The European Research Journal 2019;5(3):515-521 ORIGINAL ARTICLE

Comparison of laboratory and imaging methods associated with bone metabolism in patients with or without renal failure under the age of 45 years with elevated parathyroid hormone levels

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DOI: 10.18621/eurj.378720

ABSTRACT

Objectives: Although bone biopsy is considered the gold standard for the definitive diagnosis of renal osteodystrophy; it is not suitable for routine clinical practice due to its invasive nature. The present study was aimed to evaluate and compare the bone mineral status using dual energy X-ray absorptiometry of patients with or without chronic kidney disease in young population with elevated parathyroid hormone levels.

Methods: This was a single center, cross-sectional, retrospective study conducted in patients younger than 45 years of age. The study was performed in the outpatient clinic of a university hospital. Patients with elevated parathyroid hormone levels were included.

Results: Among them, 29 had renal insufficiency, 158 had normal renal function. Measured bone mineral density with dual energy X-ray absorptiometry and laboratory values were collected from patient files. The primary end point was to assess the efficiacy of dual energy X-ray absorptiometry in patients with or without renal failure. Except Z score at Ward's triangle, all of the T and Z scores at lomber, femur neck, trochanteric, and intertrochanteric areas were found significantly lower in patients with chronic kidney disease compared to those without ($p < 0.001$).

Conclusion: Dual energy X-ray absorptiometry seemed to be a reliable method for detection of osteoporosis in premenopausal female and male patients younger than 45 years of age with or without renal failure with elevated parathyroid hormone levels.

Keywords: hyperparathyroidism, renal insufficiency, osteoporosis, dual energy X-ray absorptiometry

Received: January 23, 2018; Accepted: March 21, 2018; Published Online: June 4, 2018

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e-ISSN: 2149-3189

Chronic kidney disease (CKD) is a functional definition which is characterized by irreversible and progressive decrement in renal functions. Renal function impairment has many negative effects on cardiovascular, hematopoietic, and gastrointestinal system as well as bone metabolism [1]. Changes in mineral metabolism and bone structure develop early in the course of CKD and worsen with progressive loss of kidney function. The Kidney Disease: Improving Global Outcomes (KDIGO) committee refined CKD-mineral and bone disorders (CKD-MBD), as a systemic disorder of mineral and bone metabolism due to CKD and manifested by either one or a combination of (i) abnormalities of calcium, phosphorous, parathyroid hormone (PTH) or vitamin D metabolism; (ii) abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and (iii) vascular or other soft tissue calcification [2]. Hyperparathyroid-mediated high-turnover bone disease (osteitis fibrosa cystica), and adynamic bone disease are the bone diseases related to CKD.

Osteoporosis in CKD patients is only a part of a wider spectrum of metabolic bone problems. Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that leads to an increased risk of fracture [3]. Bone biopsy is considered the gold standard for the definitive diagnosis of renal osteodystrophy; however, it is not suitable for routine clinical practice due to its invasive nature. Also, requirement for special equipment and expertise are other limiting factors. For that reason, most clinicians perform bone biopsies for clinical research [4-6]. Although dual energy X-ray absorptiometry (DXA) does not discriminate between CKD-MBD, it has been widely used for the assesment of bone mineral deficiency status in renal insufficient patients. Diagnostic accuracy, the short exposure time and the low radiation dose are the advantages of this imaging method [7, 8].

Postmenopausal period and advanced age are the other important unmodifiable risk factors for osteoporosis. In this study, we aimed to evaluate and compare the laboratory, imaging, and treatment methods associated with bone metabolism in patients with or without renal failure in premenopausal women and men younger than 45 years with elevated PTH levels.

METHODS

Study population

After getting an approval from the local ethics committee, patients with or without renal failure younger than 45 years with elevated PTH levels who applied to internal medicine, endocrinology and nephrology outpatient clinics of Uludağ University School og Medicine Hospital between January 2011 and January 2012 were searched retrospectively and included in the study. The study was conducted in accordance with the Declaration of Helsinki. Patients aged 18-45 years, having parathyroid hormon increasement and files fulfilling the laboratory and imaging data were included while patients aged > 45 years, who had malignancy, having the diagnosis of diseases known to affect bone metabolism (such as hyperthyroidism, rheumatological disease), who had undergone hysterectomy, who were using steroids and who were on therapy for osteoporosis were excluded from the study.

Study protocol

Patients with elevated PTH levels were divided into two groups depending on whether they had renal insufficiency or not. Patients' age, gender, co-morbidities, and the type and duration of dialysis if present were recorded. Serum urea, creatinine, albumin, sodium, potassium, chloride, calcium, phosphorus, PTH and 25-OH-vitamin D with 24-hour urinary excretion of calcium and phosphorus values were determined. Chemiluminescent method was used for determination of PTH and 25-OH-vitamin D. ARCHITECT assay (Abbott Diagnostics, Abbott Park, IL, USA) were performed for their measurement. T and Z scores of the lumbar vertebrae 1-2-3-4, total lumbar, femur neck, trochanteric and intertrochanteric area, Ward's triangle and total femur monitored by DXA (Hologic) were recorded from patients' files. The side of the parathyroid adenoma determined by neck ultrasonography (USG) and/or parathyroid scintigraphy and the histopathological diagnosis of the patients who had undergone surgery were evaluated. The treatment modalities as well as the frequency of follow-up visits were analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS

software version 20.0. Shapiro Wilk test was used to determine normality. Mann Whitney U test and Kruskal Wallis tests were used for comparison of non normally distributed data. The categorical data were analyzed with Pearson Chi-Square Test and Fisher's Exact test. The level of significance was defined as $p < 0.05$.

RESULTS

The records of 300 patients were analyzed and 187 patients fulfilling the inclusion criteria were enrolled to the study. Among all patients with elevated PTH, 29 had renal insufficiency while 158 had normal renal function. Sixteen of CKD patients (55.2%) were women, and 13 (44.8%) were men and the mean age was 40.5 (range 20-48) years. Among the patients without CKD, 143 (90.5%) were women, and 15 (9.5%) were men and the mean age was 36 (22-47) years. Except one patient with compansated CKD, 4 patients were managed with peritoneal dialysis, 19 with hemodialysis, and 5 with both. During follow-up, 17 patients underwent renal transplantation. The causes of CKD were hypertension (HT) in 7 patients, glomerulonephritis in 5, vesicoureteral reflux in 4, polycystic kidney disease in 2, neurogenic bladder in 1, both kidney agenesia + nephrectomy in 1, analgesic nephropathy in 1, and tacrolimus nephropathy in 1. The primary kidney diseases of 7 patients were not known. Duration of dialysis ranged from 3 years to 24 years, mean duration was 11.78 years. The most common comorbidity was HT (62.07%) in patients with CKD, and thyroid disease in those without CKD (24.7%). None of the patients had hyperthyroidism that may affect DXA results.

The laboratory data of the patients with and without renal failure was shown in Table 1. Serum urea, creatinine, phosphorus, PTH, and 25-OH-D levels were statistically significantly elevated and chloride level were statistically significantly decreased in patients with CKD compared to those without.

T and Z scores of lumbar 1-2-3-4, total lumbar, femur neck, trochanteric, intertrochanteric area, Ward's triangle, and total femur of the patients monitored by DXA were shown in Table 2. DXA imaging were performed before transplant procedure for 17 patients who underwent renal transplantation.

Table 1. The laboratory values of the patients with or without chronic kidney disease and their comparisons

	Normal Reference Interval	Patients with CKD (min-max)	Patients without CKD (min-max)	*p* value
Urea (mg/dL)	10-50	82.5 (27-277)	24 (11-63)	**< 0.001**
Creatinine (mg/dL)	0.6-1.3	6.15 (0.6-15.1)	0.7 (0.4-1.1)	**< 0.001**
Albumin (g/dL)	3.5-5.0	4 (2.9-4.7)	4.1 (2.8-5.1)	0.062
Sodium (mmol/L)	136-145	138.5 (109-143)	139 (133-147)	0.249
Potassium (mmol/L)	3.5-5.1	4.45 (3.3-7.3)	4.3 (3.1-5.4)	0.265
Chloride (mmol/L)	98-107	103 (96-112)	105 (97-141)	**0.002**
Calcium (mg/dL)	8.4-10.2	9.7 (7.5-12.2)	9.9 (7.6-18.9)	0.285
Phosphorus (mg/dL)	2.3-4.7	3.9 (2.4-7.5)	3 (1.1-4.6)	**< 0.001**
Parathormone (pg /mL)	15-68.3	824 (99-2839)	125.1 (54-2600)	**< 0.001**
25-OH-vitamin D (µg/L)	> 30	16 (3.7-35)	10.3 (2-48.87)	**0.024**
Urinary calcium excretion (mg/ day)	80-320	155 (24-417)	204 (14-1137)	0.405
Urinary phosphorus excretion (mg/ day)	250-1000	558 (290-558)	693 (0-1930)	0.170

CKD = chronic kidney disease

Table 2. The T and Z scores of the patients with or without with or without chronic kidney disease and their comparisons

	Patients with CKD (min-max)	Patients without CKD (min-max)	*p* value
Lumbar 1 T score	-1.6 (-3.4 - 0.6)	-0.7 (-6.30 - 6.5)	**0.022**
Lumbar 2 T score	-1.5 (-4.3 - 0)	-0.3 (-6.9 - 17)	**< 0.001**
Lumbar 3 T score	-2.15 (-5.4 - 0.2)	-0.9 (-7.4 - 5)	**< 0.001**
Lumbar 4 T score	-2.5 (-5.1 - 0.1)	-1.1 (-7.8 - 4.2)	**< 0.001**
Total lumbar T score	-2.1 (-4.2 - 0.1)	-0.9 (-7.2 - 5.3)	**< 0.001**
Lumbar 1 Z score	-1.15 (-3.4 - 0.7)	-0.4 (-6.6 - 6.5)	**0.015**
Lumbar 2 Z score	-1.6 (-4.1 - 0.7)	-0.5 (-6.5 - 5.8)	**< 0.001**
Lumbar 3 Z score	-1.9 (-4.6 - 0.3)	-0.7 (-7 - 5)	**< 0.001**
Lumbar 4 Z score	-2.35 (-5.1 - 0.9)	-0.8 (-7.5 - 4.3)	**< 0.001**
Total Lumbar Z score	-1.9 (-3.6 - 0.3)	-0.7 (-6.8 - 5.3)	**< 0.001**
Femur neck T score	-1.75 (-2.7 - 4.2)	-0.7 (-5.3 - 5)	**0.003**
Femur trochanteric T score	-1.55 (-2.8 - 0.2)	-0.8 (-5.7 - 5.9)	**< 0.001**
Femur intertrochanteric T score	-1.1 (-2.5 - 0.5)	-0.1 (-3.9 - 4)	**< 0.001**
Femur wards T score	-1.35 (-3 - 0.3)	-0.9 (-4.6 - 8)	**0.048**
Femur total T score	-1.4 (-3 - 0.3)	-0.2 (-4.7 - 5.3)	**< 0.001**
Femur neck Z score	-1.2 (-2.4 - 4.5)	-0.4 (-5 - 5.1)	**0.031**
Femur trochanteric Z score	-1.35 (-2.4 - 0.3)	-0.6 (-5.5 - 5.9)	**0.001**
Femur intertrochanteric Z score	-0.85 (-2.6 - 0.5)	0 (-3.8 - 4.1)	**< 0.001**
Femur wards Z score	-0.6 (-2.5 - 0.7)	-0.1 (-3.9 - 8.1)	0.066
Femur total Z score	-0.95 (-3.9 - 0.5)	0.1 (-4.5 - 5.3)	**< 0.001**

DXA = Dual energy X-ray absorptiometry, CKD = chronic kidney disease

Except Z score at Ward's triangle, all of the T and Z scores were statistically significantly lower in CKD patients.

Twenty-one (72.4%) of 29 patients with CKD had neck USG. Among 13 patients who had parathyroid adenomas, 4 had on the right side, 3 on the left side, and 6 on both sides. Twenty-two patients (75.9%) were scanned with parathyroid scintigraphy and parathyroid adenomas were detected in 10 of them. Four of these 10 patients had on the right side, 3 on the left side, and 2 on both sides. The information about localization was missing in 1 patient.

Ninety-nine of 158 (67.7%) patients without CKD were examined by neck USG for detecting parathyroid adenomas. Adenomas were not detected in 51 patients. Among 48 patients with parathyroid adenomas, 31 patients had on the right side, 15 on the left, and 1 on both sides and information about localization was missing in 1 patient. One hundred and eighteen (74.7%) patients were scanned with parathyroid scintigraphy and parathyroid adenomas were found in 46 of them. Twenty-seven patients had on the right side, 15 on the left side, and 1 patient on both sides. The information about localization was missing in 3 patients.

Thirteen of the 29 patients (44.8%) with CKD had parathyroidectomy. Histopathological examination revealed 2 adenomas, 10 hyperplasias, and 1 normal parathyroid tissue. Except 1 patient who was lost to follow up and 1 patient who had recurrent disease, there weren't any problems during follow-up visits of the rest of the patients. Forty-five of 158 patients without CKD (27.8%) underwent surgery and had 34 (75.6%) adenomas, 3 hyperplasias, 1 carcinoma and 7

normal parathyroid tissue on pathological examination. In 37 patients (90.2%) recurrence was not detected and 3 patients lost follow-up.

DISCUSSION

Osteoporosis is a condition of the skeleton characterized by an increased risk of bone fracture resulting from deficient mechanical resistance. The mechanical resistance of bones is conditioned by bone mineral density (BMD) and the quality of bone tissue [9]. Osteoporosis criteria according to the World Health Organization are based on the BMD evaluation of the proximal end of the femur (hip) or vertebrae in postmenopausal women, given as the T−score expressed as the number of standard deviations (SD); the baseline is the maximum bone mass: >−1 SD: normal value, from −1 to –2.5 SD: osteopenia, <−2.5 SD: osteoporosis, <−2.5 SD and osteoporotic fracture: advanced osteoporosis. The Z−score should be considered in children and premenopausal female and male subjects; the normal values are obtained from normal sex and age matched reference population [10].

Senility and postmenopausal status are important unchangeable risk factors for osteoporosis [11]. CKD is also an additional facilitiating factor. Mineral and bone disorders related to CKD result from the imbalance between calcium, phosphorus, PTH, and vitamin D. Decreased renal synthesis of 1,25(OH)2D3, phosphorus accumulation, increased fibroblast-growth factor (FGF)-23, decreased intestinal calcium, bone resistance to PTH action, hypocalcemia, chronic metabolic acidosis, and vitamin D deficiency are the metabolic disturbances related to the pathophysiology of CKD-MBD [12-15].

In this study we evaluated and compared the bone mineral status of patients with or without CKD in young population with elevated PTH levels. We used DXA for evaluating bone mineral status. Although DXA is the most commonly used technique to assess BMD in patients with and without CKD, it has some limitations. DXA measures areal BMD, rather than volumetric BMD. In addition, it cannot distinguish between cortical and trabecular bone, and it cannot assess bone microarchitecture or bone turnover [16, 17].

A study performed to determine the prevalence and associated risk factors of CKD between 1999-2004 in the United States has been reported to occur more frequently in men over 60 years old [18]. Of our patients, 55.2% were female. It may be due to the selected group or the number of the patients with CKD. The most common cause of CKD is diabetes mellitus (DM) and the second one is HT [18, 19]. In our study, HT was the most common cause of CKD. This result may be related to the younger age of our patients because type 2 DM is usually diagnosed at a later age. Besides, it takes approximately 10 years in patients with type 2 DM and 20 in patients with type 1 DM to develop renal failure.

Serum urea, creatinine, phosphorus, PTH, and 25-OH-D levels were statistically significantly elevated and chloride level was statistically significantly decreased in patients with CKD compared to those without. Vitamin D deficiency was shown to be more prevalent even in the early stages of CKD in comparison to the general population [20]. In contrast to the expected, 25-OH-D levels were statistically significantly elevated in our patients with CKD probably due to the replacement therapies. Another important result of our study was that, 25-OH-D levels in patients without CKD were low although our country has advantage of sunshine exposure. Our finding is also in line with the data from one of the largest studies done in Turkey by Satman *et al*. [21]. They found that the overall prevalence rate of vitamin D deficiency was 93%, with the highest rate seen in younger (< 40 years) age group (96.2%) in women, and elderly (≥ 65 years) age group (91.9%) in men [21].

Effect of CKD on bone mineral density using DXA has not yet been clearly elucidated. Some studies have shown that low BMD measurements were more prevalent in patients with CKD like our findings while several other studies have reported no relationship between CKD and low BMD measurements [22-25]. In our study, except Z score at Ward's triangle, all of the T and Z scores were found statistically significantly lower in CKD patients especially T and Z scores at lumbar 3 and 4 [7, 26-28]. In our study, we found that the BMD measurement at L2-L4 region was significantly higher than that at femur neck in both genders ($p < 0.01$). Although, Z-scores were affected more in some studies that were done in

postmenopausal women with CKD, in our study we found T scores to be affected as much as Z-scores in premenopausal women and men. In addition, postmenopausal and senile osteoporosis may coexist with all forms of bone disease in kidney dysfunction. Most of the studies were done in postmenopausal women in the literature. In our study we chose a group that was not influenced by menopause and senility. In the patients wihout CKD, there was no risk factor other than vitamin D deficiency.

Although dual-phase dual-isotope iodine 123 (^{123}I)/technetium Tc 99m (^{99}mTc) sestamibi scintigraphy and ultrasonography and their comparison for determination of enlarged parathyroid glands in primary hyperparathyroidism has been discussed in many studies, their utility in renal hyperparathyroidism is rarely addressed [29, 30]. Périé *et al*. [31] reported that a series of 20 patients consecutively referred for parathyroidectomy, hyperplastic parathyroid glands were detected by USG in 75%, dual-phase ^{123}I/^{99}mTc sestamibi scintigraphy in 66%, and both methods in 88%. Most missed glands at scintigraphy corresponded to superior glands, whereas false-negative results at USG correlated with low gland weight [31]. In another study which aimed to detect the usefulness of the combination of USG and 99mTc-sestamibi scintigraphy in the preoperative evaluation of uremic secondary hyperparathyroidism it was reported that the sensitivities of scintigraphy and USG were 62% and 55% respectively, and the specificity was 95% for both procedures. The sensitivity of combined techniques was 73% [32]. In our study, 21 (72.4%) of 29 patients with CKD had neck USG and 13 patients had parathyroid adenomas. Twenty-two patients (75.9%) were scanned with parathyroid scintigraphy and parathyroid adenomas were detected in 10 of them. It was seen that 99 of 158 (67.7%) patients without CKD examined with neck USG and 48 patients had adenomas. It was found that 118 (74.7%) patients were scanned with parathyroid scintigraphy and parathyroid adenomas were found in 46 of them. From these results cervical USG and parathyroid sintigraphy seem to be useful radiologic techniques to localize parathyroid lesion before considering surgery.

Limitations

The limitations of our study are the cross-sectional design and the relatively small sample size in CKD group. They precluded us from drawing certain causal conclusions.

CONCLUSION

The patients with CKD have lower BMD scores (both T and Z scores at all sites) and higher levels of vitamin D may be observed due to replacement therapies. Low vitamin D level seemed to be an additional risk factor for osteoporosis in patients without CKD although our country has advantage for sunshine exposure. Besides, DXA seemed to be a reliable method for osteoporosis detection in both groups.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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