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Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study

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Abstract

Background. In chronic kidney disease stage 5D, diagnostic usefulness of bone mineral density (BMD) in predicting fracture has not been established because of variable results in previous studies. The reason for this may be the heterogeneity of underlying pathogenesis of the fracture.

Methods. BMD was measured annually and serum biochemistry monthly for 485 hemodialyzed patients from April 2003 to March 2008, and all fractures were recorded.

Results. Forty-six new episodes of any type of fracture and 29 cases of prevalent spine fracture were recorded. Serum bone-specific alkaline phosphatase (b-AP) was a very useful surrogate marker for any type of incident fracture risk [area under curve (AUC) = 0.766, $P < 0.0001$]. A significantly greater risk of any type of incident fracture was associated with parathyroid hormone (PTH) levels either <150 pg/mL [hazard ratio (HR) = 3.47, $P < 0.01$] or >300 pg/mL (HR = 5.88, $P < 0.0001$) compared with 150–300 pg/mL. Receiver-operating characteristic analysis demonstrated a significant predictive power for incident of any type of fracture by BMD at the total hip (AUC = 0.760, $P < 0.0001$) and other hip regions in females in the lower PTH group (PTH < 204 pg/mL). BMDs at every site but whole body or lumbar spine had significant power to discriminate prevalent spine fracture regardless of gender or PTH.

Conclusions. Hemodialyzed patients with low or high PTH or increased b-AP had a high fracture risk. BMD by Dual Energy X-ray Absorptiometry (DEXA), especially at the total hip region, was useful to predict any type of incident of fracture for females with low PTH or to discriminate prevalent spine fracture for every patient.

Keywords: bone mineral density; bone-specific alkaline phosphatase; dialysis; fracture; parathyroid hormone

Introduction

In postmenopausal and senile osteoporosis, a decrease in bone mineral density (BMD) in the lumbar spine and the femoral neck has been known to be a reliable marker in predicting fracture [1]. This is because a decrease in bone mass results in bone fragility causing fracture in these patients. However, in chronic kidney disease (CKD) stage 5D patients, this rule cannot always be applied. The chronic kidney disease–mineral and bone disorder (CKD–MBD) clinical practice guideline by KDIGO suggests that 'BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of renal osteodystrophy (statement 3.2.2)' [2]. This evidence level is 2B, meaning a weak recommendation with moderate grade of evidence. In this evidence review, 14 studies were evaluated and only one study was graded as A. All were cross-sectional studies. The results varied among the studies and were inconclusive. This discrepancy in the Dual Energy X-ray Absorptiometry (DEXA) studies may be due to the heterogeneity of the pathogenesis of the fractures among different types of renal osteodystrophy. A recent study employed high-resolution peripheral quantitative computed tomography and demonstrated not only an abnormal microarchitecture but also a decrease in cortical volumetric BMD in patients with hyperparathyroid bone. On the other hand, cortical BMD was higher in adynamic bone, while trabecular BMD was lower than hyperparathyroid bone [3, 4]. These differences in histology among different types of renal osteodystrophy may cause variations in the diagnostic value of DEXA and also in the predictive value among the measurement sites because DEXA cannot discriminate bone loss between the trabecula and cortex. In this context, we hypothesize that the diagnostic usefulness of DEXA is dependent on the pathogenesis of the type of fracture. In this report, we conducted a single-center cohort study to re-examine the diagnostic value of DEXA and the biochemical surrogate bone markers that are used to

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predict incidence of any type of fracture or to discriminate prevalent spine fracture in CKD stage 5D patients on hemodialysis.

Materials and methods

Study population

CKD stage 5D patients who received hemodialysis in our dialysis unit from April 2003 to March 2008 were investigated in this single-center cohort study. Exclusion criteria included the following: patients who received <3 months of hemodialysis by the end of March 2008 or were bedridden ($n = 23$). Forty-seven patients died during the study. None of the patients received hormone replacement therapy, lanthanum carbonate, any aluminum-containing medications, cinacalcet hydrochloride or immunosuppressive agents. Two patients received 5 mg of prednisolone daily to treat systematic lupus erythematosus and Anti-Neutrophic Cytoplasmic Antibody-associated nephritis (at remission). All symptomatic fractures were recorded as an outcome, except for pathological fractures due to metastatic cancer. Prevalent (including asymptomatic, unrecognized or pre-existing) spine fracture was also diagnosed by yearly examined lateral abdominal radiograph between 2006 and 2008 retrospectively. By the end of the study period, 485 patients were successfully analyzed. This study was carried out in accordance with the Declaration of Helsinki (2004) and informed consent was obtained from all patients.

CKD–MBD treatment strategy

In this study, patients were treated according to a uniform algorithm of the 2003 K/DOQI Bone and Mineral Guideline or as otherwise mentioned [5]. Phosphate binders included sevelamer hydrochloride ($n = 171$), calcium carbonate ($n = 392$) or both ($n = 138$) at the end of the study. Most of the patients ($n = 377$) received either oral or intravenous vitamin D_3 (calcitriol or maxacalcitol) to maintain serum intact parathyroid hormone (PTH) levels within the range of 150–300 pg/mL. Dialyzate Ca was 2.5 mEq/L. Parathyroidectomy was performed on 49 patients during the study period.

Biochemical measurements

Most of the laboratory tests were performed once a month and blood samples were withdrawn at the start of the first dialysis session of each week. Laboratory data were analyzed at baseline or at incidence (the nearest timing before the fracture or at the end of the study). Serum bone-specific alkaline phosphatase (b-AP) was measured by CLEIA assay (Access Ostase®; Beckman Coulter Inc., Fullerton, CA) and serum intact PTH was measured by ECLIA assay ('Elecsys PTH'; Roche Diagnostics GmbH, Mannheim, Germany). These assay methods do not require any correction factor with Nichols' 'Allegro intact PTH' [6, 7].

Bone density measurements and lateral abdominal radiograph

BMD was measured once a year annually at the same interval using DEXA on a QDR Delphi™ bone densitometer (Hologic Inc., Waltham, MA) expressed as an exact value in g/cm^2. In our laboratory, short-term *in vivo* precision of the BMD measurement was 1.6% for the 1/3 distal of the radius (side of arm without blood access), 3.2% for the lumbar spine (L2 through L4) in the lateral projection, 2.5% for the femoral neck and 0.9% for the total hip region (same side of the arm) and 1.0% for the whole body. T score was calculated according to the reference values for the Japanese (lumbar spine, femoral neck, total hip and 1/3 distal of the radius) [8]. WHO Fracture Risk Assessment Tool (FRAX®) was also tested for secondary osteoporosis in this population (http://www.sheffield.ac.uk/FRAX/tool.jsp?country=3). BMD was analyzed by a single measurement at baseline or at incidence (the nearest timing before the fracture or at the end of the study). Yearly change rate of BMD was also analyzed in 228 patients (26 new fracture episodes), who successfully took more than three consecutive measurements. Lateral abdominal radiograph, which included vertebrae at least from Th11 to L5, was recorded once a year starting from 2006 at the same interval for every patient, unless the patient required this for diagnosis of lumbar pain. Spine fracture was diagnosed based on the criteria created by the research group on osteoporosis of the Ministry of Health and Welfare of Japan [9].

Statistical analysis

Kaplan–Meier survival analysis was used to calculate the hazard ratio (HR) for fractures associated with the three PTH groups; log-rank tests were calculated and compared with the survival curves between the groups. Cox proportional hazards model was used to calculate HRs for fractures associated with calcium, phosphorus, b-AP, PTH or BMD (various parts). All models were adjusted by age, gender, dialysis vintage and diabetes. The receiver-operating characteristic (ROC) curve was analyzed to estimate diagnostic values [area under curve (AUC), sensitivity, specificity and cutoff value] of each surrogate marker. The cutoff value corresponds to the highest average of sensitivity and specificity. AUCs were compared according to the method of Delong [10]. Differences in mean values between patients with and without fractures were evaluated using the unpaired Student's *t*-test for parametric data and the Mann–Whitney *U*-test for nonparametric data. Categorical data were compared between groups using Pearson's chi-square test. Data are presented as the mean ± standard deviation or as median with ranges where appropriate. P-values <0.05 are regarded as significant.

Statistical analyses were performed using the software MedCalc™11.2.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

Demographics, laboratory data and BMD with and without fracture

During this study, 46 new episodes of fracture (incident fracture) cases were recorded; 10 rib or clavicle, 2 spine (traumatic), 3 humerus, 6 wrist (Colles' fracture), 11 hip, 5 tibia or fibula, 6 ankle and 3 at other sites. Lateral abdominal radiograph also demonstrated prevalent spine fracture in 29 patients. There was no difference in gender, diabetes prevalence, parathyroidectomy, age, history of other fractures, body mass index (BMI), hemoglobin, serum albumin, creatinine, inorganic phosphorus, C-reactive protein (CRP), b-AP or PTH between the patient groups with and without fracture at baseline. Significant differences were, however, found for pre-existing spine fracture ($P = 0.005$), greater dialysis vintage ($P < 0.001$), higher serum calcium ($P = 0.01$) and lower BMD measurement at every site except lateral lumbar spine at baseline in patients with fracture. When incident laboratory data were compared with the data at entry, b-AP was significantly higher in patients with fracture ($P < 0.001$) and remained high, while b-AP significantly reduced in patients without fracture. There was no significant difference in yearly change in BMD at any site (Table 1).

Fracture risk associated with demographics, serum markers and BMD

The median follow-up time was 39.9 months (interquartile range: 38.0–41.8 months). The overall unadjusted new fracture rate was 1.9 fractures per 100 patient-years. Among the biochemical markers, higher b-AP was a significant predictor of any type of fracture if measured at the nearest point or at 6 (0–6), 12 (7–12), 18 (13–18) and 24 (19–24) months before fracture (Table 2). History of fracture (HR = 2.71, P = 0.02), baseline BMD at the femoral

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Table 1. Baseline characteristics of the 462 patients[a]

	No fracture ($n = 416$)	New fracture ($n = 46$)	P
Male gender	271 (65.1%)	25 (54.3%)	0.2
Diabetes	163 (39.2%)	15 (32.6%)	0.48
PTX	45 (10.8%)	4 (8.7%)	0.85
Age (years old)	60 ± 13	61 ± 12	0.7
Pre-existing spine fracture	18 (4.9%)	7 (17.5%)	0.005
History of other fracture	31 (7.5%)	7 (15.2%)	0.09
BMI (kg/m^2)	21.6 ± 3.6	20.8 ± 3.1	0.22
Dialysis vintage (month)	19 [0–96]	68 [17–189]	0.0006
Hemoglobin (g/dL)	10.0 ± 1.2	10.2 ± 1.5	0.34
Albumin (g/dL)	3.7 ± 0.4	3.7 ± 0.4	0.32
Creatinine (mg/dL)	10.6 ± 3.5	10.8 ± 3.2	0.87
Calcium (mg/dL)	9.0 ± 0.9	9.3 ± 0.8	0.01
Phosphorus (mg/dL)	5.7 ± 1.4	5.8 ± 1.5	0.5
CRP (mg/dL)	0.45 ± 1.32	0.32 ± 0.63	0.31
b-AP (μg/L)	24 [18.6–31.6]	25.8 [20.7–33.7]	0.17
b-AP-0 (μg/L)	15.4 [11.5–21.9]	27.4 [18.2–38.7]	<0.0001
PTH (pg/mL)	220 [116–360]	172 [100–369]	0.39
PTH-0 (pg/mL)	203 [123–322]	285 [89–415]	0.35
1/3 distal radius BMD (g/cm^2)	0.635 ± 0.124	0.566 ± 0.148	0.005
Percent change (%/year)	99.6 [98.3–100.6]	99.8 [99.1–100.4]	0.33
Lumbar spine BMD (g/cm^2)	0.614 ± 0.174	0.571 ± 0.164	0.15
Percent change (%/year)	99.4 [97.3–102]	100.7 [98.1–102.8]	0.19
Femoral neck BMD (g/cm^2)	0.636 ± 0.141	0.567 ± 0.133	0.001
Percent change (%/year)	99.6 [98.1–101.1]	99.4 [98–100.3]	0.2
Femoral trochanter BMD (g/cm^2)	0.556 ± 0.137	0.480 ± 0.128	0.0006
Percent change (%/year)	99.6 [98.2–100.5]	99.1 [98.2–100.2]	0.21
Total hip BMD (g/cm^2)	0.743 ± 0.163	0.646 ± 0.176	0.0006
Percent change (%/year)	99.0 [97.4–100.5]	98.8 [97.8–99.7]	0.4
Whole body BMD (g/cm^2)	0.970 ± 0.119	0.917 ± 0.106	0.006
Percent change (%/year)	99.3 [98.4–100.2]	99.6 [98.6–100.7]	0.51

[a]Data are given as the mean ± SD. Differences in mean and median values between groups were evaluated by using the unpaired Student's *t*-test or Mann–Whitney *U*-test. Categorical data were compared between groups by using the chi-square test. All of the data represent baseline values except for b-AP-0 and PTH-0, which are the values just prior to a fracture episode or at the end of the study in a non-fracture case.

neck (HR = 0.96, P = 0.01) and trochanter (HR = 0.95, P = 0.003) and total hip (HR = 0.97, P = 0.005) were also associated with significantly greater risk of fracture in both unadjusted and adjusted by demographic parameters (Table 2). FRAX® parameters (major osteoporotic and hip fracture) were successfully calculated only in 252 patients retrospectively but a significant association with fracture risk was not shown in this population by Cox-hazard analysis. Since U-shaped curve association of fracture risk and PTH level was suspected, patients were stratified by different PTH levels according to either the K/DOQI target level (150–300 pg/mL) or the KDIGO target level (130–585 pg/mL) and quartile of PTH level. Kaplan–Meier survival analysis demonstrated that only the lower (<150 pg/mL: HR = 3.27, P < 0.01, $n = 148$) or higher PTH (>300 pg/mL: HR = 2.69, P < 0.01, $n = 141$) groups were associated with a significantly greater risk of fracture compared with the K/DOQI target PTH group (150–300 pg/mL, $n = 173$) when PTH levels at incidence were employed as shown in Figure 1a. No significant difference was found among the PTH groups according to the KDIGO PTH target at either baseline or incidence (Figure 1b). The highest quartile of PTH level was a significantly higher risk than the second or third quartiles but no significant difference between the first and second or third quartiles was found (Figure 1c).

Diagnostic accuracy of serum markers and BMD to predict any type of fracture risk

By ROC analysis, we demonstrated that the AUC was the largest in b-AP at incidence (0.766, P < 0.0001) among the other biochemical parameters and BMDs (significantly greater than BMD at any site) (P < 0.05) (Figure 2). Among the sites of BMD measurement, the AUC was significant in 1/3 distal radius (0.588, P < 0.05), femoral neck (0.610, P < 0.05) and total hip (0.659, P < 0.001) as shown in Figure 2. The AUCs were also calculated for serum markers and BMDs at incidence by stratifying patients into two PTH groups according to the median value of PTH at incidence; lower (PTH < 204 pg/mL) and higher (PTH > 204 pg/mL) (Table 3). The cutoff value for b-AP (at incidence) was ≥19.9 μg/L (P < 0.0001) in the lower PTH group and >29.1 μg/L (P < 0.0001) in the higher PTH group, respectively. The cutoff value for PTH was ≤100 pg/mL for the lower PTH group and >290 pg/mL for the higher PTH group, respectively. In BMD measurements, the AUC at the same site as mentioned above remained significant and was enhanced in the lower PTH group but was not significant at any site in the higher PTH group after stratification. When this result in the lower PTH group was stratified with gender, significance in AUC remained only for females at 1/3 distal radius (0.686,

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Table 2. Cox-proportional hazard analysis on the risk of any type of fracture associated with patient demographics, serum markers and BMD[a]

	Unadjusted HR	95% CI	P	Adjusted HR	95% CI	P
History of fracture	2.33	1.05–5.20	0.04	2.71	1.20–6.11	0.02
BMI (kg/m^2)	0.94	0.86–1.03	0.21	0.98	0.89–1.08	0.69
Albumin (g/dL)	0.82	0.37–1.82	0.64	1.14	0.44–2.94	0.79
Calcium (mg/dL)	1.17	0.84–1.63	0.35	1.10	0.75–1.61	0.64
Phosphorus (mg/dL)	0.99	0.81–1.23	0.1	1.02	0.82–1.27	0.87
CRP (mg/dL)	0.95	0.67–1.30	0.74	0.92	0.64–1.31	0.64
b-AP (μg/L)	1.01	0.99–1.02	0.45	0.99	0.98–1.02	0.65
b-AP-0 (μg/L)	1.04	1.03–1.06	<0.0001	1.04	1.03–1.06	<0.0001
b-AP-6 (μg/mL)	1.03	1.02–1.04	<0.0001	1.03	1.01–1.04	0.0003
b-AP-12 (μg/mL)	1.03	1.02–1.04	<0.0001	1.03	1.02–1.04	<0.0001
b-AP-18 (μg/mL)	1.03	1.02–1.04	<0.0001	1.03	1.01–1.04	0.0001
b-AP-24 (μg/mL)	1.03	1.01–1.04	0.0003	1.02	1.01–1.04	0.01
PTH (pg/mL)	0.99	0.99–1.00	0.52	0.99	0.99–1.00	0.37
PTH-0 (pg/mL)	1.00	1.00–1.00	0.14	1.00	1.00–1.00	0.12
1/3 distal radius BMD (per 10 mg/cm^2)	0.97	0.95–0.99	0.004	0.97	0.94–1.01	0.12
1/3 distal radius BMD (per -1 SD)	0.82	0.71–0.95	0.007	0.87	0.73–1.04	0.12
Lumbar spine BMD (per 10 mg/cm^2)	0.98	0.96–1.00	0.07	0.98	0.96–1.00	0.13
Lumbar spine BMD (per -1 SD)	0.87	0.74–1.03	0.1	0.87	0.73–1.03	0.1
Femoral neck BMD (per 10 mg/cm^2)	0.96	0.94–0.98	0.0006	0.96	0.94–0.99	0.01
Femoral neck BMD (per -1 SD)	0.59	0.44–0.80	0.0007	0.65	0.47–0.90	0.009
Femoral trochanter BMD (per 10 mg/cm^2)	0.95	0.93–0.98	0.0001	0.95	0.92–0.98	0.003
Total hip BMD (per 10 mg/cm^2)	0.96	0.94–0.98	0.0003	0.97	0.94–0.99	0.005
Total hip BMD (per -1 SD)	0.62	0.48–0.80	0.0002	0.65	0.49–0.87	0.004
Whole body BMD (per 10 mg/cm^2)	0.97	0.94–0.99	0.007	0.97	0.94–1.00	0.08
FRAX® for major osteoporotic ($n = 252$) (%)	1.03	0.99–1.07	0.13	1.03	0.98–1.08	0.24
FRAX® for hip fracture ($n = 252$) (%)	1.04	0.98–1.10	0.22	1.03	0.96–1.09	0.4

[a]HR is adjusted by age (years old), gender, dialysis vintage (month) and the presence or absence of diabetes. All of the data represent baseline values except for b-AP-0 and PTH-0, which are the values just prior to a fracture episode in a fracture case or at the end of the study in a non-fracture case. b-AP-6, -12, -18 and -24 are the values measured at 6-month intervals prior to the fracture or at the end of the study.

P = 0.03), femoral neck (0.706, P = 0.01), trochanter (0.721, P = 0.006) and total hip (0.787, P = 0.0001). Multiple regression analysis revealed that serum PTH ($r = 0.26$, P = 0.008), phosphorus ($r = 0.096$, P < 0.05) and albumin ($r = 0.21$, P = 0.009) had a significant correlation with serum b-AP in fracture patients with higher PTH ($n = 24$), but significance was only found in serum albumin ($r = 0.25$, P < 0.05) and age ($r = 0.26$, P < 0.05) in fracture patients with lower PTH ($n = 19$). There was no significant correlation of b-AP with other independent variables (BMI, serum calcium, CRP and dialysis vintage) in either group.

Diagnostic accuracy of BMD to discriminate prevalent spine fracture

Since many cases of prevalent spine fractures ($n = 29$) were found by lateral abdominal radiograph retrospectively, discriminatory power (instead of predictive power) of DEXA was examined by a cross-sectional study utilizing the first available DEXA measurements between 2006 and 2008. ROC analysis revealed that AUC was significant at the femoral neck (0.827, P = 0.0001), femoral trochanter (0.776, P = 0.0001), total hip (0.808, P < 0.0001), lumbar spine (0.674, P = 0.001), 1/3 distal radius (0.724, P = 0.0001) and whole body (0.680, P = 0.008). When these patients were stratified by gender, the BMD at total hip or femoral neck was found to be very useful in both genders, as shown in Table 4.

Discussion

The BMD measurement for predicting any type incident fracture was gender and PTH specific in this cohort. We found that either baseline or incident BMD at the total hip, femoral neck/trochanter or 1/3 distal radius (in this order) was useful to predict fracture risk in female patients with PTH <204 pg/mL (median PTH value at incidence). This was also true when PTH was l<150 pg/mL (lower level of K/DOQI PTH target). This level of PTH strongly suggests that histological change in these patients with fracture is likely due to it being an adynamic bone or osteomalacia. However, in patients with higher PTH, the main cause of fractures is likely to be due to osteitis fibrosa, which is prone to developing fractures, despite frequently increased trabecular bone mass [11]. In contrast to any type of incident fracture, discriminatory power of BMD for prevalent spine fracture was significant regardless of gender or PTH. Among the measurement sites, total hip or femoral neck was found to be better than spine, even for spine fracture and this agrees well with a recent study for nondialyzed CKD patients [4].

Kaplan–Meier survival analysis demonstrated that fracture risk was U-shaped and associated with serum PTH levels when patients were stratified according to the target PTH level by the K/DOQI guideline [5]. When we stratified the target PTH level by the KDIGO guideline, it did not show any predictive ability for fracture risk. However, the distribution of patients according to

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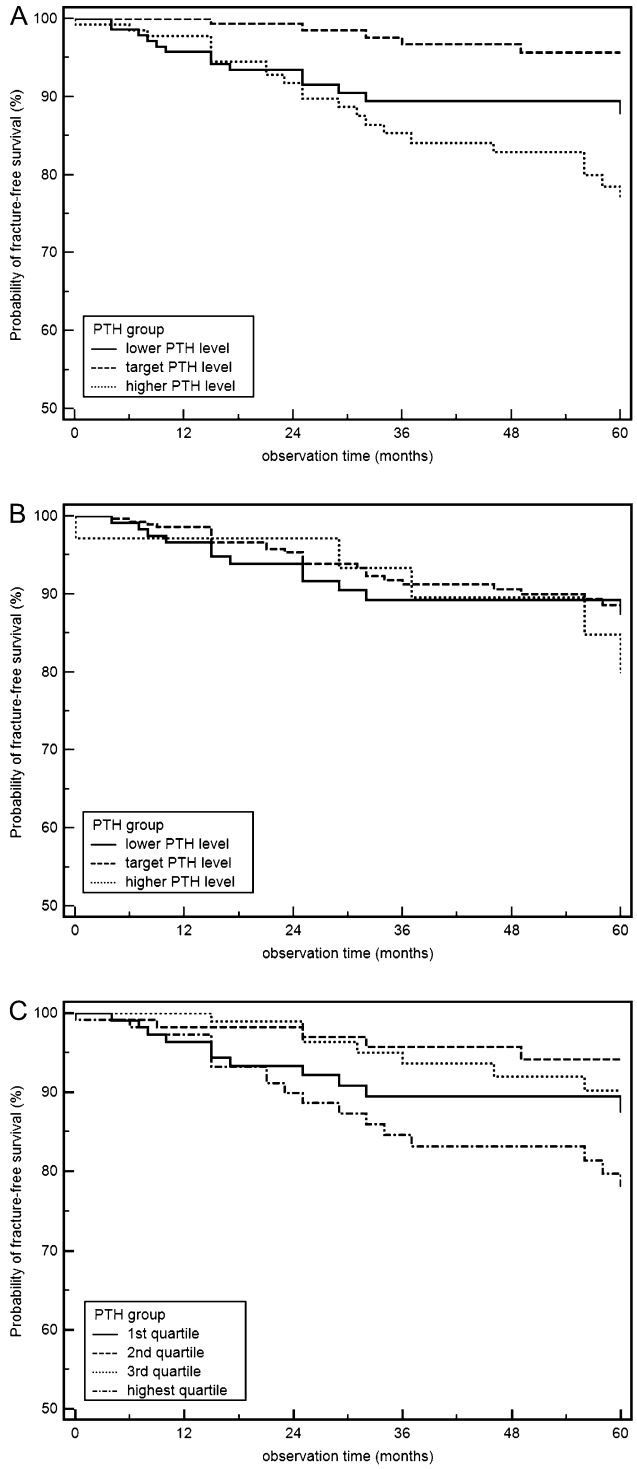

Fig. 1. Fracture survival rate among patients with different incident PTH levels stratified by the K/DOQI (**a**), KDIGO (**b**) guideline target levels and the quartile of PTH level (**c**). (a) Fracture (any type) survival rate among patients with different incident PTH levels stratified by the K/DOQI guideline target level. 'Incident PTH levels' are those just prior to a new fracture or at the end of the study. If baseline PTH levels were analyzed, no difference was found (data not shown). Both lower (<150 pg/mL: HR = 3.47, $P < 0.01$, $n = 148$) and higher PTH (>300 pg/mL: HR = 5.88, $P < 0.0001$, $n = 141$) were associated with significantly greater risk of fracture compared with target PTH (150–300 pg/mL, $n = 173$). **(b)** Fracture (any type) survival rate among patients with different incident PTH levels stratified by the KDIGO guideline target level. 'Incident PTH levels' are those just prior to a new fracture or at the end of the study. If baseline PTH levels were analyzed, no difference was found (data not shown). Neither lower (<130 pg/mL: HR = 1.20, $P < 0.60$, $n = 126$) nor higher PTH (>585 pg/mL: HR = 0.65, $P = 0.37$, $n = 35$) was associated with risk of fracture compared with target PTH (130–585 pg/mL, $n = 301$). (c) Fracture (any type) survival rate among patients with different incident PTH levels stratified by quartile of PTH level. 'Incident PTH levels' are those just prior to a new fracture or at the end of the study. If baseline PTH levels were analyzed, no difference was found (data not shown). The highest quartile (PTH > 366 pg/mL, $n = 114$) of PTH level was significantly higher risk than the second (PTH 116–210 pg/mL: HR 4.0, $P = 0.003$, $n = 115$) or third (PTH 214–363 pg/mL: HR 2.7, $P = 0.02$, $n = 114$) quartile but no significant difference between the first (PTH < 115 pg/mL, $n = 114$) and second or third quartile was found.

the KDIGO target was too uneven in our cohort to support this negative result. There have been four large cohort studies in CKD 5D patients that relate serum PTH to fractures. The results were as follows: higher risk with low PTH for only hip fracture cases [12], low or high PTH for hip, spine and pelvis fractures [13], high PTH (>900 pg/mL) for any type of fracture [14] and high PTH for only fracture-related hospitalization cases [15]. These results, including ours, are mostly consistent with a higher risk associated with higher PTH when any type of fracture is studied. This is reasonable because the classic presentation of severe osteitis fibrosa is fracture [11]. However, there remains an inconsistency with lower PTH for fracture risk. This discrepancy could be caused by a different stratification method of PTH levels because we did not find a significant risk in lower PTH when we stratified by quartile or by the KDIGO target, although the K/DOQI target and ROC analysis worked. Another explanation is that a heterogenous spectrum of histology can be suspected in this lower PTH group. In this study, we found that higher b-AP levels are associated with fracture risk not only in patients with higher PTH but also in patients with lower PTH. Atsumi *et al.* [9] also demonstrated that low PTH and high alkaline phosphatase was a high risk for spine fracture in male hemodialyzed patients. There are two possible explanations for this discrepancy between PTH and b-AP levels. One is that hyperparthyroid bone may exist in some patients in the lower PTH group. This possibility was rejected by the multiple regression analysis, which showed no significant correlation between PTH and b-AP in fracture patients with lower PTH, although a strong correlation existed in the higher PTH group. Second is that high b-AP, the surrogate marker for bone formation, makes osteomalacia more likely than adynamic bone, which is defined by a dramatic decrease in bone formation, when PTH is low. In overall performance, b-AP is a better surrogate marker than PTH because high level or increasing tendency can predict fracture risk.

We examined 13 studies that were reviewed by the KDIGO CKD–MBD guideline for the association between BMD and fractures in CKD [2]. Our analysis is somehow different from the one explained in the guideline rationale. The results were indeed variable: seven studies did not find a relationship between BMD and fracture rate [16–22],

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whereas six studies found a relationship in at least one skeletal site [9, 23–27]. If we select only the studies that use DEXA for BMD in CKD 5D patients receiving hemodialysis, nine studies (four negative and five positive results) remain. In fact, the number of patients does not reach even 100 in four of the studies that report a negative association and therefore should be disregarded because of the insufficient power for conclusion. Also, the five other studies with a positive association could not demonstrate multiple sites of fracture. If multiple sites of fracture were not recorded, then patients with any fracture could be misclassified as a nonevent. Finally, all of these studies were performed by a cross-sectional design and could only show discriminatory power for fracture, not predictive power.

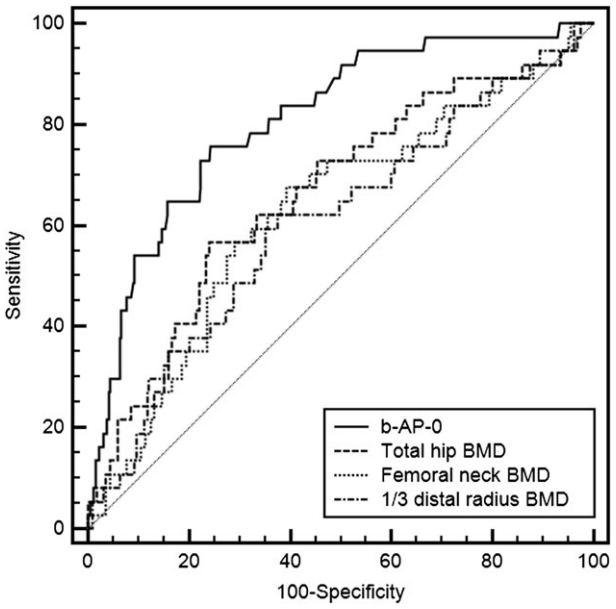

Fig. 2. ROC analysis on the prediction of any type of fracture. The results without stratifying PTH level or gender for AUCs are: 0.766 (b-AP-0, $P < 0.0001$), 0.659 (total hip BMD, $P < 0.001$), 0.61 (femoral neck BMD, $P < 0.05$), 0.616 (femoral trochanter BMD, $P < 0.01$) and 0.588 (1/3 distal radius BMD, $P < 0.05$). Cutoff values are >20.1 μg/L (b-AP), ≤0.624 g/cm^2 (total hip BMD), ≤0.585 g/cm^2 (femoral neck BMD), ≤0.474 g/cm^2 (femoral trochanter BMD) and ≤0.589 g/cm^2 (1/3 distal radius BMD).

In the WHO guideline for osteoporosis, a T score of the femoral neck or lumbar spine <2.5 is considered to be a high risk for fracture [28]. The AUC was between 0.8 and 0.9 in the studies that were considered for the WHO guideline in determining the cutoff value of fracture risk prediction [29]. As a matter of fact, the AUC and cutoff T score of the total hip for discriminating prevalent spine fracture in our study is as good as those values for osteoporosis. WHO also recommends the FRAX® algorithm, which enhances a positive predictive value for hip BMD measurement by integrating the patient's demographics such as gender, age, smoking, alcohol, history of fracture and family history of hip fracture in order to give a 10-year probability of fracture in primary osteoporosis. In this study, we could not find any significant difference in either of the FRAX® scores (major osteoporotic or hip fracture) between patients with and without fracture. However, both the inaccuracy of the patient's history obtained retrospectively and the insufficient study period could contribute to this negative result.

In summary, serum b-AP measured at regular intervals was very useful in predicting any type fracture in CKD 5D patients. Not only a high b-AP level but also increasing trend suggests a high fracture risk. Fracture risk associated with a higher PTH level was consistent, but a lower level was not associated according to the PTH stratification method. The predictive ability of BMD for any type of incident fracture was only significant in females with low PTH, while the discriminatory ability of BMD for prevalent spine fracture was as effective as that for primary osteoporosis, regardless of gender or PTH level. The site of BMD measurement was suggested to be the total hip region for any type of fracture and for spine fracture in part due to good precision.

Table 3. ROC analysis on serum markers and bone mineral densities stratified by median value of PTH for any type of fracture[a]

	PTH < 204 pg/mL, $n = 230$, Fx = 20					PTH > 204 pg/mL, $n = 232$, Fx = 26				
	AUC	Cutoff value	P	Sensitivity	Specificity	AUC	Cutoff value	P	Sensitivity	Specificity
b-AP-0 (μg/L)	0.796	>19.9	0.0001	70.0	82.4	0.756	>29.1	0.0001	65.4	82.2
PTH-0 (pg/mL)	0.639	≤100	0.02	70.0	62.4	0.634	>290	0.03	88.5	41.3
1/3 distal radius BMD (g/cm^2)	0.623	≤0.589	0.06	66.7	59.1	0.555	≤0.578	0.36	50.0	67.5
T score		≤−0.7					≤−3.3			
Lumbar spine BMD (g/cm^2)	0.579	≤0.546	0.25	58.8	61.4	0.528	>0.798	0.66	21.7	90.2
T score		≤−3.6					>−0.5			
Femoral neck BMD (g/cm^2)	0.717	≤0.549	0.0001	72.2	75.0	0.512	≤0.615	0.85	65.2	47.4
T score		≤−2.5					≤−2.0			
Femoral trochanter BMD (g/cm^2)	0.712	≤0.469	0.0001	77.8	69.9	0.537	≤0.476	0.55	47.8	67.6
Total hip BMD (g/cm^2)	0.760	≤0.571	0.0001	66.7	84.9	0.588	≤0.624	0.16	50.0	75.8
T score		≤−2.7					≤−2.2			
Whole body BMD (g/cm^2)	0.610	≤0.952	0.13	78.6	52.7	0.538	≤0.946	0.55	65.2	50.6

[a]b-AP-0: bone-specific alkaline phosphatase (at incidence), PTH-0: parathyroid hormone (at incidence). The T score was calculated for males and females independently first and then an average of the T scores of both sexes was determined and is presented in this table. Reference values to calculate T score are for the Japanese population.

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Table 4. ROC analysis on bone mineral densities for spine fracture stratified by gender[a]

	Male ($n = 270$, VF = 11)					Female ($n = 156$, VF = 18)				
BMD (g/cm^2)	AUC	Cutoff value	P	Sensitivity	Specificity	AUC	Cutoff value	P	Sensitivity	Specificity
1/3 distal radius	0.749	≤0.653	0.0004	90.9	63.7	0.683	≤0.397	0.03	58.3	83.1
T score		≤−1.8					≤−4.4			
Lumbar spine	0.631	≤0.535	0.09	63.6	70.5	0.675	≤0.559	0.02	91.7	43.4
T score		≤−3.9					≤−2.6			
Femoral neck	0.896	≤0.546	0.0001	90.9	86.0	0.730	≤0.419	0.009	54.6	87.7
T score		≤−2.5					≤−3.4			
Femoral trochanter	0.832	≤0.535	0.0001	90.9	65.5	0.700	≤0.370	0.04	63.6	77.9
Total hip	0.869	≤0.654	<0.0001	81.8	83.6	0.749	≤0.569	0.0002	80.0	63.8
T score		≤−1.9					≤−2.7			
Whole body	0.700	≤0.890	0.06	70.0	84.1	0.624	≤0.835	0.25	70.0	62.3

[a]VF, Spine fracture.

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