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CLINICAL STUDY

## Effect of arteriovenous fistula and usage of arm with fistula on bone mineral density in hemodialysis patients

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### ABSTRACT

We aimed to determine the incidence of osteoporosis in hemodialysis patients, to evaluate the differences due to arteriovenous fistula on bone mineral density (BMD) and to investigate whether usage of arm with fistula has an effect on BMD. In this cross-sectional study, 96 patients with chronic renal disease undergone to dialysis were included. Place of fistula (radial and brachial) and dominant hand were recorded. All patients were asked to complete Likert's scale in order to determine the frequency of their usage of arm with fistula. Patients were assigned in two groups: age >51 and <50 years. Age-matched control group included 60 subjects. BMD measurements were done on lumbar vertebra, femur and both forearms. BMD measurement of proximal femur and total radius were significantly lower in patients >50 years compared to healthy controls and bone density measurement of lumbar vertebra, proximal femur, 1/3 distal and total radius were significantly lower in patients <50 years compared to healthy controls ( $p < 0.05$ ). BMD measurement was significantly lower in arms with fistula, especially with radial fistula, compared to both arms without fistula and healthy controls ( $p < 0.05$ ). When all patients were evaluated, BMD scores were lowering by increasing age, duration of dialysis and fistula and decreasing usage of arm with fistula. BMD in hemodialysis patients is lower than normal population. BMD of arm with fistula is lower than arm without fistula and healthy controls. Both radial and brachial fistula affect negatively ipsilateral BMD. Movement of arm with fistula has positive effects on BMD.

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### Introduction

In general population, demographics and biological features such as age, gender, sex hormones and body mass index are the most important determining factors of bone mineral density (BMD), whereas impairment in bone mineral metabolism is developed due to vitamin D deficiency, hyperparathyroidism and mineral anomalies in patients with chronic renal disease.<sup>1</sup> Particularly in dialysis patients with chronic renal disease, renal osteodystrophy is characterized by increased bone turnover. Increased secondary hyperparathyroidism leads to clinical features resulting in fibro-osteoclasia and osteomalacia. Mineralization of atypical bone fibrils is reduced and collagen tissue is changed. This type of biomechanical properties of bone is decreased, therefore fracture incidence is increased and fracture improvement is impaired.<sup>2</sup>

Similar to general population, dialysis patients are associated with fracture risk related to low bone

density.<sup>3</sup> However, low BMD in dialysis patients, is one of many etiological causes of renal bone disease. There are certain studies showing inconsistent results of routine BMD measurements or highly variable values at different measurement phases in hemodialysis patients.<sup>4</sup> There is no sufficient consensus on this subject, however, National Kidney Organization recommends measuring BMD by dual X-ray absorptiometry (DXA) in patients with chronic renal disease.<sup>5</sup>

Trabecular bone loss is a major problem in osteoporosis patients and lumbar vertebra and proximal femur is critical site of damage. However, cortical bone damage is higher than trabecular bone in hemodialysis patients.<sup>6,7</sup> Therefore, certain authors indicate that radius measurements are more useful than lumbar vertebra in hemodialysis patients and they recommend using distal radius measurement in estimate of fracture risk.<sup>8</sup>

One of the major problems in patients with late stage of renal disease is entrance to vascular system for

continuation of dialysis. During few experimental studies, the effect of arteriovenous fistula (AVF) on the bone was investigated and a decrease in perfusion pressure and blood flow in forearm and hand and certain alterations due to these conditions were determined.<sup>2,5,9–11</sup> However, these studies do not include any data on the structural effect of these changes onto the bone mass.

In this study, we aimed to determine the incidence of osteoporosis in hemodialysis patients, to evaluate the difference due to AVF on distal radius BMD by DXA, and to investigate whether usage of arm with fistula has an effect on BMD.

## Material and method

In this cross-sectional study, 96 patients with chronic renal disease undergone to dialysis were included. The study was conducted between January 2013 and June 2014. Patients included in this study, were receiving dialysis for 3 times weekly and they had radial or brachial fistula. The exclusion criteria were as following: conditions leading to a difference in BMD between two forearms which confound the results (i.e. presence of closed fistula on the other arm or previously improved fracture on the forearm), previous history of renal transplantation, presence of thyroid disease and past history of glucocorticoid administration.

The height, weight, place of fistula, dominant hand, duration of dialysis and fistula were recorded for all patients. Likert scale was completed in order to determine how long the patients were using their arm with fistula. Likert scale was scored from 1 to 5 as following: (1) Never used, (2) Occasionally used, (3) Quietly used, (4) Frequently used and (5) Highly used. Patients were assigned in two groups based on age.

Age-matched 60 volunteers were evaluated as control group (30 subjects aged >51 years and 30 subjects aged <50 years). Subjects with disease known as affecting the bone metabolism (hyperthyroidism, hyperparathyroidism, renal disease, collagen tissue disorder, ovarian tumor) and those who were under medical treatment for this condition, were not included in the study. In total, 60 subjects were included in the study as for age-matched control group.

BMD measurements of lumbar vertebra, femur and both radius were done by DXA method with Hologic Explorer-w device with same experienced operator according to standard Hologic protocols.<sup>12</sup> Bone density was determined from lumbar vertebra (L1–4) and right femur (femur neck and total femur). Measurement from forearms was recorded bilaterally from 1/3 distal radius and total radius. BMD ( $\text{g}/\text{cm}^2$ ),  $t$  and  $z$  scores were

recorded in all areas. The  $t$  and  $z$  scores were used for the patients older than 51 years of age and younger than 50 years of age respectively.<sup>13</sup>

## Statistical analysis

The data were analyzed with the statistical package for the social sciences software (SPSS Version 17, Chicago, IL). Descriptive data were presented as mean  $\pm$  SD or frequency (percentage). Mean values of the groups were compared using Student's  $t$ -test and categorical variables were compared using chi-squared test. Paired- $t$  test was used for comparison of mean values between fistulized and healthy arms. Pearson's correlation coefficient was used for correlation analysis. Statistical significance was set at  $p < 0.05$ .

## Results

In hemodialysis group >51 years (Group 1), 30 males (47.6%) and 33 females (52.4%), totally 63 patients were included and among them, 53 patients had radial and 10 patients had brachial fistula. Mean age was  $65.7 \pm 7.8$ ; BMI was  $27.7 \pm 4.8$ ; dialysis time was  $77.9 \pm 56.1$  months. In hemodialysis group <50 years (Group 2), 22 males (66.7%) and 11 females (33.3%), totally 33 patients were included and among them, 28 patients had radial and 5 patients had brachial fistula. Mean age was  $40.5 \pm 8$ ; BMI was  $23.1 \pm 4$ ; dialysis time was  $87 \pm 60.5$  months.

In control group >51 years (Group 3), there were 15 males and 15 females, in total 30 subjects. Mean age was  $62.7 \pm 8.5$  and BMI was  $28.1 \pm 3.5$ . In control group <50 years (Group 4), 20 males (66.7%) and 10 females (33.3%), totally 30 subjects were included. Mean age was  $41.4 \pm 7.2$  and BMI was  $26.3 \pm 3.3$ . There was no significant difference between hemodialysis group and control group of >51 years (Group 1 and 3) and of <50 years (Group 2 and 4) in respect of age, gender and BMI ( $p > 0.05$ ). There was no difference between dominant and non-dominant arm 1/3 distal radius and total radius BMD within Group 3 and Group 4 themselves as well as  $t$  and  $z$  scores ( $p > 0.05$ ).

In comparison of Group 1 and 3, no significant difference was noted between lumbar vertebra scores ( $p > 0.05$ ).  $t$  score of femur neck and also femur total  $t$  scores were significantly decreased in hemodialysis group ( $p < 0.05$ ) (Table 1). In comparison of Group 2 and 4,  $z$  scores of all areas were significantly decreased in Group 2 ( $p < 0.05$ ) (Table 1).

In comparison of arms with and without fistula, no difference was present in BMD scores of 1/3 distal radius between hemodialysis patients >50 years of age and those who are <50 years of age, however, total radius

BMD was significantly decreased in arm with fistula (Table 2).

The arm with and without fistula of hemodialysis patients >51 years old was compared with non-dominant and dominant arms of controls, respectively and no difference was found for 1/3 distal radius BMD scores; however, total radius scores were significantly decreased in hemodialysis group (Table 3). Hemodialysis patients <50 years old were compared with controls <50 years old and both 1/3 distal radius and total radius BMD scores in arms with fistula were significantly lower than controls, although significant decrease was only detected in 1/3 distal radius of hemodialysis group in comparison of arm without fistula with dominant arm (Table 4).

Patients with radial and brachial fistula were separately evaluated in order to determine the effect of fistula site on forearm BMD scores; both 1/3 distal radius and total radius BMD scores were significantly decreased in hemodialysis patients >50 years old with radial fistula compared to controls, while there was no difference in those with brachial fistula (Table 5). In hemodialysis

patients <50 years old, 1/3 distal radius and total radius BMD scores were significantly lower in those with both radial and brachial fistula compared to controls. In comparison of the arm without fistula of patients <50 years old with dominant arm of controls, only 1/3 distal radius scores were significantly lower than controls (Table 6).

When the correlation of 1/3 distal radius and total radius BMD scores with the level of the use of this arm, age, duration of dialysis and fistula in all group ( $n = 96$ ) and it was found that forearm BMD scores were significantly increased as the use of arm increased. The negative correlation was present for all of other parameters, however, statistical significance was detected only between total radius BMD and age and duration of dialysis (Table 7).

## Discussion

According the results of our study, BMD measurements of proximal femur in patients >50 years old as well as lumbar vertebra and proximal femur scores in

**Table 1.** Comparisons of bone mineral density scores of hemodialysis patients >51 and <50 years of age with age-matched controls.

	<i>t</i> Score of hemodialysis patients >51 years old ( $n = 63$ )	<i>t</i> Score of control patients >51 years old ( $n = 30$ )	<i>p</i> Value	<i>z</i> Score of hemodialysis patients <50 years old ( $n = 30$ )	<i>z</i> Score of control patients <50 years old ( $n = 30$ )	<i>p</i> Value
Lumbar 1–4	$-1.8 \pm 1.65$	$-1.13 \pm 1.65$	0.14	$-1.07 \pm 1.64$	$0.08 \pm 1.23$	0.009
Femur neck	$-1.56 \pm 1.16$	$-0.58 \pm 0.91$	0.001	$-0.35 \pm 1.44$	$0.6 \pm 0.98$	0.003
Total femur	$-1.08 \pm 1.26$	$-0.10 \pm 0.98$	0.001	$-0.60 \pm 1.61$	$0.78 \pm 0.84$	0.001

**Table 2.** Comparisons of bone mineral density scores of arms with fistula and without fistula in dialysis patients >51 and <50 years of age.

	Arm with fistula in patients >51 years old ( $n = 63$ )	Arm without fistula in patients >51 years old ( $n = 63$ )	<i>p</i> Value	Arm with fistula in patients <50 years old ( $n = 33$ )	Arm without fistula in patients <50 years old ( $n = 33$ )	<i>p</i> Value
1/3 distal radius BMD $\text{g/cm}^2$	$0.57 \pm 0.14$	$0.59 \pm 0.14$	0.07	$0.60 \pm 0.12$	$0.61 \pm 0.11$	0.53
Total Radius BMD ( $\text{g/cm}^2$ )	$0.47 \pm 0.11$	$0.48 \pm 0.11$	0.03	$0.50 \pm 0.09$	$0.51 \pm 0.09$	0.02

**Table 3.** Comparison of arm with fistula of hemodialysis patients >51 years old with non-dominant arm of controls and comparison of their arm without fistula with dominant arm of healthy controls.

	Arm with fistula in patients >51 years old ( $n = 63$ )	Non-dominant arm in control subject >51 years old ( $n = 30$ )	<i>p</i> Value	Arm without fistula in patients >51 years old ( $n = 63$ )	Dominant arm in control subject >51 years old ( $n = 30$ )	<i>p</i> Value
1/3 distal radius BMD $\text{g/cm}^2$	$0.57 \pm 0.14$	$0.613 \pm 0.11$	0.20	$0.59 \pm 0.14$	$0.615 \pm 0.13$	0.3
Total radius BMD ( $\text{g/cm}^2$ )	$0.47 \pm 0.11$	$0.534 \pm 0.10$	0.01	$0.48 \pm 0.11$	$0.54 \pm 0.10$	0.02

**Table 4.** Comparison of arm with fistula of hemodialysis patients <50 years old with non-dominant arm of controls and comparison of their arm without fistula with dominant arm of controls.

	Arm with fistula in patients <50 years old ( $n = 33$ )	Non-dominant arm in control subject <50 years old ( $n = 30$ )	<i>p</i> Value	Arm without fistula in patients <50 years old ( $n = 33$ )	Dominant arm in control subject <50 years old ( $n = 30$ )	<i>p</i> Value
1/3 distal radius BMD $\text{g/cm}^2$	$0.60 \pm 0.12$	$0.722 \pm 0.08$	0.001	$0.61 \pm 0.11$	$0.73 \pm 0.07$	0.001
Total radius BMD ( $\text{g/cm}^2$ )	$0.50 \pm 0.09$	$0.624 \pm 0.07$	0.001	$0.51 \pm 0.09$	$0.591 \pm 0.21$	0.05

**Table 5.** Comparison of distal radius BMD of arm with fistula of hemodialysis patients >51 years old with non-dominant arm of controls and comparison of their arm without fistula with dominant arm of controls according to fistula localization.

	Patient group arm with fistula	Control group non-dominant arm	p Value	Patient group arm without fistula	Control group dominant arm	p Value
Patient group >51 years old with radial fistula (n = 53)						
1/3 distal radius BMD g/cm <sup>2</sup>	0.582 ± 0.14	0.613 ± 0.11	0.001	0.596 ± 0.13	0.615 ± 0.13	0.01
Total radius BMD (g/cm <sup>2</sup> )	0.473 ± 0.11	0.534 ± 0.10	0.001	0.486 ± 0.11	0.54 ± 0.10	0.07
Patient group >51 years old with brachial fistula (n = 10)						
1/3 distal radius BMD g/cm <sup>2</sup>	0.529 ± 0.14	0.613 ± 0.11	0.09	0.529 ± 0.17	0.615 ± 0.13	0.15
Total radius BMD (g/cm <sup>2</sup> )	0.467 ± 0.11	0.534 ± 0.10	0.13	0.475 ± 0.11	0.54 ± 0.10	0.11

**Table 6.** Comparison of distal radius BMD of arm with fistula of hemodialysis patients <50 years old with non-dominant arm of controls and comparison of their arm without fistula with dominant arm of controls according to fistula localization.

	Patient group arm with fistula	Control group non-dominant arm	p Value	Patient group arm without fistula	Control group dominant arm	p Value
Patient group <50 years old with radial fistula (n = 28)						
1/3 distal radius BMD g/cm <sup>2</sup>	0.616 ± 0.12	0.722 ± 0.08	0.001	0.613 ± 0.11	0.73 ± 0.07	0.001
Total radius BMD (g/cm <sup>2</sup> )	0.499 ± 0.009	0.624 ± 0.07	0.001	0.511 ± 0.009	0.591 ± 0.21	0.07
Patient group <50 years old with brachial fistula (n = 5)						
1/3 distal radius BMD g/cm <sup>2</sup>	0.573 ± 0.14	0.722 ± 0.08	0.001	0.60 ± 0.6	0.73 ± 0.07	0.003
Total radius BMD (g/cm <sup>2</sup> )	0.480 ± 0.12	0.624 ± 0.07	0.001	0.494 ± 0.13	0.591 ± 0.21	0.31

**Table 7.** Correlation of distal radius BMD scores of whole group with usage of the arm, age, duration of dialysis and fistula (usage of the arm by Likert scale).

	Usage of the arm by Likert scale		Age (year)		Duration of dialysis (months)		Duration of fistula (months)	
	r	p	r	p	r	p	r	p
1/3 distal radius BMD g/cm <sup>2</sup>	0.303	0.003	-0.313	0.01	-0.07	0.37	-0.146	0.25
Total radius BMD (g/cm <sup>2</sup> )	0.246	0.001	-0.301	0.01	-0.258	0.04	-0.164	0.2

patients <50 years of age were decreased in hemodialysis group compared to healthy controls. BMD measurements of arms with fistula, especially onto the forearm, were lower than both healthy controls and arms without fistula. In evaluation of all patients, it was found that BMD measurements were correlated negatively with age, duration of dialysis and fistula, and positively with usage of arm.

Presence of osteoporosis in hemodialysis patients has been investigated in many studies. Lumbar vertebra and proximal femur measurements showed reduced BMD, especially more prominently in proximal femur.<sup>14-19</sup> In our study, BMD was similarly decreased in both areas of patients <50 years of age and in proximal femur of patients >51 years of age in hemodialysis group compared to healthy subjects. In uremic patients, it is recognized that loss of density in cortical bone is higher than trabecular bone. Abnormal Vit D metabolism and PTH secretion result in impairment of trabecular micro-architecture, thinning of cortex and increase in cortical porosity.<sup>6,20</sup> Thinning of corex is related to increased endosteal bone resorption and reduced periosteal bone production.<sup>6</sup> The reasons of lack of difference in

trabecular BMD are considered as increased calcification of aorta and soft tissue or insufficiency of DXA to discriminate between cortical and trabecular bone compartments.<sup>20</sup>

Muxi et al.<sup>5</sup> classified 30 hemodialysis patients as younger and older than 50 years of age; they used the arm without fistula as control group of the arm with fistula and they compared BMD of lumbar vertebra, proximal femur and distal radius (ultradistal radius, 1/3 distal radius and total radius). Consequently, all measurements in distal radius were significantly lower in arm with fistula compared to the arm without fistula. In another study, in which BMD was evaluated by phalangeal BMD, BMD in fistula side was significantly lower than that of side without fistula.<sup>21</sup> In the study conducted by Fontaine et al.,<sup>22</sup> in hemodialysis patients with fracture, they determined that fractures were especially on distal radius and costa and that z scores of lumbar vertebra, femur neck and distal radius in these patients were significantly lower than patients without fractures. In this study, fractures at distal radius were mostly on the arm with fistula, although BMD scores were comparable with the arm without fistula. In our

study, BMD comparisons were done between fistula side with the side without fistula and non-dominant side of healthy controls by considering fistula localization. BMD scores of distal radius in the arm with fistula were decreased in patients older and younger than 50 years of age compared to both the arm without fistula and healthy subjects. However, in our study, an association of this decrease with location of fistula was detected. In patients >50 years of age with radial fistula, distal radius measurements were significantly lower and the presence of brachial fistula did not affect BMD scores when comparing with healthy subjects and arm without fistula. At side of fistula in patients <50 years of age, decreased BMD was present only in patients with radial fistula compared to healthy subjects; however, in comparison of upper extremities of same patient, both radial and brachial fistula negatively affected the BMD. Our study is the first study evaluating fistula localization and we think that our results support local alterations such as decreased blood flow and perfusion pressure due to fistula.

In addition to local alterations, changes in the forearm BMD have been related with factors such as immobilization in the arm with fistula,<sup>23</sup> inactivity<sup>24,25</sup> or sympathetic tonus.<sup>26</sup> Early mobilization or using the dominant arm which is more frequently in daily life for fistula may provide reduced bone loss.<sup>27,28</sup> In the study of Kekilli et al.,<sup>27</sup> bone loss in dominant and non-dominant arm was investigated in patients surgically treated for acute tendon-artery-nerve incision in distal forearm; during follow up of 12 weeks there was no significant change in dominant forearm ulna and radius BMD, however, there was significant decrease in BMD of mid-diaphysis and distal ulna and ultradistal radius at non-dominant arm. In dialysis patients, fistula is created onto the non-dominant arm and patients use less this arm due to fistula. In our patients groups, the side with fistula was compared with the side without fistula, the side with fistula was compared with non-dominant arm of controls and the side without fistula was compared with dominant side of healthy subjects and BMD results were significantly decreased in both groups especially for total radius.

In cases of both local and general immobilization, a decrease in BMD is expected in general or on the affected area.<sup>29–31</sup> In a study conducted in stroke patients, functional scores of hand and superior extremity were positively correlated with radius BMD.<sup>23</sup> Marchetti et al.<sup>32</sup> investigated immobilization osteoporosis in patients of had shoulder surgery and they found significant decrease in BMD at post-operative 6 weeks. The alterations were reduced at week 6 following remobilization, however, statistically significant difference was still present. According to our results, there is a

positive correlation between the utilization of arm and forearm BMD scores in dialysis patients and our study is the first investigating distal radius BMD and immobilization in dialysis patients. Exercises on fistula site of dialysis patients are considered to increase blood flow, however, it is not clear whether this has an effect on BMD measurements.<sup>33,34</sup>

According to our results, distal radius BMD scores were decreasing while age, duration of dialysis and fistula increased, even not statistically significant. Various results have been obtained during the studies about this subject. In their study, Yamaguchi et al.<sup>35</sup> showed a negative correlation between 1/3 distal radius BMD and duration of dialysis in male patients undergoing to hemodialysis and there was a negative and strong correlation between age and 1/3 distal radius scores in female patients.<sup>35</sup> In the study conducted by Polymeris et al.,<sup>36</sup> dialysis time did not affect BMD. In the study of Bakan et al.,<sup>21</sup> both ipsilateral and contralateral BMD scores were negatively correlated with age and dialysis duration was only negatively correlated with ipsilateral BMD.

Lack of investigating laboratory parameters is one of limitations of our study. In hemodialysis patients, BMD of 1/3 distal radius is closely related with parathyroid hormone levels, however, it is also suggested that there is close relationship with all types of fractures of this area requiring assessment.<sup>35,37–40</sup>

In conclusion, osteoporosis is more common in dialysis patients than normal population. Although BMD of the arm with fistula is lower in patients especially with radial fistula than the other arm, forearm BMD is affected in patients <50 years of age with brachial fistula. Frequent usage of the arm with fistula has positive effect on BMD, however, future studies are required to determine the effects of exercises with arm with fistula on BMD.

## Disclosure statement

None of the authors has any conflict of interest, financial or otherwise.

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