

^{99m}Tc MDP Bone Scan Findings in CKD-MBD: Could the “Superscan” Image be Useful in Excluding Adynamic Bone Disease?

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ABSTRACT

Objective: To explore the association of superscan image in technetium 99m-labeled methylene diphosphonate bone scans with chemical parameters of high turnover bone disease and bone mineral density measurement findings in chronic peritoneal dialysis patients.

Methods: Technetium 99m-labeled methylene diphosphonate bone scans of 15 chronic peritoneal dialysis patients with superscan images were matched by their age, gender, dialysis vintage, body mass index, and Kt/V values with 20 patients with no superscan image. Serum iPTH, Ca, P, 25(OH)D3, 1-25(OH)2D3, total and bone alkaline phosphatases, dual-energy X-ray absorptiometry-based bone mineral density results were measured.

Results: Serum iPTH levels were significantly higher in superscan patients (587.3 ± 515.9 pg/ml vs 214.8 ± 224.9 pg/ml, $P = .001$) and correlated with the existence of superscan image ($P = .007$, $r = -0.450$) in bone scans. Total alkaline phosphatase levels were also significantly higher in superscan patients (414.7 ± 400.6 vs 235.6 ± 117.6 U/L, $P = .046$). Ca, P, CaXP, 25(OH)D3, 1-25(OH)2D3, bone alkaline phosphatase levels, and bone mineral densities were not different between groups.

Conclusion: Superscan image in technetium 99m-labeled methylene diphosphonate bone scans correlated well with serum iPTH and total alkaline phosphatase levels, and therefore, it may be suggestive for high turnover bone disease in chronic peritoneal dialysis patients. Lack of any difference between groups regarding their bone mineral densities suggests that the main difference between groups may be a metabolic one, rather than being structural. We believe that superscan images may be a diagnostic tool for high turnover bone disease, and they may have a role as an excluding tool of a dynamic bone disease especially before the use of bisphosphonates.

Keywords: CKD, ^{99m}Tc MDP bone scan, superscan, high turnover bone disease, bone mineral density

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INTRODUCTION

Disturbances in mineral and bone metabolism are major components in the pathophysiology of chronic kidney disease (CKD). The diagnosis, management, and follow-up of bone problems in CKD patients are different from the general population. In CKD patients, individualization of both diagnosis and treatment options for CKD-mineral bone disease (CKD-MBD) is necessary. Chronic kidney disease in CKD-MBD leads to significant morbidity and mortality, not only as a major contributor for bone-related problems like bone fractures and bone

pain, but also as a major cause of increased cardiovascular mortality and morbidity.¹⁻³

Bone-related disturbances seen in CKD-MBD are complex processes affected by a combination of several parameters, such as pathologic changes in parathormone (PTH), fibroblast growth factor 23 (FGF23), and levels of calcium (Ca) and inorganic phosphorus (P). Histopathologic changes in CKD-MBD result in altered bone microstructure and mineralization. CKD aggravates abnormal bone physiology through resistance for the



PTH effect, increasing oxidative stress. There is an increase in P and FGF23 levels, accompanied by decreased synthesis of active vitamin D.⁴ CKD-MBD-related metabolic changes such as elevated levels of FGF23 and serum PTH, start as early as eGFR levels of slightly below 60 mL/min/1.73 m.^{2,5,6}

One of the leading clinical problems at any stage of CKD-MBD is increased low-trauma fracture risk, which is known to be closely related with osteoporosis in the general population.⁷⁻⁹

Although osteoporosis in the non-CKD population is simply defined as a decrease in bone volume, in CKD patients, it is only a part of the wider spectrum of metabolic and structural changes in bone tissue occurring secondary to CKD-MBD. Therefore, the definition, diagnosis, and treatment of osteoporosis in CKD patients are as yet incompletely understood.²

The measurement of bone mineral density (BMD), as measured by dual-energy X-ray absorptiometry (DXA), has been widely used to define osteoporosis, and it has been shown to predict fracture risk accurately in both CKD and non-CKD populations.¹⁰⁻¹² Quantitative computed tomography and heel ultrasonography techniques are the leading alternatives for DXA in assessing BMD and evaluating bone microarchitecture, respectively. Newer techniques, such as ultrahigh resolution peripheral quantitative computerized tomography and micro-magnetic resonance imaging, still remain as investigational techniques.^{13,14} Although it is not completely validated for the CKD population, due to its lower cost, relative accuracy, short scan time, and low radiation dose, DXA is the most widely used method for BMD measurements in CKD patients. Some studies suggest that in CKD patients with low DXA-based BMD values, the risk of low-trauma fracture may be increased

significantly.^{11,12,15} Therefore, DXA seems to be a reasonable and practical option to measure BMD and predict fracture risk in CKD patients.¹⁰

In CKD patients, the use of bisphosphonates has been reported safe, with good clinical results in CKD stages 1-3. In patients with CKD-MBD, coexistence of a decreased BMD and high cellular activity, otherwise known as high-turnover bone disease, may be an optimal indication for the use of bisphosphonates. However, the exclusion of low-turnover bone disease is highly recommended in CKD stages 4 and 5, in order to avoid blocking bone cellular activity in patients with adynamic bone disease, which may lead to vicious consequences such as jaw necrosis and further deterioration in bone strength.¹⁶⁻¹⁸ Therefore, the exclusion of adynamic bone disease with a bone biopsy is recommended as the best tool known for discrimination between low and high-turnover bone states. Unfortunately, bone biopsy is a costly and a highly invasive procedure and its evaluation requires experienced pathological support which is not easily available everywhere.² Therefore, we still need more accurate non-invasive evaluation methods based on biochemical markers, radiological methods, and other available tools such as bone scintigraphy, in assessing the rate of bone turnover.

Serum PTH level is one of the most decisive parameters of bone turnover rate, and its interpretation plays a major role in assessing bone turnover status in CKD-MBD patients.¹⁰ However, due to poor method comparability and method-related differences among PTH assay techniques, the age and race-related differences in PTH secretion, the modifying effects of medications used, and confounding comorbidities like diabetes mellitus and malignancies, serum PTH level is not a reliable indicator of bone turnover in many CKD patients. For PTH levels between 2 and 9 times the upper limit of normal, the sensitivity and specificity of PTH levels in discriminating between low and non-low-turnover bone diseases were found to be only 65.7% and 65.3%, and 37.0% and 85.8%, for high and non-high bone turnover status respectively.¹⁹⁻²² Total alkaline phosphatase (ALP) and/or bone alkaline phosphatase (bALP) levels are other promising additional biomarkers used in the assessment of bone turnover in CKD-MBD.¹ Sprague et al¹⁹ have reported that in dialysis patients, bone ALP assays were useful in discriminating both low from non-low and high from non-high bone formation rates. The clinical values of newer bone biomarkers such as FGF23, amino-terminal propeptide of type 1 procollagen (P1NP), PTH 1 receptor, receptor activator of nuclear factor- κ B, sclerostin, and osteoprotegerin are not clearly established yet.¹

On the other hand, bone scintigraphy with technetium ^{99m}Tc-labeled methylene diphosphonate (^{99m}Tc MDP) is known to be an inexpensive, simple, and widely accessible tool in the diagnostic evaluation of numerous pathologic conditions of bone tissue. It is known that the late phase of ^{99m}Tc MDP uptake by bone reflects bone turnover, and is known to be intensified in high bone turnover states such as malignancies, new fractures,

Main Points

- Superscan images in technetium ^{99m}Tc-labeled methylene diphosphonate (^{99m}Tc MDP) bone scans correlate well with serum iPTH and total ALP levels, which may be suggestive of high-turnover bone disease in CPD patients. Evidences from our biochemistry laboratory and ^{99m}Tc MDP bone scan findings suggest that a superscan image may be an additional evidence of chronic kidney disease (CKD)-induced high-turnover bone disease in chronic peritoneal dialysis (CPD) patients.
- The lack of any difference between the 2 groups regarding their bone mineral density (BMD) suggests that the main difference may be metabolic, rather than structural.
- ^{99m}Tc MDP bone scans possibly can be used along with other non-invasive tests in the exclusion of adynamic bone disease. Therefore, there may be a potential for the use of Tc99m bone scan findings in the diagnosis and decision making process for the treatment of CKD-mineral bone disease (CKD-MBD).
- We believe that bone scans, especially when they present as superscan images, may be a potential diagnostic tool for high-turnover bone disease, and may have a supportive role in the deciding the treatment approach.

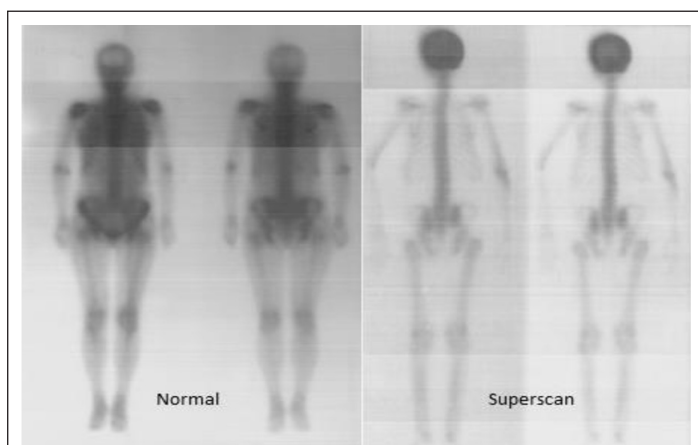


Figure 1. ^{99m}Tc MDP whole-body bone scans with normal and “superscan” images showing intense symmetric activity in the bones, compared with diminished soft tissue activity in the superscan image.

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and joint problems. However, its clinical value in discriminating high and/or low-turnover variants of CKD-MBD have not been studied properly. Increased uptake of ^{99m}Tc MDP by bone tissue is reported to be secondary to increased osteoblastic activity.²³ A unique finding, known as “superscan” (SS), is a bone scintigraphy image that demonstrates unusually increased bone ^{99m}Tc MDP uptake compared with soft tissues (Figure 1). If the bone is hypermetabolic, absorption of isotope increases, as seen in some diseases such as metastatic cancers (prostate, lung, and breast cancers), metabolic bone diseases (CKD-MBD, Paget’s disease), and some hematologic diseases (leukemia, lymphoma, myelofibrosis).²³

In this study, we aimed to assess the consistency of ^{99m}Tc MDP bone scintigraphy findings, more specifically, “superscan” images, with biochemical clues of high and non-high bone turnover states and DXA-based evidences of osteoporosis, in chronic peritoneal dialysis (CPD) patients.

PATIENTS AND METHODS

This cross-sectional, multicenter study was approved by the Ethics Board of Akdeniz University Medical School and patients read and signed a detailed consent form. Eighty-five patients, (46 female and 39 male) with a mean age of 42 ± 11 years (23-71 years) were included in the study. Eighty-five adult patients who had been treated with continuous ambulatory peritoneal dialysis (CAPD) ($n = 62$) or automated peritoneal dialysis (APD) ($n = 23$) for at least 3 months, were investigated. Inclusion criteria were having no thyroid disorders, having no active infections for at least 2 months, and no prior history of steroid use, parathyroidectomy, organ transplantations, or malignancies.

The patients had been on general CKD-MBD and other CKD-related treatment protocols, with the recommended doses and

types of medications indicated by valid guidelines. Tc-99m MDP bone scans, intact parathyroid hormone (iPTH) (chemiluminescence method, DPC; Diagnostic Products, Los Angeles, CA, USA), albumin, corrected serum Ca, P, and total and bone ALP levels were measured by standard clinical techniques.

Patients underwent a Tc-99m MDP whole-body bone scintigraphy, along with L2–L4 anteroposterior lumbar spine and femoral neck bone DXA studies. The *t*-scores were defined as numbers of standard deviations below the mean BMD for sex-matched young controls. Z-scores were defined as the number of standard deviations below the mean BMD of age- and sex-matched controls. All bone scans were evaluated by the same nuclear medicine specialist.

In the study, 15 patients with a superscan image (group SS) were matched to 20 patients without a superscan image (group N) Tc-99m MDP bone scintigraphy. The 2 groups were similar in terms of their age, gender, body mass index (BMI), dialysis vintage, and Kt/V values.

Among the 35 study patients, the primary renal diseases were identified as hypertensive nephrosclerosis in 5 patients, amyloidosis in 5, tubulointerstitial nephritis in 4, and different types of biopsy-proven glomerulonephritis in 4 patients. The cause of end-stage renal disease (ESRD) was unknown in 17 patients.

All patients had given their written informed consent, after their physician had explained the study to them. Tourniquet effect was eliminated.

Statistical Analysis

The results were statistically evaluated, using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Normal distribution was evaluated by Shapiro–Wilk’s test. Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation, and continuous variables with abnormal distribution were expressed as median (minimum-maximum). Categorical variables were expressed as frequency and percentage. According to the presence of normal distribution of the parameters, for the analysis of continuous variables, the Mann–Whitney *U*-test and the *t*-test (independent samples *t*-test) were used. Pearson and Spearman’s rho tests were used for correlation analysis. A *P* value less than .05 was considered to be statistically significant.

RESULTS

The mean age and dialysis vintage of group SS versus group N patients were 43.1 ± 13.8 years versus 42.9 ± 11.5 years, and 84.1 ± 22.2 months versus 77.9 ± 19.9 months, respectively. There were also no age, gender, dialysis vintage, body metabolic index (BMI), and Kt/V differences between the 2 groups (Table 1).

Table 1. Demographics and Laboratory Parameters of the Study Group*

	Group SS, n = 15	Group N, n = 20	P	Correlation With Superscan Image Existence P/r
Age (years)	43.1 ± 13.8	42.9 ± 11.5	.78	.4/0.7
Gender (female/male)	4 (27%)/11 (73%)	5 (25%)/15 (75%)	.9	.7/0.35
Dialysis vintage (months)	84.1 ± 22.2	77.9 ± 19.9	.8	.45/0.4
Body mass index (kg/m ²)	26.6 ± 4.9	24.7 ± 5.7	.6	.5/0.3
Intact parathyroid hormone (pg/mL)	565 (92-765)	220 (56-455)	.001	.007-0.450
Calcium (mg/dL)	9.8 ± 1.2	9.9 ± 1.4	.4	.4/0.35
Phosphorus (mg/dL)	5.1 ± 1.6	4.7 ± 1.4	.35	.6/0.7
CaXP (mg ² /dL ²)	50.2 ± 16.9	46.5 ± 15.3	.2	.4/0.25
Albumin (g/dL)	3.8 ± 0.3	3.7 ± 0.3	.3	.7/0.3
25 (OH)D ₃ (ng/mL)	7.4 (4.5-15)	8.5 (4-27.1)	.36	.9/0.45
1-25(OH) ₂ D ₃ (pg/mL)	9.3 (3.4-15.4)	10.5 (4.1-22.3)	.1	.7/0.35
Total alkaline phosphatase (U/L)	405 (85.5-815)	265 (63-356)	.046	.06-0.314
Bone alkaline phosphatase (U/L)	132 (39-396)	89 (41-155)	.15	.7/0.4
Kt/V	1.9 ± 0.3	2.1 ± 0.5	.45	.4/0.8

*Results are shown as mean ± standard deviation for normal distribution, and median (minimum-maximum) for abnormal distribution.

The values of iPTH, Ca, P, Albumin, 25 (OH) D₃, 1-25(OH)₂D₃, ALP, bALP and Kt/V in the 2 groups are shown in Table 1. No differences between the 2 groups were observed regarding their serum Ca, P, CaXP, albumin, 25 (OH) D₃, and 1-25(OH)₂D₃ levels. The levels of iPTH and ALP were significantly higher in the SS group compared to the N group [565 (92-765) vs. 220 (56-455) pg/mL; $P = .001$], and [405 (85.5-815) vs. 265 (63-356) U/L, $P = .046$], respectively. The iPTH levels were also correlated with the SS appearance ($P = .007$, $r = -0.45$). ALP values had no correlation with the superscan finding ($P = .06$, $r = -0.314$).

Both lumbar and femoral neck BMD measurements did not show any difference between the 2 groups. Again, no statistical significance was found regarding history of fractures between the 2 groups (Table 2).

DISCUSSION

CKD-MBD may present in different rates of bone turnover, starting from low-turnover or adynamic bone disease up to a high-turnover bone state, which is also known as osteitis fibrosa cystica. High-turnover bone disease, specifically, is characterized by an increase in both osteoblastic and osteoclastic activities along with some degree of fibrosis in bone marrow, and a diminished bone skeletal mass, as the rate of resorption exceeds that of formation. However, in ESRD, bone disease is a dynamic state that changes over time, depending on progression of the underlying disease, medications used, diet, and modes of treatment.¹⁰ Therefore, before deciding on the treatment plan, assessing the current bone status of the patient is essential. Although bone biopsy is accepted as the gold standard of assessing the state of bone turnover, it is invasive, costly,

Table 2. Dual-Energy X-Ray Absorptiometry Results*

	Group SS, n = 15	Group N, n = 20	P	Correlation With Superscan Finding P/r
Lumbar vertebra bone mineral density (g/cm ²)	0.85 ± 0.34	0.94 ± 0.15	.33	.3/0.2
Femoral neck bone mineral density (g/cm ²)	0.71 ± 0.17	0.72 ± 0.11	.95	.9/0.4
Lumbar vertebra t-score	-0.8 (-2.6 to 1.7)	-0.6 (-2.2 to 1.4)	.75	.2/0.6
Lumbar vertebra Z-score	-0.4 (-2.1 to 1.4)	-0.7 (-2.5 to 1.9)	.5	.4/0.7
Femoral neck t-score	-0.9 (-2.5 to 1.8)	-1.0 (-2.1 to 1.8)	.09	.5/0.3
Femoral neck Z-score	-1.0 (-2.7 to 1.6)	-0.7 (-2.8 to 1.4)	.057	.6/0.4
Number of patients with fractures	4	2	.25	.45/0.34

*Results are shown as mean ± standard deviation for normal distribution, and median (minimum-maximum) for abnormal distribution.

and may not be available. Therefore, biochemical bone markers such as levels of PTH, bone or total ALPs, bone radiology, DXA, and heel ultrasound have been used to evaluate the degree of bone loss, rate of turnover, bone structure, and the possible histological type of CKD-MBD.^{10,24}

Bone turnover, which is the main predictor of the histological type of CKD-MBD, is directly influenced by serum PTH levels. Increased presence of PTH augments both bone formation, by increasing osteoblastic activity, as well as bone resorption, through stimulating osteoclasts.^{5,25,26} Increased levels of serum bALP also provide useful information regarding the increased rate of bone turnover in dialysis patients.^{25,27}

On the other hand, low-turnover bone disease is characterized by low PTH levels associated with a diminished rate of bone formation, decreased osteoblastic and osteoclastic activities, and increased incidence of soft tissue calcifications. The diagnosis of adynamic low-turnover bone disease is supported by low serum PTH and ALP levels.¹⁰

Unfortunately, none of these tools provide a clear-cut definition of bone turnover. Anterior iliac crest bone biopsies of 84 hemodialysis patients have shown significant differences for the same bone turnover level, indicating a poor diagnostic performance of the 5 different iPTH measurement techniques available. At 80% specificity, the cut-off values of the 5 available (as of 2009) iPTH assays for low bone turnover varied from 165 to 550 pg/mL, and for high bone turnover from 404 to 1.003 pg/mL. Sensitivities at these cut-off values also remained at less than acceptable standards.^{20,21,28} In another study, iPTH, whole PTH, and bone ALP measurements were found to be able to discriminate low from non-low bone formation rates, whereas iPTH and bALP were able to discriminate high from non-high rates of bone formation.¹⁹ More recently, in 630 dialysis patients, PTH levels were found to be a predictor of high bone turnover in both Black and White patients, and of low bone turnover in White but not Black patients.²⁹ PTH, bone ALP, and bALP isoform B1x have been shown to have similar diagnostic accuracy in distinguishing low from non-low bone turnover. The presence of B1x was diagnostic of low bone turnover, whereas elevated bALP and PTH levels were useful for the diagnosis of non-low bone turnover.^{10,30}

Therefore, the diagnostic accuracy of biochemical markers in distinguishing different turnover rates of CKD-MBD is not reliable, and there is room for more reliable and practical diagnostic tools in assessing the rate of bone turnover in CKD patients. When possible, it might be helpful while making critical diagnostic and treatment decisions, especially the ones regarding the initiation of antiresorptive treatment modalities such as use of bisphosphonates, teriparatide, raloxifene, or denosumab against osteoporotic bone loss in patients with CKD stages 3a-5d.¹⁰

At that point, bone scintigraphy with ^{99m}Tc MDP, may provide an additional inexpensive, simple, and widely accessible tool,

already used in the diagnostic evaluation of numerous pathologic conditions of bone tissue. The late phase of ^{99m}Tc MDP uptake by bone reflects bone turnover, and is known to be intensified in high bone turnover. Increased uptake of ^{99m}Tc MDP by bone is mainly secondary to increased osteoblastic activity.²³

Although the first bone scintigraphic examinations in CKD patients date back to the 1960s, bone scintigraphy has not been a frequently used diagnostic tool in CKD patients. Sy et al.,³¹ have described the major bone scintigraphic abnormalities seen in 14 hemodialysis patients as increased activity in the calvarium, mandible, vertebrae, and pelvis, which were all well correlated with higher serum ALP activity. In other studies, it was confirmed that CKD patients with high-turnover bone disease and osteitis fibrosa have presented with increased bone activities in the calvarium, mandible, acromioclavicular areas, sternum, and vertebrae, along with reduced soft tissue uptake, prominent costochondral junction, and the “tie” sign in the sternum. On the other hand, decreased uptake of Tc-99m is expected in low-turnover, adynamic bone disease.^{23,32} Quantitative methods and whole-body retention of ^{99m}Tc-methylene diphosphonate have also been described.³³

A unique finding known as “superscan” is a bright bone scintigraphic image that demonstrates unusually augmented bone ^{99m}Tc MDP uptake compared with soft tissue (Figure 1). The SS image may be seen when bone tissue is hypermetabolic, as seen in diseases such as metastatic prostate, breast, and lung cancers, leukemia and lymphomas, myelofibrosis, Paget’s disease, and finally, CKD-MBD.²⁶ In CKD-MBD-induced hyperparathyroidism, increased radionuclide uptake occurs throughout the skeleton, causing the characteristic SS appearance.

In our 15 patients with SS image, the mean iPTH levels were found to be significantly higher than in 20 patients with normal ^{99m}Tc MDP uptake. Additionally, the presence of an SS finding in bone scans was correlated with iPTH levels. As we have discussed above, high PTH levels are a known predictor of high bone turnover in CKD-MBD patients. Based on our findings, we believe the SS image may have a predictive value for high-turnover state in patients with CKD-MBD. Total ALP level was also significantly higher in the SS group, supporting that idea. We were not able to find any significant differences for Ca, P levels, and CaXP between our 2 patient groups.

Osteoporosis is also a part of bone disturbances observed during CKD-MBD, and also a topic of significant controversy. In CKD patients, the etiology and pathogenesis of osteoporosis is different from that in the non-CKD population, and may be more complicated. However, in CKD patients, osteoporosis-induced impairment in bone strength and bone fragility predisposes to increased risk of low-trauma bone fractures. Bone scintigraphy has been useful in investigating different types of metabolic bone disease, determining the age of vertebral fractures, and evaluating the response to osteoporosis treatment, although

its use as a diagnostic tool for osteoporosis is not common. Osteoporosis is manifested as areas of diminished activity and/or vertebral collapse on bone scans.^{31,34,35} In patients with osteomalacia, bone scan and BMD were shown to be of value in the assessment of bone status. A bone scan may also provide some additional information in determining non-visible pseudo fractures, compared to conventional radiology.³⁶

The number of studies in which bone scan has been used as a diagnostic tool for osteoporosis in patients with CKD-MBD is limited.³⁷ Technetium 99m uptake in cortical bone has been shown to have a linear relationship with PTH levels in hemodialysis patients, although findings in trabecular bone have been conflicting.^{27,37,38}

Patients in the early stages of CKD may share the typical risk factors of osteoporosis with the non-CKD community, such as age, gender, and malnutrition, and after excluding and treating abnormalities specific to CKD-MBD-related to bone metabolism, these people may be diagnosed as having osteoporosis and be offered standard treatments, including bisphosphonates.^{10,39-41} However, on the other hand, the value and standards for use of antiresorptive treatments such as bisphosphonates in CKD 4-5 patients is controversial. The use of bisphosphonates and denosumab is still considered to be risky in patients with overt adynamic bone disease, due to the potential risk of decreasing bone turnover further. In case of any uncertainty with the turnover status of CKD-MBD, exclusion of adynamic bone disease with bone biopsy is still recommended.¹⁰ Bone biopsy is not a widely available technique in most clinics, and therefore, CKD-MBD, patients with bALP <20 ng/mL and iPTH <100 pg/mL may be directly considered as having low bone turnover and may be deprived from antiresorptive therapies.⁴²

Although femoral neck Z-scores in the SS group were numerically lower, the difference between the 2 groups did not any reach statistical difference in our study. Lumbar and femoral neck Z-scores, t-scores, and bone mineral densities between the 2 groups were all comparable. There was also no statistically significant correlation between the existence of the SS image and DXA-based lumbar or femoral neck Z- and t-scores. Similarly, BMDs were not different between the SS and normal bone scan groups, suggesting that the main difference between the 2 groups may be metabolic, rather than structural. Patients with superscan had histories of 4 fractures, and the non-superscan group had histories of 2 fractures, also a difference which was not statistically different.

In conclusion, our results suggest that the ^{99m}Tc MDP bone scan may provide some additional information about both bone turnover and possibly also BMD status in CKD-MBD. Our biochemistry laboratory and Tc99m bone scan finding-based evidences suggest that the superscan image may be an additional evidence of CKD-induced high-turnover bone disease in CPD patients. ^{99m}Tc MDP bone scans possibly can be used along with

other non-invasive tests in the exclusion of adynamic bone disease. Therefore, there may be a potential for the use of Tc99m bone scan findings in the diagnostic and treatment decisions of CKD-MBD. However, there is a need for new studies with reference to histological data.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Board of Akdeniz University Medical School (22.05.2001, No:9).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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REFERENCES

1. Covic A, Voroneanu L, Apetrii M. PTH and/or Bone Histology: Are we still waiting for a verdict from the ckd-mbd grand jury? *Am J Kidney Dis.* 2016;67(4):535-538. [\[CrossRef\]](#)
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int.* 2009;76(suppl 113):S3-S8.
3. Suchowierska E, Myśliwiec M. Mineral and bone disturbances associated with chronic kidney disease. *Pol Merkur Lekarski.* 2010;28(164):138-143.
4. Iwasaki Y, Kazama JJ, Fukagawa M. Molecular abnormalities underlying bone fragility in chronic kidney disease. *BioMed Res Int.* 2017;2017:3485785. [\[CrossRef\]](#)
5. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. *Kidney Int.* 2007;71(1):31-38. [\[CrossRef\]](#)
6. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol.* 2005;16(7):2205-2215. [\[CrossRef\]](#)
7. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396-399. [\[CrossRef\]](#)
8. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis.* 2000;36(6):1115-1121. [\[CrossRef\]](#)
9. Šimunović I, Pavlović D, Kudumija B, et al. Bone fragility fractures in hemodialysis patients: Croatian surveys. *Coll Antropol.* 2015;39(1):71-74

10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* (2011). 2017;7(1):1-59. [\[CrossRef\]](#)
11. Nickolas TL, Stein E, Cohen A, et al. Bone mass and microarchitecture in CKD patients with fracture. *J Am Soc Nephrol*. 2010;21(8):1371-1380. [\[CrossRef\]](#)
12. West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res*. 2015;30(5):913-919. [\[CrossRef\]](#)
13. Bacchetta J, Boutroy S, Vilayphiou N, et al. Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. *J Bone Miner Res*. 2010;25(4):849-857. [\[CrossRef\]](#)
14. Wehrli FW, Leonard MB, Saha PK, Gomberg BR. Quantitative high-resolution magnetic resonance imaging reveals structural implications of renal osteodystrophy on trabecular and cortical bone. *J Magn Reson Imaging*. 2004;20(1):83-89. [\[CrossRef\]](#)
15. Jamal SA, Hayden JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: A meta-analysis. *Am J Kidney Dis*. 2007;49(5):674-681. [\[CrossRef\]](#)
16. Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol*. 2009;4(1):221-233. [\[CrossRef\]](#)
17. Ersoy FF. Osteoporosis in the elderly with chronic kidney disease. *Int Urol Nephrol*. 2007;39(1):321-331. [\[CrossRef\]](#)
18. Miller PD, Roux C, Boonen S, et al. Safety and efficacy of risendronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: A pooled analysis of nine clinical trials. *J Bone Miner Res*. 2005;20(12):2105-2115. [\[CrossRef\]](#)
19. Sprague SM, Bellorin-Font E, Jorgetti V, et al. Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis. *Am J Kidney Dis*. 2016;67(4):559-566. [\[CrossRef\]](#)
20. Andrade MC, Carvalhaes JT, Carvalho AB, Lazarretti-Castro M, Brandão C. Bone mineral density and bone histomorphometry in children on long-term dialysis. *Pediatr Nephrol*. 2007;22(10):1767-1772. [\[CrossRef\]](#)
21. Hajizadeh N, Mehrkash M, Fahimi D, Qorbani M, Shafa N. Association of bone mineral density with biochemical markers of bone turnover in hemodialysis children. *J Ren Inj Prev*. 2016;5(4):174-178. [\[CrossRef\]](#)
22. Sturgeon CM, Sprague SM, Metcalfe W. Variation in parathyroid hormone immunoassay results—a critical governance issue in the management of chronic kidney disease. *Nephrol Dial Transplant*. 2011;26(11):3440-3445. [\[CrossRef\]](#)
23. Buckley O, O'Keefe S, Geoghegan T, et al. ^{99m}Tc bone scintigraphy superscans: A review. *Nucl Med Commun*. 2007;28(7):521-527. [\[CrossRef\]](#)
24. Jamal SA, Chase C, Goh YI, Richardson R, Hawker GA. Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have fractures. *Am J Kidney Dis*. 2002;39(4):843-849. [\[CrossRef\]](#)
25. Kurata S, Ishibashi M, Nishida H, Hiromatsu Y, Hayabuchi N. A clinical assessment of the relationship between bone scintigraphy and serum biochemical markers in hemodialysis patients. *Ann Nucl Med*. 2004;18(6):513-518. [\[CrossRef\]](#)
26. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. *Endocr Rev*. 1993;14(6):690-709. [\[CrossRef\]](#)
27. Ureña P, De Vernejoul MC. Circulating biochemical markers of bone remodeling in uremic patients. *Kidney Int*. 1999;55(6):2141-2156. [\[CrossRef\]](#)
28. Herberth J, Monier-Faugere MC, Mawad HW, et al. The five most commonly used intact parathyroid hormone assays are useful for screening but not for diagnosing bone turnover abnormalities in CKD-5 patients. *Clin Nephrol*. 2009;72(1):5-14. [\[CrossRef\]](#)
29. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: Analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res*. 2011;26(6):1368-1376. [\[CrossRef\]](#)
30. Haarhaus M, Monier-Faugere MC, Magnusson P, Malluche HH. Bone alkaline phosphatase isoforms in hemodialysis patients with low versus non-low bone turnover: A diagnostic test study. *Am J Kidney Dis*. 2015;66(1):99-105. [\[CrossRef\]](#)
31. Sy WM, Mittal AK. Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *Br J Radiol*. 1975;48(575):878-884. [\[CrossRef\]](#)
32. Ghesani N, Jung J, Patel S, Ramchand T. Superscan caused by renal osteodystrophy: Observed on 18F FDG PET/CT scan. *Indian J Nucl Med*. 2013;28(4):251-252.
33. Fogelman I, Collier BD, Brown ML. Bone scintigraphy: Part 3. Bone scanning in metabolic bone disease. *J Nucl Med*. 1993;34(12):2247-2252.
34. Fan YL, Peh WC. Radiology of osteoporosis: Old and new findings. *Semin Musculoskelet Radiol*. 2016;20(3):235-245. [\[CrossRef\]](#)
35. Moore AE, Blake GM, Taylor KA, et al. Changes observed in radionuclide bone scans during and after teriparatide treatment for osteoporosis. *Eur J Nucl Med Mol Imaging*. 2012;39(2):326-336. [\[CrossRef\]](#)
36. El-Desouki M, Al-Jurayyan N. Bone mineral density and bone scintigraphy in children and adolescents with osteomalacia. *Eur J Nucl Med*. 1997;24(2):202-205. [\[CrossRef\]](#)
37. Salam SN, Eastell R, Khwaja A. Fragility fractures and osteoporosis in CKD: Pathophysiology and diagnostic methods. *Am J Kidney Dis*. 2014;63(6):1049-1059. [\[CrossRef\]](#)
38. Sarikaya A, Sen S, Hacimahmutoglu S, Pekindil G. ^{99m}Tc(V)-DMSA scintigraphy in monitoring the response of bone disease to vitamin D3 therapy in renal osteodystrophy. *Ann Nucl Med*. 2002;16(1):19-23. [\[CrossRef\]](#)
39. Hruska KA, Teitelbaum SL. Renal osteodystrophy. *N Engl J Med*. 1995;333(3):166-174. [\[CrossRef\]](#)
40. Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporos Rep*. 2005;3(1):5-12. [\[CrossRef\]](#)
41. Cunningham J. Pathogenesis and prevention of bone loss in patients who have kidney disease and receive long-term immunosuppression. *J Am Soc Nephrol*. 2007;18(1):223-234. [\[CrossRef\]](#)
42. Ureña P, Hruby M, Ferreira A, Ang KS, de Vernejoul MC. Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. *J Am Soc Nephrol*. 1996;7(3):506-512. [\[CrossRef\]](#)