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Bone Mineral Density and Hemodialysis Vintage [Version 1, 1 Approved, 1 Approved with Reservation]

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Abstract

Metabolic bone disease occurs early in chronic kidney disease and bone mineral loss could be one of the clinical manifestations. The aim of this work was to investigate the possible correlation between hemodialysis vintage and bone mineral loss in dialysis patients.

A total of 134 hemodialysis patients were included in the study. They were divided into three groups based on hemodialysis vintage. The first group was made up of patients who were in treatment for up to one year (n=37), the second between one and five years (n=57), and the third for more than five years (n=40). In all patients bone mineral density (BMD) was measured by dual energy x-ray absorptiometry.

There were no statistically significant differences in age between the groups. Patients on hemodialysis for more than five years had a significantly lower value for body mass index (P=0.02), a significantly higher serum concentration of parathyroid hormone (P=0.0004) and a lower value for BMD at all measuring points. The most significant difference were in the forearm (P to 0.002 from 0.006).

We can conclude from the results obtained that the duration of treatment by hemodialysis is linked to increased values of PTH and reduced BMD at all measuring points, especially in the area of the forearm.

Keywords

Bone Mineral Density; Dual Energy X-Ray Absorptiometry; Duration of Hemodialysis; Parathyroid Hormone

Introduction

Thanks to the methods for replacing kidney functions that began more than 50 years ago, the lives of many patients with chronic kidney failure have been significantly prolonged. With time, nephrologists have become acquainted with the many complications that are linked to dialysis treatment. In 1966, a case was described involving 22 patients on dialysis, among 47% of whom fractures in different parts of the skeleton appeared [1]. By prolonging the lives of dialysis patients, the many complications were growing, as was the understanding of the problem and the ability to prevent it. In the last 10 years, there have been major advancements in understanding the pathogenesis of bone disease in patients with chronic kidney disease and the possibility of diagnosis and treatment.

Renal osteodystrophy, whose pathogenesis is very complicated, is one of the frequent complications and appears in the majority of patients with chronic kidney disease. Phosphate retention, hypocalcaemia and a deficiency of vitamin D are the most significant factors in the pathogenesis of renal osteodystrophy [2,3] that are, in fact, only a part of a much more complicated disorder that we call chronic kidney disease - mineral and bone disorder [CKD MBD] [4]. Other factors also contribute to the pathological changes in these patients, for example, premature menopause in women, possible aluminum intoxication, etc. Based on a new classification, we can histologically differentiate slow or accelerated bone change, reduced or normal bone volume, and reduced or normal mineralization [4,5]. Regardless of the type of bone lesion in a patient with renal osteodystrophy, an increased risk of pathological fracture has been proven [5,6].

The aim of the present cross-sectional study was to investigate the relationship between bone mineral density [BMD] in different skeletal regions and hemodialysis vintage and to see which areas of the skeleton show the greatest loss of bone mass.

Patients and Methods

Patients

One hundred thirty-four hemodialysis patients, 62 women and 72 men, were included in the study. All of the patients were from one dialysis center. They were divided into three groups based on hemodialysis vintage. The first group consisted of patients who were being treated for one year or less. The second group of patients was being treated from one to five years. The third group was made up of patients that were being treated for more than five years. All of the patients were measured for height, weight and body mass index [BMI].

Patients were informed of the purpose and method of the search. Written consent was obtained from each participant. The study was approved by the Local Ethics Committee of the University Hospital and the School of Medicine in accordance with the Helsinki Declaration.

All of the patients were on dialysis for 12 hours per week. In all patients dialysis filters with polysulphone membranes were sterilized with steam. The concentration of calcium in the dialysate was 1.5 mmol/L. All of the patients were taking a phosphate binder [calcium carbonate, sevelamer hydrochloride] and an active metabolite of vitamin D, calcitriol, based on clinical indication [7,8].

Patients who had taken corticosteroid and bisphosphonates at any time in their lives, patients who had had a malignant disease, and any patient who had used aluminum hydroxide as a phosphate binder were not included in the research.

Bone Mineral Density

All patients were measured for BMD by the dual energy x-ray absorptiometry [DXA] method. DXA was measured on a Hologic apparatus, model Delphi W [S/N 70616]. Measurements were made at the following measuring points: lumbar spine [antero-posterior orientation from L1-L4 and latero-lateral orientation from L1-L2], hip [neck, trochanter, intertrochanter, total and Ward's triangle] and in the area of the forearm [ultradistal, mid, proximal third and total]. The results of the measuring are expressed as BMD g/cm^2, T-score and Z-score.

Biochemical Measurements

For all patients the concentration of serum calcium, phosphate, alkaline phosphate, albumin, cholesterol, hemoglobin and C-reactive protein [CRP] was determined. All patients were measured for the concentration of parathyroid hormone [PTH]. Plasma PTH was measured by a commercial chemiluminescence method for intact PTH [chemiluminescence method - DPC; Diagnostic Products, Los Angeles, USA]. The range of normal values was between 1.1-7.3 pmol/L.

Statistical Analyses

The clinical characteristics of the patient groups are presented as a mean ± standard deviation. Comparisons between the groups were made by the ANOVA. Statistical significance was defined as $P<0.05$.

Results

There was no statistically significant difference in the age of the groups. The patients who were on dialysis for more than five years had a significantly lower BMI [$p< 0.02$], [Table 1]. Patients who were on dialysis treatment for more than five years also had the highest levels of PTH, 101.9 ± 78.3 pmol/l, while patients in the other groups had an average concentration of 47.6 ± 32.3 pmol/l and 54 ± 53.6 pmol/l [$p< 0.004$], [Table 2].

Patients on hemodialysis for more than five years had significantly less bones mass, expressed as BMD. At all measuring points, except in the area of the lumbar vertebrae L-L projection, the neck of the hip and Ward's triangle, the difference was also statistically significant [Table 3]. All patients had a negative T-score [-0.8 do -2.8], as well as a Z-score [-0.4 do -0.9],

except in the area of the lumbar vertebrae [A-P scan] in the first two groups of patients. The lowest value of the T-scores and Z-scores was in the group of patients who were on hemodialysis for more than five years [Table 4].

If the T-score is also analyzed, the highest percentage of patients with a T-score ≤-2.5 was in the group of patients who were on hemodialysis treatment for more than five years [Table 5].

Table 1: Characteristics of the study patients on the basis of the duration of hemodialysis.

	<1year duration HD	1-5 years duration HD	>5 years duration HD
Total	32 [27.6%]	57 [42.6%]	40 [29.8%]
Female [N,%]	20 [54.1%]	22 [38.6%]	20 [50%]
Male [N,%]	17 [45.9%]	35 [61.4%]	20 [50%]
Age [mean ± SD]	54.8±12.2	58.1±13.1	56.1±11.4*
BMI kg/m² [mean ± SD]	26.1±4.9	25.4±3.7	23.8±3.5†
Etiology of CKD [N,%]			
Glomerulonephritis	7 [18.9%]	20 [35%]	21 [52.5%]
Pyelonephritis	3 [8.1%]	4 [7%]	5 [12.5%]
TIN	3 [8.1%]	5 [8.8%]	3 [7.5%]
Nephrosclerosis	8 [21.6%]	5 [8,8%	3 [7.5%
Diabetic nephropathy	6 [16.2%]	4 [7%]	0 [0%]
Polycystic kidney disease	3 [8.1%]	3 [5.3%	3 [7.5%
Other	7 [18.9%]	16 [28.1%]	5 [12.5%]

*P=NS, †P=0.02

BMI=Body Mass Index; CKD=Chronic Kidney Disease; HD=Hemodialysis; TIN= Tubulointerstitial Nephritis.

Table 2: Comparison of data of all patients on the basis of the duration of hemodialysis.

	<1 year duration HD	1-5 years duration HD	>5 years duration HD	
Parameter	Mean ± SD	Mean ± SD	Mean ± SD	**P**
iPTH [pmol/L]	47.6±32.3	54.0±53,6	101.9±78.3	**0.0004**
Calcium [mmol/L]	2.2±0.2	2.3±0.2	2.5±0.5	0.181
Phosphate [mmol/L]	1.8±0.5	1.8±0.4	1.8±0.3	0.622
Ca x P [mmol²/L²]	3.9.±1.1	4.3±1.1	4.6±2.5	0.221
AP [UL]	89.0±37.7	83.2±39.7	127.0±131.8	0.058
Albumin [g/L]	37.7±2.9	38.2±2.3	38.3±2.7	0.501
Cholesterol [mmol/L]	4.7±1.1	4.7±1.1	4.7±1.3	0.494
Hemoglobin [g/L]	100.2±14.4	105.1±15.5	107.1±15.8	0.115
CRP [mg/L]	5.3±7.1	6.7±9.2	4.7±1.3	0.722

ALP=Total Alkaline Phosphates; BMI=Body Mass Index; Ca x P= Calcium Phosphate Product; CRP=C-reactive protein; HD=Hemodialysis; iPTH=Intact Parathyroid Hormone.

Table 3: Comparison bone mineral density of all patients on the basis of the duration of hemodialysis.

BMD g/cm²					
		<1 year duration HD	1-5 years duration HD	>5 years duration HD	P *[ANOVA]*
L-S	PA	0.979±0.142	0.982±0.202	0.871±0.173	**0.01**
	LL	0.702±0.150	0.708±0.205	0.693±0.219	0.94
HIP	Neck	0.764±0.136	0.767±0.136	0.709±0.121	0.12
	Troch	0.638±0.129	0.650±0.140	0.565±0.115	**0.01**
	Inter	1.013±0.192	1.034±0.178	0.973±0.198	**0.02**
	Total	0.874±0.163	0.886±0.157	0.801±0.166	**0.01**
	Ward's	0.562±0.183	0.554±0.151	0.523±0.192	0.21
FORE-ARM	UD	0.406±0.121	0.381±0.093	0.325±0.091	**0.003**
	MID	0.573±0.117	0.562±0.111	0.490±0.121	**0.003**
	1/3	0.683±0.131	0.668±0.123	0.610±0.139	**0.006**
	Total	0.558±0.112	0.547±0.109	0.478±0.115	**0.002**

BMD= Bone Mineral Density; HD=Hemodialysis; Inter= Intertrochanter; L-L= Lateral-Lateral; L-S=Lumbar Spine: MID= Mid; PA= Posterior-Anterior; Troch= Trochanter; UD=Ultradistal; Ward's= Ward's triangle; 1/3= One-Third.

Table 4: Comparison T-score and Z-score of all patients on the basis of the duration of hemodialysis.

			<1 year duration HD	1-5 years duration HD	>5 years duration HD	P [*ANOVA*]
L-S	PA	T-score	-0.8±1.3	-1.3±1.7	-1.8±1.5	**0.006**
		Z-score	0.1±1.4	0.1±1.8	-0.9±1.4	**0.005**
HIP	Neck	T-score	-1.1±1.0	1.1±1.0	-1.4±1.3	0.22
		Z-score	-0.1±0.9	-0.1±0.9	-0.5±1.1	0.07
	Troch	T-score	-0.9±1.1	-0.9±1.1	-1.4±1.1	0.06
		Z-score	-0.4±0.9	-0.3±1.0	-0.9±0.8	**0.01**
	Inter	T-score	-0.8±1.0	-0.7±1.0	1.3±1.2	**0.04**
		Z-score	-0.3±1.0	-0.2±0.9	-0.8±1.0	**0.01**
	Total	T-score	-0.9±1.1	-0.8±1.1	-1,3±1.3	0.14
		Z-score	-0.3±1.0	-0.2±1.0	-0.8±1.0	**0.008**
	Ward's	T-score	-1.6±1.4	-1.6±1.8	-1.9±1.4	**0.06**
		Z-score	0.1±1.3	0.0±1.1	-0.2±1.3	0.7
FOREARM	UD	T-score	-1.2±1.3	-0.9±1.5	-2.6±1.3	**0.0002**
		Z-score	-0.4±1.3	-0.8±1.4	-1.8±1.3	**<0.0001**
	MID	T-score	-1.2±1.6	-1.6±1.7	-2.8±1.8	**0.0002**
		Z-score	-0.3±1.4	-0.7±1.6	-1.9±1.3	**<0.0001**
	1/3	T-score	-1.1±1.9	-1.4±1.6	-2.5±1.8	**0.0006**
		Z-score	-0.1±1.5	-0.3±1.6	-1.6±1.8	**0.0001**
	Total	T-score	-1.2±1.5	-1.6±1.6	-2.4±2.1	**0.016**
		Z-score	-0.3±1.4	-0.6±1.6	-1.8±1.6	**<0.0001**

HD=Hemodialysis; Inter= Intertrochanter; L-L= Lateral-Lateral; L-S=Lumbar Spine: MID= Mid; PA= Posterior-Anterior; Troch= Trochanter; UD=Ultradistal; Ward's= Ward's triangle; 1/3= One-Third.

Table 5: Number and percent patients with T-score ≤-2.5 on the basis of the duration of hemodialysis.

T-score ≤2.5 N [%]				
		<1 year duration HD	1-5 years duration HD	>5 years duration HD
L-S	AP	4 [10.8%]	10 [17.5%]	15 [37.5%]
HIP	Neck	3 [8.1%]	4 [7%]	6 [15%]
	Troch	2 [5.4%]	4 [7%]	6 [15%]
	Inter	3 [8.1%]	1 [1.7%]	7 [17.5%]
	Total	3 [8.15]	2 [3.5%]	6 [15%]
	Ward's	6 [16.2%]	8 [14%]	25 [62.5%]
FOREARM	UD	5 [13.5%]	14 [24.5%]	22 [55%]
	MID	7 [18.9%]	16 [28.1%]	20 [50%]
	1/3	6 [16.2%]	10 [17.5%]	18 [45%]
	Total	5 [13.5%]	19 [33.3%]	17 [42.5%]

HD=Hemodialysis; Inter= Intertrochanter; L-L= Lateral-Lateral; L-S=Lumbar Spine: MID= Mid; PA= Posterior-Anterior; Troch= Trochanter; UD=Ultradistal; Ward's= Ward's triangle; 1/3= One-Third.

Discussion

Analyzing BMD at all measuring points, patients who were on hemodialysis for more than five years had the lowest values. It is obvious that the duration of dialysis is unquestionably linked to a loss of bone mass, which some other studies have also shown [9,10]. But other studies did not show a correlation between hemodialysis vintage and bone mineral density [11,12]. If the losses are analyzed at individual measuring points, the greatest differences are in the area of the forearm. The area of the forearm is dominated by cortical bone [in the diaphyseal radius it amounts to 95%], compared to the lumbar vertebrae, which is dominated by trabecular bone amounting to 75% [13]. Cortical bones are less active metabolically, but it has been proven that PTH works more on them and also that in primary and secondary hyperthyroidism the loss of bone mass is more strongly expressed in the appendicular part of the skeleton. Our patients who were being treated longer by dialysis had a higher level of PTH and also a greater loss of bone mass in the appendicular portion of the skeleton. Many studies that analyzed BMD in hemodialysis patients did not measure the area of the forearm, which may be one of the reasons for different results between the duration hemodialysis and BMD.

It is interesting to note that patients in the first group, who were on dialysis treatment for less than one year and had the lowest PTH values, also had reduced bone mass and negative T and Z scores. It is apparent that the changes in mineral bone metabolism begin in the early phase of kidney failure before the beginning of dialysis, i.e. when glomerular filtration is 60 ml/min [14]. In several studies the percentage of people with low BMD was greater in people with reduced kidney function [15,16]. The explanation for this could be that the patients with chronic kidney disease are older and have less muscular mass and less body weight. The same study did not find a significant reduction in BMD in patients with chronic kidney disease [17,18].

All patients analyzed had an expected negative T-score at all measuring points with regard to their age. A Z-score, which compares populations of the same age, gender and race, was also negative at all measuring point in all three groups, with the exception of the lumbar vertebrae [A-P projection] in the group of patients who were on hemodialysis treatment between one and five years. The lowest T-scores and Z-scores were for the group of patients who were on regular hemodialysis for more than five years. Studies have shown that the frequency of fractures in dialysis patients is linked to the duration of dialysis and low values of the T-score and Z-score [5,6,19,20]. In our group of patients [although this was not the goal of the research] only two patients had pathological fractures.

The determination of PTH in chronic kidney failure is the gold standard in the diagnosis of hyperthyroidism and an indirect indicator of the speed of bone change [21,22]. Although there is an overlap, the majority of patients with a PTH 10 times above normal have accelerated bone change, while patients with a concentration of PTH up to two times greater than normal have a slower bone change. Biochemical indicators of bone change [bone alkaline phosphate, osteocalcin, beta cross laps and procollagens] can be useful in estimating bone change in dialysis patients, especially bone alkaline phosphate. Not one of the cited parameters emphasizes bone mass or is a predictor for the loss of bone mass.

Of several methods, DXA is today accepted as the method of choice for determining a diagnosis of osteoporosis and the monitoring of bone mass. It is simple, cheap and accessible. In 1994, a working group of the World Health Organization [WHO] established the criteria for making a diagnosis in a general population [23]. There are numerous proofs for the DXA method, not only in the diagnosis of osteoporosis but also in evaluating the risk of bone fracture. The lower the bones mass, the greater the risk of fracture [24]. Today, we still do not have criteria for making a diagnosis of osteoporosis in the fourth and fifth stage of chronic kidney failure [25,26].

Of course, other techniques, such as quantitative computed tomography [QTC] and bone biopsy might be better and more precise in estimating the amount, density and loss of bone mass. QTC has an advantage because it measures bone density in three dimensions and the result is expressed in g/cm^3 [27]. Because of the greater dose of x-rays, price and accessibility it is of limited use in our everyday work, as is a bone biopsy because of the method of conducting and interpreting it.

In patients with renal osteodystrophy there is proof of a loss of bone mass that depends both on the length of dialysis and on age. Unfortunately, there is no proof on the optimal measuring point for determining bone mass and for estimating the risk of fracture. We can sometimes obtain a false, good finding because of pathological calcification or sclerosis of the trabecular portion of the skeleton [28]. Also, for now, we do not know how frequently a determination of bone mass should be repeated in these patients, every two to three years, as in other patients, or more frequently.

In this work, which has shortcomings because it is a cross-over study with a relatively small number of patients, we have proven how hyperthyroidism and the duration of dialysis treatment are linked to the loss of bone mass. It is certain that in these patients, in addition to determining bone mass in the axial portion, determining bone mass in the appendicular portion of the skeleton [distal portion of the forearm] is equally, if not more, important. Longitudinal monitoring with simultaneous determination of PTH and biochemical indicators of bone change and the monitoring of the incidence and prevalence of fractures most probably will show us the significance of DXA in these patients. For now, although we cannot claim it on the basis of our results, it seems to us that it would be reasonable to determine bone mass in all patients at the beginning of dialysis treatment and to repeat the examination later in a specified time frame of two to three years.

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