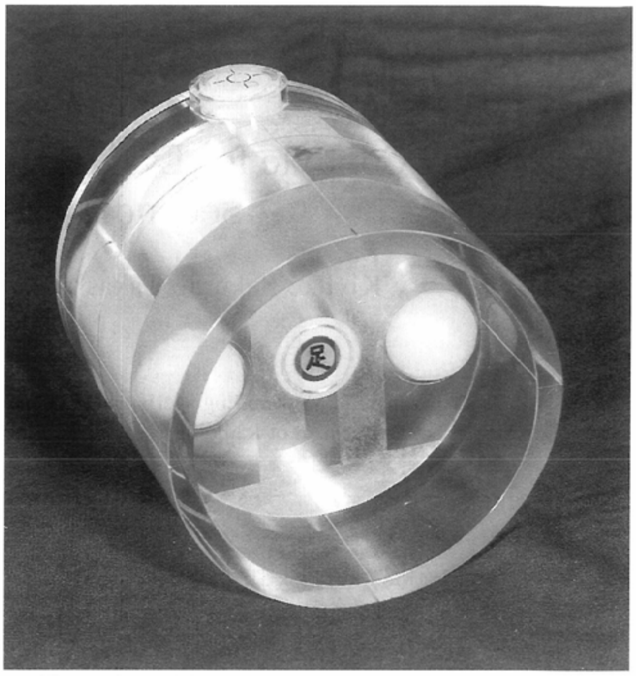


Fig.1 One of the phantoms used in the present study

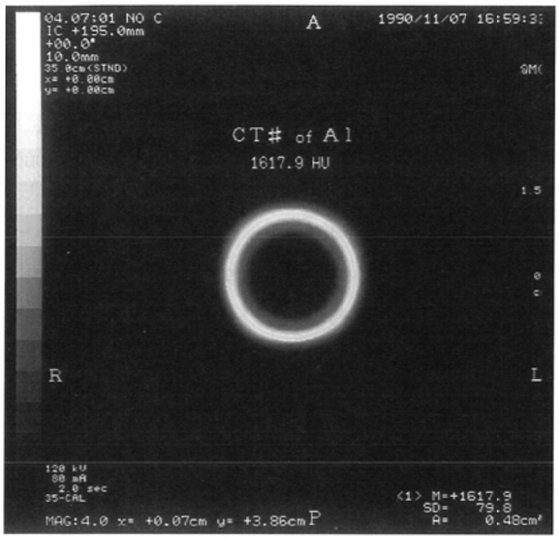
Table 2 Summary of the measured parameters

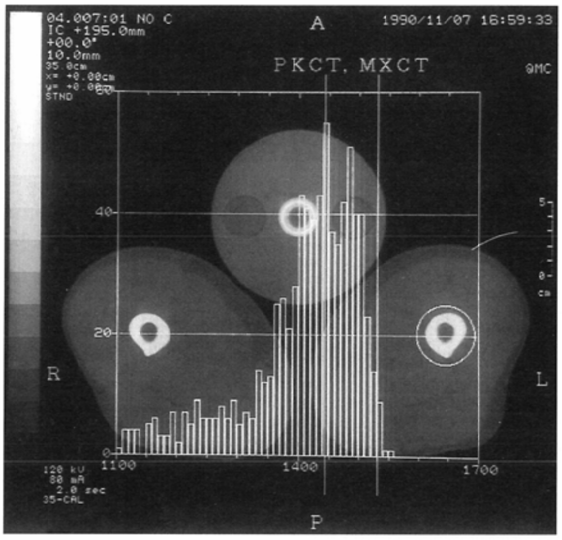
Symbol	Name	Examined location	Analyzed area
BOCT*,**	Bone CT number	Femoral shaft at 20cm from the distal end	Cortex
PKCT*,**	Peak CT number	Femoral shaft at 20cm from the distal end	Cortex
MXCT*,**	Maximum CT number	Femoral shaft at 20cm from the distal end	Cortex
BMD:LC**	BMD of femoral lateral condyle	Femoral lateral condyle at 2cm from the distal end	Spongiosa
BMD:L3	BMD of the 3rd lumbar vertebra	The 3rd lumbar vertebral body at the center	Spongiosa

* BOCT, PKCT and MXCT are cortical parameters.
**The cortical parameters together with BMD : LC are femoral parameters.

In these subjects, we obtained 3 cortical parameters from the BMD of the femoral shaft, the BMD of the spongiosa in the lateral condyle, and the BMD of the spongiosa in the third lumbar vertebral body, which was a common measurement site in a conventional QCT method (Table 2). We used a Quantex apparatus (YMS Co., Tokyo) for CT scanning. The tube voltage was 120kVp for the femoral shaft and 80kVp for the lateral condyle and the vertebra, and the slice thickness was 10mm.

In the QCT of the femoral shafts, we used a phantom consisting of an aluminum pipe inserted at the center of an acrylic acid resin column (Fig. 1) to obtain the standard CT number[8]. The obtained CT image was analyzed with the console of the CT scanner. The 3 CT numbers (BOCT, PKCT, and MXCT) and the aluminum CT number (ALCT) were obtained, as elaborated in Table 3 and Fig. 2. To counter the influence on the CT number caused by variations in the body size and the conditions of the CT scanner, we calibrated the obtained CT numbers of the cortex with the aluminum CT number. The mean of the calibrated CT numbers for both





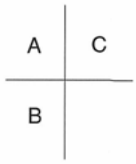


Fig.2 Extraction of the CT numbers of cortical bone in the femoral shaft (refer to Table 3).
(A) ALCT, aluminum CT number; (B) BOCT, bone CT number; and (C) PKCT, peak CT number, and MXCT, maximum CT number.

the right and left femurs was adopted as the CT number for each patient.

In the QCT of the femoral lateral condyles, we used the standard phantom of the BMD package (YMS Co., Tokyo), which was prepared for QCT of the spine and included $Ca_{10}(PO_4)_6(OH)_2$ at 3 densities (50, 100, 150 mg/cm^3). The BMD of the spongiosa in the lateral condyle (BMD: LC) was obtained using the software system of the BMD package. The region of interest (ROI) was circumscribed with a circle with the nominal diameter of 12.4mm (the actual area of 107mm^2). The ROI was localized within a region of the spongiosa such that the mean CT number within it was the largest of those for all possible locations (Fig. 3).

The center of the third lumbar vertebral body was scanned under the same conditions as the lateral condyles, and the BMD of the spongiosa in the vertebral body (BMD: L3) was obtained with a circular ROI using the BMD package.

The Z-scores of these 5 parameters for each patient relative to the healthy group were calculated using the following equation, taking the difference in sex and age into consideration:

$$Z-\text{score} = (X - M_{sex,age})/SD_{sex}$$

where X represents the parametric value for each patient, and $M_{sex,\ age}$ and SD_{sex} represent the sex- and age-matched mean and the sex-matched standard deviation in the healthy group, respectively.

These 5 parameters and their Z-scores were analyzed using the SAS statistical analysis program system in consideration of age, sex, duration of hemodialysis, and differences between the patients and the healthy volunteers as well as between the patient subgroups.

RESULTS

[Means and standard deviations of the parameters]

The means and standard deviations (SD) of the five param-

Table 3 CT numbers obtained from CT images of the phantom and femoral shaft

Symbol	Name	Comments on Fig.2
ALCT	Aluminum CT number	Mean CT number of the aluminum pipe in a phantom. The CT numbers obtained in Fig.2 (B) and (C) were calibrated by the equation: calibrated CT number = 1620 × (obtained CT number) /ALCT. The mean ALCT of 124 subjects, 1620 (HU: Hounsfield unit), was used a standard CT number of aluminum.
BOCT	Bone CT number	Mean CT number within bone region, which was defined as the region with the following CT numbers: CT number≧ALCT × 0.4 (HU).
PKCT	Peak CT number	CT number at the peak of the frequency distribution of CT numbers (mode CT number) with the interval of histogram of 10 (HU), namely, most frequently appearing CT number within bone region.
MXCT	Maximum CT number	Maximum CT number (highest CT number) within bone region.

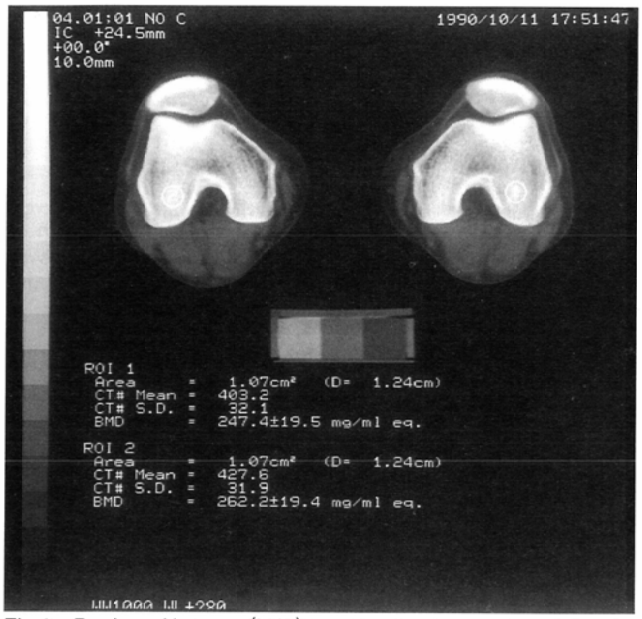


Fig.3 Region of interest (ROI) for obtaining bone mineral density of the femoral lateral condyle

Table 4 Means and standard deviations of the five measured parameters in the healthy males and females, and the means and standard deviations of the Z-scores of the patient subgroups relative to the data in the healthy males and females. Data for one patient were omitted because of extremely low parametric values.

	Mean±S.D. of measurement Healthy group		Mean±S.D. of Z-score	
	male	female	CNV group	PLS/PTX group
BOCT	1299±36 (HU)	1266±40 (HU)	−0.86±1.34*	−3.13±1.63**
PKCT	1461±34 (HU)	1438±48 (HU)	−0.39±1.34	−3.30±2.63**
MXCT	1540±32 (HU)	1508±39 (HU)	−0.19±1.22	−1.90±1.29**
BMD: LC	280±42 (mg/cc)	244±54 (mg/cc)	−0.89±1.14*	−1.46±1.64
BMD: L3	122±25 (mg/cc)	113±40 (mg/cc)	+0.74±2.19	+1.63±2.45

* significant difference from the healthy group at p=0.01
**significant difference from the CNV group at p=0.001
+ Z-scores of 0 and 1 correspond to the mean and one standard deviation, respectively, in the healthy group.

eters in each group are shown in Table 4. The means for BOCT and BMD: LC in the CNV group were significantly lower than those in the healthy group. The means for the 3 cortical parameters in the PLS/PTX group were significantly lower than those in the CNV group, and the means for BOCT and PKCT in the PLS/PTX group were less than 3SD below the means in the healthy group.

[Relationships of the parameters with age]

The relationship of BOCT with age is shown in Fig.4. The BOCT value decreased considerably with age in females (Pearson's correlation coefficient (r) = – 0.66, p = 0.0001), but the value changed little with age in males. The other cortical parameters, PKCT and MXCT, were not correlated with age. However, the measures of BMD of the spongiosa BMD: LC and BMD: L3 were well correlated with age in females (p = –0.71, p = 0.0001 and r = – 0.83, p = 0.0001), but not in males.

We compared the frequencies of patients with BOCT below the lower 90% confidence limit in the patient subgroups. As shown in Fig. 4, the values for many patients were located outside the 90% confidence limits. In the CNV subgroup, fewer patients had BOCT value below the lower limit, while in the PLS/PTX subgroup, the opposite trend was seen. The results of chi-square analysis of the difference between the subgroups for the BOCT is summarized in Table 5, together with those for the other parameters. The frequencies of the patients below the lower limit for BOCT and MXCT were significantly greater in the PLS/PTX subgroup than in the CNV group.

[Relationships of the parameters with the duration of hemodialysis]

The relationship of MXCT with the hemodialysis duration is shown in Fig. 5. The correlation coefficient was – 0.40 (p = 0.015) for data for all patients but one. Almost the same result was found for PKCT. The correlation coefficient of BOCT and of BMD: LC with the duration was – 0.48 (p = 0.0029) and – 0.50 (p = 0.0024), respectively, for data for all patients but one. BMD: L3 did not show a significant correlation with

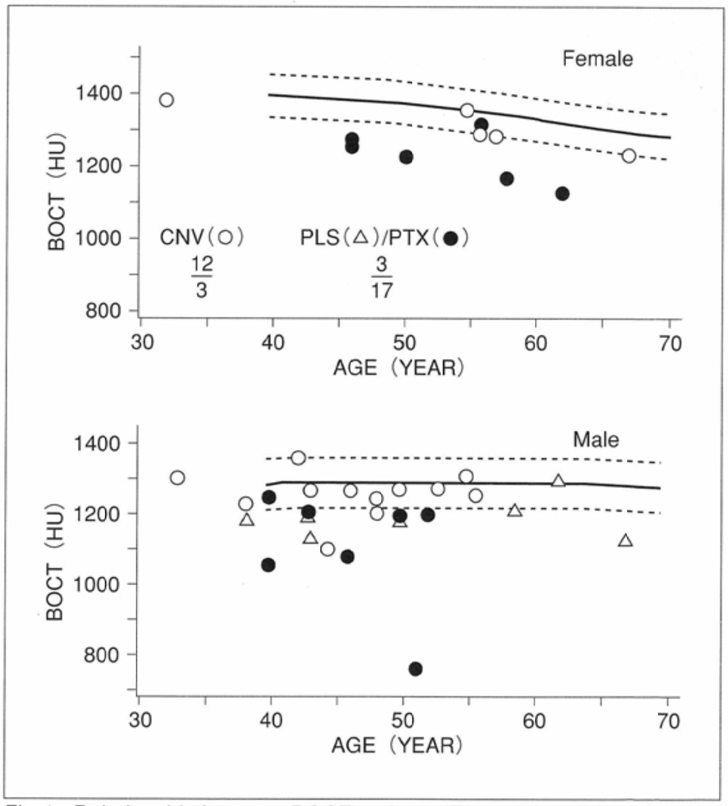


Fig.4 Relationship between BOCT and age. The solid and dotted curves represent the regression curve and the 90% confidence limits yielded by a cubic equation for the healthy volunteers. The ratios inserted in the figure represent the numbers of patients whose BOCT lies above to below the lower 90% confidence limit for each of the patient subgroups.

Table 5 Chi-square analysis of difference between the patient subgroups

	ratio with value below the lower 90% confidence limit CNV	PLS/PTX	χ^2
BOCT	0.20	0.85	14.8**
PKCT	0.27	0.70	6.4
MXCT	0.07	0.65	12.2**
BMD:LC	0.13	0.58	7.0*
BMD:L3	0.07	0.05	0.04

* significant at p=0.01 ** significant at p=0.001

the duration, but the value of BMD: L3 showed a tendency to increase with the duration.

We compared the ratio of patients above to below the regression line in the patient subgroups. In the CNV subgroup, it was larger than 1, while in the PLS/PTX subgroup, it was smaller than 1. The ratio in the CNV subgroup was significantly different from that in the PLS/PTX subgroup ($p = 0.001$, chi-square analysis).

DISCUSSION

[Bone mineral density of the radius]

Ruegsegger et al. measured the trabecular and compact bone densities (TBD and CBD) of the radius with a special purpose CT scanner[11] and reported that, in the few females with hyperparathyroidism (HPT), the TBD was somewhat lower than that in healthy females of the same age, but the CBD was greatly reduced and the reduction differed greatly from patient to patient. Moreover, they reported that the group of osteoporotic females had mean TBD 40% below the mean value for the healthy females of the same age, but that the difference in CBD was only 1.9%. The TBD and CBD were reported to be 217 ± 64 and 1860 ± 31 mg/cm^3, respectively, for healthy elderly women, 190 ± 43 and 1635 ± 245 mg/cm^3, respectively, for women with HPT, and 128 ± 56 and 1825 ± 29 mg/cm^3, respectively, for women with osteoporosis. These results regarding the radii of healthy women and those with HPT, obtained with a special CT scanner, are consistent with our results for the femur, obtained with a general CT scanner.

[Some problems with the CT number]

Our cortical parameters were expressed, not in terms of the BMD value, but in terms of the CT number. It was impossible to express them as BMD value because we could not obtain any standard phantom containing such a high density of bone mineral equivalent material as that of the cortex.

The CT number is not assured to be linear with X-ray attenuation coefficient over the broad range of CT numbers ranging from that for air to that for cortical bone. However, we consider it reasonable to assume that the CT number varies linearly with the attenuation coefficient within the narrow range for the CT number of the cortex. Moreover, in such a high CT-number region, there is a possibility that the CT numbers obtained for the same material using different CT scanners would differ from each other.

[Precision]

The precision of reproducibility of our previous QCT system[8] was 1.8% for the cortex and 3.6% for the spongiosa. The precision for the spongiosa is considered to be improved with the present method because the standard phantom used consists of more stable materials. These values are comparable to the precision of the common QCT of the lumbar vertebra.

[Characteristics of the 5 parameters]

The studied 5 parameters differed from each other in character. BMD: LC first decreased in mild 2HPT, and it seemed to be useful for evaluating the bone loss of the patients who were maintained with a conventional dosage of 1,25(OH)$_2$D$_3$.

The mean PKCT, interestingly, did not differ in the CNV and the healthy groups, but the PKCT values of 27% of the patients in the CNV group were below the lower 90% confidence limit for the healthy group. The

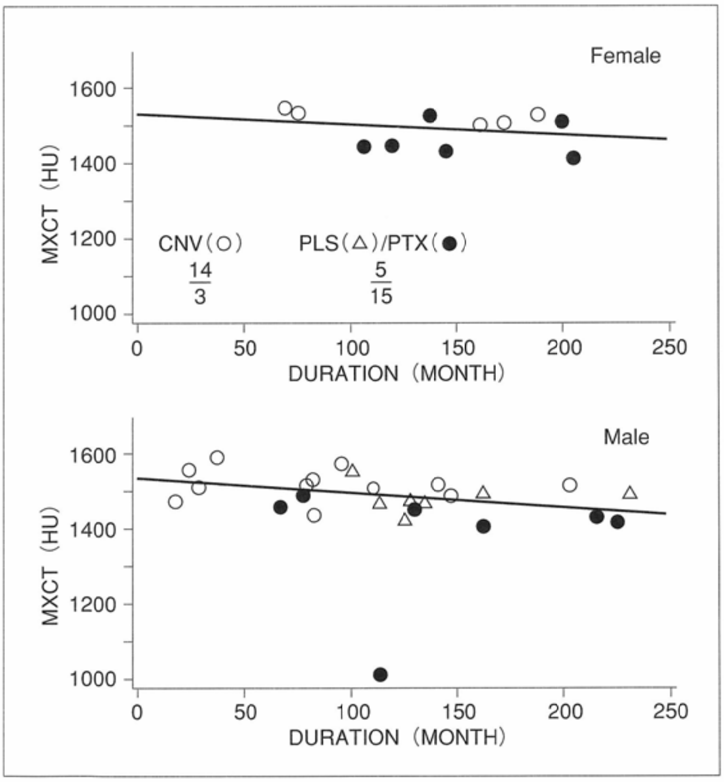


Fig.5 Relationship between MXCT and the duration of hemodialysis. The lines are the regression lines for all female and male patients except one patient for whom data were omitted because of extremely low value. The ratios inserted in the figure represent the numbers of patients whose MXCT lies above to below the regression line for each of the patient subgroups.

PKCT values in most of the patients in this group thus were almost as high as those in the healthy subjects, but the values in some patients were markedly reduced. The mean PKCT in the PLS/PTX group, in contrast, was less than 3SD below the mean in the healthy group, and it was significantly lower than the mean in CNV group. Moreover, PKCT showed the largest SD of Z-score among the parameters. The CT-number histogram was so complicated in some patients that the PKCT value could not be easily specified.

These observations suggest that PKCT is very sensitive to the change in the state of cortical bone. In normal bone, one sharp peak appears on the right side of the CT-number histogram. However, as the bone status deteriorates, the peak splits into several small ones, with an overall shift to the left on the histogram. We consider that the splitting of the peak occurs at the transitional stage from mild to moderate 2HPT. Therefore, we conclude that among the studied parameters PKCT is the earliest to indicate that the patient can no longer be maintained with a conventional dosage of $1,25(OH)_2D_3$ and should undergo pulse therapy or surgical treatment.

MXCT is the CT number of the most compact part of the cortex, and it therefore is not considered to decline substantially, as our results indicate. Moreover, the results of chi-square analyses in the age-matched and duration-matched subjects suggested that MXCT most clearly differentiated the patients in the PLS/PTX subgroup from those in the CNV subgroup; MXCT changed little in mild 2HPT, but began to slowly and steadily decrease in moderate 2HPT. MXCT thus may be a reliable parameter identifying the patients with severe 2HPT.

BOCT may also be useful in mild to severe 2HPT, but it should be noted that this parameter is difficult to measure with several types of commercially available CT scanners that are not equipped with a function for this purpose.

BMD: L3 did not seem to be useful for estimating the bone status of the patients with 2HPT, as previously reported[15], while the value significantly correlated with age in healthy females.

CONCLUSION

We anticipate that this improved QCT of the femur will provide useful information regarding the amount of bone mineral of the patients with 2HPT, while we conclude that the QCT of the lumbar vertebra is not a useful method. In particular, the combined set of parameters, BMD:LC, PKCT and MXCT, was found to be useful for assessing the bone status of the patients with mild to severe 2HPT, as was the BOCT by itself, if available. However, the set of parameters seemed to be more sensitive than the BOCT only. Furthermore, our QCT system was designed for practical use, just like that for the QCT of the lumbar vertbra, in combination with the large number of CT scanners available in clinics.

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