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The Osteoporotic Effect of Arteriovenous Fistula on the Ipsilateral Upper Extremity in Hemodialysis Patients

Hemodiyaliz Hastalarında Arterio-Venöz Fistülün Aynı Taraf Üst Ekstremite Üzerine Osteoporotik Etkisi

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Summary

Objective: Hemodialysis requires an arteriovenous fistula (AVF), the presence of which may influence the structure of nearby bone. This study analyzed the effect of AVF on ipsilateral upper extremity bone mineral density (BMD), as measured by phalangeal radiographic absorptiometry (RA).

Materials and Methods: In this cross-sectional study, phalangeal BMD was measured in both arms by RA in a convenience sample of end-stage renal disease (ESRD) patients with a forearm AVF. Patients were excluded if the patient had pathology which might affect distal arm circulation. BMD values (g/cm^2) from forearms with AVF were compared with values from forearms without AVF. Predialysis values of complete blood count, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, urea, creatinine, potassium, albumin, total cholesterol, HDL cholesterol, and LDL cholesterol were determined in all patients; dialysis adequacy values were also calculated.

Results: One hundred and sixteen patients agreed to participate in the study. Thirty-three patients were excluded, thus, data were analyzed from 83 patients (59% male, 41% female, mean hemodialysis time: 156±6 months, mean age: 53±16 years). AVFs were located in the nondominant hand in all patients. Phalangeal BMD in forearms with AVF (0.28±0.05 g/cm^2, range: 0.14-0.40) was significantly lower than that in the contralateral forearm (0.30±0.04 g/cm^2, range: 0.19-0.40, $p<0.05$).

Conclusion: In ESRD patients on hemodialysis, BMD is lower in the ipsilateral-to-AVF hand compared to the contralateral-to-AVF hand. In these patients, further investigations should be made to ascertain the ability of BMD assessment in determining fracture risk and to prompt physicians to initiate treatments which will preserve BMD and reduce fractures. *Turk J Phys Med Rehab 2013;59:236-41.*

Key Words: Osteoporosis, bone mineral density, phalangeal radiographic absorptiometry, arteriovenous fistula

Özet

Amaç: Hemodiyaliz hastalarındaki arterio-venöz fistül (AVF), çevresindeki kemik dokunun yapısını etkileyebilir. Bu çalışmada falangial radyografik absorbsiyometri (RA) ölçümü ile AVF'nin ipsilateral üst ekstremite kemik mineral yoğunluğu (KMY) üzerine etkisi araştırılacaktır.

Gereç ve Yöntem: Bu kesitsel çalışmada, ön kollarında AVF olan son dönem böbrek yetmezlikli hastaların (SDBY) falangial KMY değerleri her iki koldan RA ile ölçüldü. Distal kol dolaşımını etkileyebilecek herhangi bir patolojisi olan hastalar çalışma dışı bırakıldı. Fistüllü kol falangial KMY değerleri (g/cm^2) fistülsüz kol falangial KMY değerleri (g/cm^2) ile karşılaştırıldı. Tüm hastalara diyaliz öncesi tam kan sayımı yapıldı, kalsiyum, fosfor, alkalen fosfataz, paratiroid hormon, üre, kreatinin, potasyum, albümin, total kolesterol, HDL kolesterol ve LDL kolesterol değerleri ölçüldü; diyaliz yeterliliği değerleri hesaplandı.

Bulgular: Çalışmaya 116 hasta katıldı. Otuz üç hasta çalışma dışı bırakıldı, 83 hastanın sonuçları değerlendirildi. Hastaların %59'u erkek, %41'i kadın olup, hemodiyalize girme süreleri 156± 6 ay ve yaşları 53±16 yıldı. AVF tüm hastalarda nondominant koldaydı. Fistüllü kolun falangial KMY değerleri (0,28±0,05 gr/cm^2, aralık 0,14-0,40), kontralateral kola oranla anlamlı derecede düşüktü (0,30±0,04 gr/cm^2, aralık 0,19-0,40, $p<0,05$).

Sonuç: SDBY'li hemodiyaliz hastalarında fistüllü kol falangial KMY değerleri, fistülsüz kol falangial KMY değerlerine göre daha düşük bulundu. Bu hastalarda, kırık riskinin belirlenmesinde KMY ölçümünün rolünü ve koruyucu tedavinin gerekliliğini tespit etmek için daha ileri çalışmalara ihtiyaç vardır. *Türk Fiz Tıp Rehab Derg 2012;59:236-41.*

Anahtar Kelimeler: Osteoporoz, kemik mineral yoğunluğu, falangial radyografik absorbsiyometri, arterio-venöz fistül

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Introduction

Low bone mass is common in end-stage renal disease (ESRD) patients, especially those undergoing hemodialysis. Low bone mass can lead to serious bone problems such as fragility fractures (1-6). Surgically created arteriovenous fistulas (AVF) are widely used in end-stage renal failure patients to provide vascular access for hemodialysis. The incidence of fractures is greater (relative risk 4.4) in hemodialysis patients than in the general population (1,6). Fractures in this population commonly occur at the AVF forearm (3).

Forearm AVF may result in less than normal blood flow and perfusion pressure in the distal parts of the forearm and hand. Experimental studies on the effects of AVF on bone have found alterations in hand perfusion and change in bone structure, but they provided no data on the effect of these structural changes on bone mass (2). The effects of the AVF on the ipsilateral upper extremity have not been widely studied (7).

The aim of this study was to determine the effect of the forearm AVF on bone mineral density (BMD) in ipsilateral and contralateral upper extremities in hemodialysis patients.

Materials and Methods

This was a cross-sectional study, approved by our hospital ethics committee, and conducted in subjects undergoing hemodialysis at two separate dialysis centers in our city. The study was done from december 2010 to january 2011. Volunteers were recruited from among ESRD patients over 18 years of age who had been on hemodialysis three times a week for more than six months. Patients were denied participation if they had distal arm circulation disorder, previous AVF in the contralateral forearm or graft, and extremity paresis with a history of cerebrovascular disease which might cause a difference in BMD between the two hands. None of the patients had regular exercise programs or hand-strengthening exercises. After giving informed consent, laboratory tests were performed (see below) and BMD was measured in both hands by radiographic absorptiometry (RA), as detailed below. Phalangeal BMD values of the ipsilateral-to-AVF hand were compared with the phalangeal BMD of the contralateral-to-AVF hand.

The following predialysis serum/blood values were measured in all patients: hemoglobin (Hb), calcium, phosphorus, alkaline phosphatase (ALP), intact serum parathyroid hormone (iPTH), blood urea nitrogen (BUN), creatinine, potassium, albumin (Alb), total cholesterol, HDL cholesterol and LDL cholesterol. Adequacy of dialysis was also calculated by the Kt/V formal kinetic urea modeling (8).

BMD Measurements

BMD was measured from the middle phalanges of the second, third and fourth fingers of each hand, using an Alara MetriScan® phalangeal RA device (Alara Inc. Fremont, USA). The device is small enough to fit on a desktop (41 cm wide, 42 cm high, 45 cm deep) and is light enough to be transportable (<19 kg). For an exposure, the patient removes any jewelry (when possible) from the non-dominant hand, and places the hand on the moulded support plate. Hand placement is checked to ensure the fingers are flat but not pressed down hard, and that the second phalanges of the middle three digits are within the region of interest marked on the plate. The operator is able to take the exposure using either a button on the front of the device or a remote button connected by a 2 m lead (9).To record the image, the system uses a storage phosphor plate, which is scanned to extract the image. The hand radiograph is corrected according to a record reference image startup. An aluminum wedge contained in the image is used as an image positioning reference. After the system analyses the image and has segmented soft tissue and bone into separate components, the regions of interest are automatically identified and outlined (10). BMD is expressed in arbitrary units (mineral mass/area) and in grams per square centimeter (g/cm^2). T-scores (compares measured BMD with the average BMD for a young healthy subject of the same gender) was derived from a reference database provided by the manufacturer. The database contains data on 1.500 healthy females aged 20-85 years and T-scores were calculated from the group aged 20-39 years. This peripheral densitometry device has the advantages of low cost, portability and low X-ray dose (<0.02 μ SV per examination) (11).

Statistical Analyses

All data were analyzed using descriptive technique and independent t-test for continuous variables. The Pearson (product-moment) and Spearman's correlations were used to identify predictors of low bone mass. Linear regression analysis was used to measure variables influencing BMD. Analyses were performed by using SPSS version 15.0 for Windows® (SPSS, Inc., Chicago, USA). All tests were two-sided, and a p value of less than 0.05 was accepted as statistically significant.

Results

Although totally 152 patients undergone hemodialysis from two separate dialysis centers in our city, 116 ESRD patients volunteered for our study. Thirty-three subjects were excluded from the analysis due to technical errors during data storage (n=4), problems with positioning (n=7), orthopedic disorders (n=4), previous AVF in the contralateral forearm or graft (n=14), and extremity paresis with a history of cerebrovascular disease (n=4). The remaining 83 patients (59% male) had undergone hemodialysis for a mean±SD of 48.5±36.9 months (range: 6-156 months). Thirty-two of the 34 women were post-menopausal. None were involved in regular exercise programs or routinely did hand-strengthening exercises. Pre-dialysis laboratory findings and BMD results are shown in Table 1.

The AVFs were located on the non-dominant forearm in all patients. Results from both hands of the 83 patients (166 hands) revealed that the ipsilateral-to-AVF phalangeal BMD (0.28± 0.05 g/cm^2; range: 0.14-0.40 g/cm^2) was significantly lower than the contralateral-to-AVF phalangeal BMD (0.30±0.04 g/cm^2; range: 0.19-0.40 g/cm^2; $p<0.05$). One patient had ipsilateral-to-AVF digital clubbing, one patient had distal ischemia in the ipsilateral-to-AVF hand (cold hand, trophic changes, and hand pain during dialysis - diagnosis confirmed by arteriography), and two patients had an ipsilateral-to-AVF forearm fracture.

The mean Hb level was 11.7±1.6 g/dL (range: 8.7-16.2 g/dL); abnormally low (<11 g/dL) in 23 patients (27.7%). The mean serum calcium was 8.4±0.7 mg/dL (range: 6.8-9.7 mg/dL); the serum calcium was lower than normal (< 9mg/dL) in

Table 1. Pre-dialysis laboratory findings and bone mineral density (BMD) in the hands of 83 end-stage renal disease patients undergoing hemodialysis via forearm arteriovenous fistulas (AVF).

Variable (normal range)	Mean±SD	Range
Kt/V	1.42±0.27	0-1.81
Hemoglobin (11-16.5 g/dL)	11.7±1.6	8.7-16.2
Calcium (9-11 mg/dL)	8.4±0.7	6.8-9.7
Phosphorus (1.5-6.8 mg/dL)	5.3±1.5	2.0-9.2
Alkaline phosphatase (98-279 U/L)	374±285	120-1982
iPTH (15-65 pg/mL)	352±296	23-1549
Urea (8-22 mg/dL)	66±18	33-118
Creatinine (0.7-1.4 mg/dL)	8.3±2.6	2.4-15.5
Potassium (4.5-5.5 mmol/L)	5.1±0.5	3.7-6.6
Albumin (3.5-5.0 g/dL)	3.8±0.3	3.0-4.3
Total cholesterol (110-200 mg/dL)	174±43	98-298
HDL cholesterol (35-55 mg/dL)	39±10	19-70
LDL cholesterol (<130 mg/dL)	101±31	41-201
İpsilateral-to-AVF phalangeal BMD	0.28±0.05	0.14-0.40
Contralateral-to-AVF phalangeal BMD	0.30±0.04	0.19-0.40

Kt/V : Dialysis adequacy values, iPTH: Intact serum parathyroid hormone

61 subjects (73.5%). The mean serum phosphorus was 5.3±1.5 mg/dL (range: 2.0-9.2 mg/dL); the serum phosphorus was higher than normal (>6.8 mg/dL) in 12 subjects (14.5%). The mean serum ALP was 374±285 U/L (range: 120-1982 U/L). The serum ALP was high (>279 U/L) in 47 subjects (56.6%). The mean serum iPTH was 352±296 pg/mL (range: 23-1549 pg/mL); the serum iPTH was high (>65 pg/mL) in 79 subjects (95.2%). The mean serum urea was 66±18 mg/dL (range: 33-118 mg/dL).The mean serum creatinine was 8.3±2.6 mg/dL (range: 2.4-15.5 mg/dL); serum urea and creatinine levels were higher than normal (>22 mg/dL, 1.4 mg/dL) in all subjects. The mean serum potassium level was 5.1±0.5 mmol/L (range: 3.7-6.6 mmol/L); the serum potassium level was less than normal (<4.5 mmol/L) in five subjects (6.0%), normal in 69 subjects (83.1%), and higher than normal (>5.5 mmol/L) in nine subjects (10.8%). The mean serum albumin level was 3.8±0.3 g/dL (range: 3.0-4.3 g/dL); the albumin was lower than normal (<3.5 g/dL) in nine subjects (10.9%). The mean serum total cholesterol level was 174±43 mg/dL (range: 98-298 mg/dL); the serum total cholesterol was higher than normal (>200 mg/dL) in 19 subjects (22.9%). The mean serum HDL cholesterol level was 39-10 mg/dL (range: 19-70 mg/dL); the serum HDL cholesterol was lower than normal (< 35 mg/dL) in 22 subjects (26.5%).The mean serum LDL cholesterol level was 101±31mg/dL (range 41-201 mg/dL); the serum LDL cholesterol was higher than normal (>130 mg/dL) in 11 subjects (13.2%).

Correlation analysis was performed among 15 variables (Table 2): ipsilateral-to-AVF phalangeal BMD, contralateral-to-AVF phalangeal BMD, age, duration of dialysis, serum Hb, calcium, phosphorus, ALP, iPTH, BUN, creatinine, potassium, albumin, total cholesterol, HDL cholesterol, LDL cholesterol level and Kt/V. The iPTH was divided into two levels (moderate and high; table 3) There was a significant difference in BMD values

Table 2. Correlation between bone mineral density and related variables.

	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	X15
Y1	r:-0.308**a p:0.005	r:-0.245*a p:0.026	r:-0.024 a p:0.840	r:-0.073 b p:0.529	r:0.043 a p:0.708	r:-0.297*b p:0.016	r:-0.233*a p:0.034	r:0.074 a p:0.521	r:0.243* a p:0.033	r:-0.005 a p:0.967	r:-0.083 a p:0.475	r:-0.202 a p:0.080	r:-0.177 b p:0.127	r:-0.203 a p:0.079	r:-0.144 b p:-0.217
Y2	r:-0.262*a p:0.017	r:-0.032 a p:0.771	r:-0.047 a p:0.686	r:-0.084 b p:0.466	r:0.104 a p:0.368	r:-0.274*b p:0.027	r:-0.219*a p:0.046	r:0.076 a p:0.512	r:0.286* a p:0.012	r:0.100 a p:0.387	r:-0.086 a p:0.457	r:-0.188 a p:0.103	r:-0.267*b p:-0.020	r:-0.152 a p:0.189	r:-0.187 b p:0.109

Date are presented as the r and p value in pearsona and spearmanb correlation test

Y1: Ipsilateral-to AVF hand BMD, Y2: Contralateral-to AVF hand BMD, X1: Age, X2: Duration of dialysis, X3: Hemoglobin, X4: Calcium, X5: Phosphorus X6: Alkaline phosphatase, X7: Parathyroid hormone X8: Urea, X9: Creatinin, X10: Potassium, X11: Albumin, X12: Total cholesterol, X13: HDL, X14: LDL, X15: Kt/V,

*p<0.05 level (2-tailed), **p<0.01 level (2-tailed)

Table 3. Comparison of the bone mineral density in different subgroup subjects

Group variable	%	AVF Hand BMD	Contralateral Hand BMD
Age (year)			
<50	33.73	0.293±0.034	0.310±0.028
>50	66.26	0.269±0.055	0.290±0.046
		P = 0.043*	P = 0.049*
Duration of dialysis (month)			
<24	43.58	0.286±0.044	0.296±0.043
>24	56.41	0.263±0.050	0.293±0.040
		P = 0.034*	P=0.727
iPTH (pg/ml)			
100-350	43.37	0.284±0.052	0.303±0.041
>350	48.19	0.261±0.042	0.284±0.041
		P = 0.044*	P=0.044*
ALP (U/l)			
<279	41.53	0.300±0.047	0.316±0.041
>279	58.46	0.264±0.050	0.284±0.081
		P=0.006**	P=0.002**

AVF: Arterio-venöz fistül, BMD: Bone mineral density

of the ipsilateral and contralateral hands between patients with high iPTH level (>350 pg/ml) and moderate iPTH level (100-350 pg/ml) (p=0,044). Ipsilateral-to-AVF phalangeal BMD and contralateral-to-AVF phalangeal BMD were highly correlated with age, ALP, iPTH and creatinine. The age, serum ALP, and serum iPTH were negatively correlated with both ipsilateral-to-AVF phalangeal BMD and contralateral-to-AVF phalangeal BMD. Duration of dialysis was negatively associated with ipsilateral-to-AVF phalangeal BMD (r=-0.245, p=0.026) but contralateral-to-AVF phalangeal BMD was not correlated with duration of dialysis (r=-0.032, p=0.771). Other variables were not correlated with ipsilateral-to-AVF phalangeal BMD or contralateral-to-AVF phalangeal BMD (Table 2). The five variables influencing BMD were age, serum ALP, iPTH, creatinine, and duration of dialysis. On linear regression analysis, these variables, age and iPTH were identified as a risk factor for low ipsilateral-to-AVF phalangeal BMD and contralateral-to-AVF phalangeal BMD (age p=0.003, iPTH p=0.003; age p=0.017, iPTH p=0.004). Duration of dialysis was also identified as a risk factor for low ipsilateral-to-AVF phalangeal BMD, but was not found to be a risk factor for low contralateral-to-AVF phalangeal BMD (p=0.044; p=0.420).

Discussion

Our hemodialysis patients had a lower BMD in their ipsilateral-to-AVF upper extremities than in their contralateral-to-AVF upper extremities. Our results were similar to those reported by others who measured BMD from the mid-radius and distal radius in ESRD patients, not from the phalanges as we did (2,3). Muxi et al. (2) reported that forearm AVFs lowered BMD levels in ESRD patients. Fontaine et al. (3) found that hemodialysis patients with fractures had a significantly lower BMD than non-fracture ESRD patients, and a large proportion of the fractures were in the ipsilateral-to-AVF distal forearm.

BMD at lumbar spine, femoral neck and radius sites were measured by dual energy x-ray absorptiometry (DXA) in Muxi (2) and Fontaine study, whereas in our study whole body or lumbar/hip BMD was not measured by DXA which was the limitation of this study.

AVFs affect blood flow in nearby tissues, leading to decreased tissue perfusion and growth (2,7,12). An AVF may lead to alterations in hand perfusion, chronic tissue hypoxia, and distal ischemia (2). All of these effects may result in a decrease in BMD in the ipsilateral-to-AVF hand. A study of 434 accesses in children found hemodialysis access-induced distal ischemia in 9%, but high access flow in only 1% (9). Frank van Hoek et al. (13) reported a girl with a small ischemic left hand in the ipsilateral-to-AVF hand with a patent AVF, whereas the contralateral-to-AVF hand was normal. They surmised that the abnormal AVF forearm was due to chronic tissue hypoxia and speculated that the AVF resulted in decreased nutrients being supplied to the distal tissues. Roozbeh et al. (14) reported unilateral digital clubbing in a hemodialysis patient and attributed the findings to chronic tissue hypoxia. In an experimental study on the effect of AVFs on bone healing in dogs, Taşbaş et al. (7) found more dead medullary bone and fewer cartilage cells along the osteotomy line in the ipsilateral-to-AVF tibia. In our study, one patient had unilateral digital clubbing, and another had distal ischemia in the ipsilateral-to-ACF hand with hand pain, cold hand, and trophic changes defined by by clinical examination. Other factors related to AVF, such as immobilization and inactivity of the ipsilateral-to-AVF extremity could have also influenced BMD (15-16).

In patients with chronic kidney disease (CKD), primary muscle, bone, and joint problems are more severe in the extremity with an AVF (17,18). In our study also, patients generally led a sedentary lifestyle and did not use their AVF arms much, even for daily activities. Exercise in these patients is very important; if not done regularly, the patient's quality of life suffers (17,19). Musculoskeletal rehabilitation programs for hemodialysis patients usually include aerobic and strengthening exercises. Regular exercising at home in this population has been found to lower the risk of falls and increase bone density, grip strength, and proximal extremity muscle strength (17,20). Oder et al. (21) observed that ball-squeezing exercises increased the diameter of the AVF immediately afterwards. Leaf et al. (22) reported that hand squeezing exercises with a ball increased blood flow through the AVF and the diameter of the AVF itself. They concluded that these effects might prevent or mitigate vascular problems in these patients. Long-term studies of the effects of upper extremity and general body exercises on AVFs and upper extremity BMD are needed.

ESRD patients usually have accelerated bone loss due to abnormal bone turnover that leads to a high prevalence of osteopenia and osteoporosis (1,21). In the general population, osteoporosis is a main risk factor for fractures, and BMD, routinely measured by DXA, is a quantitative measure of bone mineral deficiency status (4,6). In the absence of axial DXA, current guidelines recommend using peripheral measurements from the hand, forearm or heel to aid in treatment decisions in those with clearly identified clinical risk factors and can be used safely in population screening for osteoporosis (23,24). The UK National Osteoporosis Society suggested that peripheral devices (such as the phalangeal RA device that we used) be adopted in a triage role (23-25). A variety of devices are available for assessing sites in the peripheral skeleton, such as the hand, forearm or heel (25). The phalangeal RA device that we used measured phalangeal BMD from the second phalanges of the middle three digits, which made it suitable for use in this study and other studies of screening for osteoporosis (23,24). Blake, et al. (25) recommended the hand as the preferred site for bone densitometry measurements.

Low BMD is associated strongly and consistently with increased risk of fracture in otherwise healthy men and women (4,26,27). ESRD patients with a low bone mass usually have a high incidence of fragility fracture (8,28,29). Decreased bone mass and disruption of microarchitecture occur early in the course of ESRD and worsen with the progressive decline in renal function, so much so that at the time of initiation of dialysis, at least 50% of patients have had a fracture (30). We found our ESRD patients' phalangeal BMD RA T- score to be lower than -2.5 in 40 patients (48.2%) with ipsilateral-to-AVF hand and 21 patients (25.3%) with contralateral-to-AVF hand. As in our study though, BMD values in the ipsilateral-to-AVF hand were significantly lower than those in the contralateral-to-AVF hand.

We found that age, duration of hemodialysis, iPTH, and ALP levels were negatively correlated with BMD measurements. Other studies have found, like we did, a negative relationship between age and BMD in hemodialysis patients (1,3) whereas others have not found such a relationship (31). Our finding that duration of dialysis was negatively associated with ipsilateral-to-AVF phalangeal BMD (but not contralateral-to-AVF phalangeal BMD) in patients undergoing dialysis for longer periods support our hypothesis that the AVF itself (not hemodialysis per se) is the reason for the lower BMD in the ipsilateral-to-AVF hand. Fountain et al. (3) also reported a negative correlation between duration of dialysis and BMD in hemodialysis patients. They also reported more fractures in the ipsilateral-to-AVF forearm than in the contralateral-to-AVF forearm. Muxi et al. (2) also found the BMD values of the ipsilateral-to-AVF forearm to be lower than those of the contralateral-to-AVF forearm. In their study, however, no significant correlation was found between the BMD of the forearm and duration of dialysis.

Hyperparathyroidism increases cortical porosity, thus, serum PTH level is an important indicator of BMD in patients. However, when hemodialysis is started, the relationship between iPTH and low bone mass becomes complex (1,31,32). For this reason, study results are conflicting regarding the relationship between bone cycle determinators (alkaline phosphatase, calcium, phosphorous, iPTH) and BMD in hemodialysis patients. As we found, Taal et al. (33) and Huang et al. (1), in their study of 151 hemodialysis patients, found a negative correlation between alkaline phosphatase and BMD, and between iPTH and BMD. In other studies, no significant relationship was found between iPTH and BMD (31,34). As did Sit et al. (35) in their study of 70 hemodialysis patients, and Huang GS al.(1) in their study of 63 patients who had been on hemodialysis for at least 6 months (1), we also found no relationship of BMD with calcium and phosphorous.

As a result, BMD is lower in the ipsilateral-to-AVF hand compared to the contralateral-to-AVF hand in hemodialysis patients. Future studies are needed to determine the utility of BMD values in determining fracture risk, starting treatments which preserve BMD, and guiding long-term management of hemodialysis patients, with the goal of preventing fractures and their associated complications.

Conflict of Interest

Authors reported no conflicts of interest.

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