

Concise report

Patients with diffuse idiopathic skeletal hyperostosis do not have increased peripheral bone mineral density and geometry

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Abstract

Objectives. Recent studies have suggested that areal BMD (aBMD) measured by DXA is elevated in patients with DISH. We used peripheral QCT (pQCT) to assess volumetric BMD (vBMD) and bone geometry of the radius, tibia and the third metacarpal bone.

Methods. Patients with established DISH and a control group of healthy individuals were recruited. pQCT measurements were performed at the distal epiphyses and mid-shafts of the radius, the tibia and the third metacarpal bone. At the epiphyses cross-sectional area (CSA), total BMD and trabecular BMD were measured. At the shafts, total bone CSA, cortical CSA, cortical wall thickness and cortical BMD were determined. In addition, muscle and fat CSA of the forearm and lower leg were assessed. Bone parameters were compared between the two groups using independent *t*-tests.

Results. Thirty DISH patients and 30 controls comparable with regard to age and height were included in this study. None of the measured bone parameters differed between groups.

Conclusions. In contrast to suggestions based on DXA, pQCT revealed that DISH patients do not have increased vBMD and bone geometry in the appendicular skeleton. Ossification at tendon or ligament insertion sites may lead to overestimation of aBMD if assessed by DXA.

Key words: Diffuse idiopathic skeletal hyperostosis, Peripheral quantitative computed tomography, Bone mineral density, Metacarpal bone.

Introduction

DISH is characterized by calcification and ossification of the anterolateral spinal ligaments [1]. It results in ankylosis of the spine and may lead to compression of neuronal structures [2, 3]. The prevalence of DISH is high, affecting >10% of individuals >70 years of age [4]. It is more common and more severe in men [4]. The aetio-pathogenesis of this disorder is largely unknown. Described associations with various metabolic and endo-

crine conditions, including hyperinsulinism, obesity, dyslipidaemia and hypertension suggest contributing metabolic factors [5, 6].

It has recently been suggested that DISH patients have higher areal BMD (aBMD) at the distal radius measured by DXA [7]. In addition, Haara *et al.* [8] confirmed earlier findings of a higher metacarpal index (MI; greater cortical thickness at the metacarpal bone shaft) in DISH patients. They suggested a joint metabolic factor responsible for the skeletal hyperostosis and the elevated bone mass [8].

The decisive limitation of all existing studies is the fact that 2D methods have been used, that at best allow an estimation of bone mass and a crude assessment of bone geometry. The aim of the present study was, therefore, to measure volumetric BMD (vBMD) and bone geometry of peripheral skeletal sites by means of peripheral QCT (pQCT). In order to minimize the effect of potential confounding factors, we decided to assess all bony and soft

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tissue parameters at three appendicular sites: the third metacarpal bone, the radius and the tibia.

Methods

Subjects

Patient rolls of the Department of Rheumatology, Inselspital Bern, were screened for DISH patients. Inclusion criteria were age ≥ 18 years and radiographic diagnosis of DISH [9] of the thoracic or lumbar spine. Scoring of thoracic and lumbar spine was performed by a study-independent experienced radiologist. Exclusion criteria were pregnancy, previous or current bisphosphonate therapy, malignancies and endocrinopathy such as thyroid and parathyroid disorder, previous vitamin A therapy, RA and AS.

DISH patients satisfying inclusion/exclusion criteria according to patient histories in the hospital databank were invited to participate in the present study by phone. For the control group, we recruited healthy male and female volunteers aged 20–90 years by locally distributed flyers and advertisements in a local newspaper. Exclusion criteria for control subjects were bone metabolic disease, hyper/hypoparathyroidism, malignancies, chronic renal disease, pregnancy, lactation, previous or current bisphosphonate use and drug addiction. All patients gave written informed consent. The study was approved by the ethics committee of the Canton of Bern.

Bone measurements

Measurements were performed with a Stratec XCT 3000 scanner (Stratec Medical, Pforzheim, Germany). This pQCT apparatus measures attenuation of X-rays, which are linearly transformed into hydroxylapatite (HA) densities. Unlike some other pQCT scanners, the Stratec XCT 3000 is calibrated with respect to water, which is set at 60 mg HA, so that fat results in 0 mg HA [10]. HA equivalent densities are automatically calculated from the attenuation coefficients by employing the manufacturer's phantom which itself is calibrated with respect to the European Forearm Phantom (EFP; QRM, Erlangen, Germany) [10]. Radius and metacarpal measurements were performed on the non-dominant side and tibia scans on the contra-lateral side.

Radius and tibia measurements

Tibia length was determined to the nearest 5 mm with a measuring tape by palpation from the medial knee joint cleft to the end of the medial malleolus. Radius bone length was set equal to ulnar length, which was measured from the olecranon to the ulnar styloid. A scout view of the distal end of the tibia and radius and the automated detection algorithm provided by the manufacturer was used to place the reference line at the distal bone end. Scans were performed at 4 and 66% of the bone's total length measured from the reference line. Slice thickness was 2.3 mm and voxel size was set at 0.5 mm with a scanning speed of 20 mm/s.

Metacarpal measurements

Length of metacarpal bone III was palpated and measured from base to head by a measuring tape to the nearest 5 mm. A scout view was performed of the head of ossa metacarpalia III and the reference line was placed at the distal end of the bone. Scans were performed at 4 and 50% of total bone length measured from the distal bone end. Scanning speed was set at 15 mm/s and voxel size was reduced to 0.3 mm edge length.

Measuring parameters

Epiphyseal scans (4%). The periosteal surface of each bone's epiphysis was found by a contour algorithm based on thresholding at 180 mg/cm³. BMC/cm of slice thickness, total cross-sectional area (CSA) and total BMD were determined. Concentric pixel layers were then peeled off from the bone's perimeter until a central area covering 45% (50% for metacarpal bone) of the total bone CSA was left. From this central area, trabecular BMD was determined.

Diaphyseal scans (66% for radius and tibia and 50% for metacarpal bone). The periosteal surface of the bone's diaphysis was found by a contour algorithm based on a threshold of 280 mg/cm³. BMC and total CSA were calculated. Cortical bone was selected by thresholding at 710 mg/cm³. Of the selected area, cortical CSA and cortical BMD were calculated. Cortical thickness was calculated based on the assumption that bone shaft is cylindrical, from total CSA, which included the bone marrow and cortical CSA of the diaphyseal scans. Subcutaneous fat CSA was determined by selecting the area with thresholds -40 to 40 mg/cm³ HA density; muscle CSA was determined by subtracting the total bone CSA (threshold 280 mg/cm³) and subcutaneous fat CSA from the total limb CSA. For the metacarpal shaft, the MI was calculated as cortical CSA/total CSA from the 50% scans.

Data analysis

Independent *t*-tests were performed separately for females and males between the DISH group and control group for age, height, weight, BMI, and muscle and fat CSA at the lower arm and lower leg. Furthermore, independent *t*-tests were also performed separately for males and females as well as for pooled sex groups for all measured bone parameters at the radius, tibia and third metacarpal bone. Statistical significance was set at 0.05. Statistical analyses were performed with SPSS version 15.1 (SPSS-Schweiz, Zürich).

Results

Subject parameters

A total of 112 DISH patients were contacted by phone, but due to mainly geographical reasons only 31 (15 females and 16 males) were willing to participate. Of the 105 control subjects recruited for a related study, 30 subjects were selected on the basis of their sex, age, height and weight in order to form two control groups for the female

and male DISH groups that were comparable with regard to age, height and weight. One male DISH subject had to be excluded because all of his pQCT scans were affected by strong movement artefacts. Subject characteristics are indicated in Table 1. Reflecting the underlying metabolic disorder of DISH patients, our pooled DISH group was 7.9 kg (10%) heavier ($P=0.027$) and had a greater BMI ($P=0.005$) than the control group. BMI was also significantly greater in DISH males compared with control males (by 3.4 kg/m^2 or 13%, $P=0.01$ in males; and by 3.2 kg/m^2 or 12%, $P=0.11$ in females). Twenty-five DISH patients and 23 control subjects had a BMI ≥ 25 . Lower leg fat CSA was 31% smaller in DISH females ($P=0.01$).

Bone parameters

The following scans had to be excluded due to movement artefacts: one radial shaft scan each in the female and male DISH groups and the female and male control groups; one total tibia scan each in the female and male control groups and two total tibia scans in the female DISH group (plus one more tibia shaft scan in the female DISH group); one metacarpal shaft scan in each of the female DISH and control groups and one total metacarpal scan in the male control group. Results for the sexes analysed separately were comparable with the pooled sex groups, therefore, only results of the pooled analyses are presented in Table 2. Remarkably, none of the measured bone parameters differed between the DISH and control groups. In fact, there was a trend for all bone density and geometric data to be smaller in the DISH group, except for outer bone circumference at the shaft (total CSA) and total BMD at the distal metacarpal bone, which was almost identical between groups.

Discussion

Radiographic signs of DISH at the thoracic or lumbosacral spine have been associated with increased aBMD at the hip [11], spine [11] and radius [7] as well as an

increased MI [8, 12]. It has been discussed whether the elevated aBMD at the spine of DISH patients is merely due to ossified ligaments [13, 14]. We present the first cross-sectional pQCT study of 30 DISH patients and 30 control subjects. The data provide evidence for unchanged vBMD and bone geometric parameters at all investigated sites, the radius, tibia and metacarpal bone. The following reasons may explain these differences: (i) ossification at tendon or ligament insertion sites in DISH patients may have led to an overestimation of aBMD at the radius, as measured in a study on 42 DISH patients by Di Franco *et al.* [7]; (ii) differences between the control populations: while the control subjects of the study by Littlejohn *et al.* [12] were either in- or outpatients of the Rheumatic Disease Unit with likely osteopenia, our control subjects were recruited by flyers and advertisements in a local newspaper and were all healthy and fit for their age; and (iii) the small number of patients in our study and a potential bias due to the relatively poor study participation rate of DISH patients. However, since we did not even find a trend for increased BMD, it is unlikely that a larger cohort would have resulted in significantly elevated vBMD.

The limitations of this study are that the control subjects were lighter and were not radiologically confirmed to be free of DISH. However, most bone parameters measured in the present study showed a trend for lower vBMD and weaker bone geometry in DISH patients compared with controls. Therefore, future studies should test whether DISH subjects have indeed weaker bone strength than control subjects who are radiologically confirmed to be free of DISH. The heavier weight of our DISH patients would normally favour greater bone mass [15, 16]; they showed, however, a trend for lower bone mass. In conclusion, vBMD or bone geometric parameters at the appendicular skeleton (radius, tibia and metacarpal bone) are not increased in DISH patients compared with healthy controls. Our findings are in contrast to previous studies that have argued for systemically elevated BMD [7, 8].

Table 1 Subject anthropometric data

Parameter	Female DISH patients	Female reference group	<i>t</i> -test <i>P</i> -value	Male DISH patients	Male reference group	<i>t</i> -test <i>P</i> -value	Pooled <i>P</i> -value*
<i>n</i>	15	15		15	15		
Age, years	68.0 (9.8)	70.3 (7.2)	0.48	67.8 (10.3)	66.2 (9.3)	0.66	0.90
Height, cm	164.1 (4.7)	165.3 (5.8)	0.56	174.9 (6.9)	177.3 (4.9)	0.28	0.40
Weight, kg	82.3 (18.4)	74.3 (8.6)	0.15	90.5 (14.3)	82.5 (7.7)	0.07	0.027
BMI, kg/m ²	30.5 (6.3)	27.3 (3.6)	0.11	29.6 (4.4)	26.2 (1.6)	0.01	0.005
Forearm muscle CSA, mm ²	2737 (413)	2463 (254)	0.07	4025 (469)	3978 (745)	0.88	0.77
Forearm fat CSA, mm ²	1877 (678)	1815 (673)	0.83	1037 (362)	1021 (389)	0.93	0.51
Lower leg muscle CSA, mm ²	6462 (1471)	6270 (443)	0.68	8020 (984)	8117 (1103)	0.81	0.87
Lower leg fat CSA, mm ²	2503 (878)	3636 (1176)	0.01	2116 (1187)	2018 (614)	0.64	0.12

Subject anthropometric data indicated as mean values (s.d.) and *P*-values of independent *t*-test. $P < 0.05$ is indicated in bold.

**P*-value for pooled groups (females and males together).

Table 2 Results of independent *t*-tests of measured bone parameters at the distal (4%) and shaft (66 or 50%) site of the radius, tibia and the third metacarpal bone (MCP3) in DISH patients and controls

Bone	Site, %	Group Parameter	Ref (<i>n</i> = 30)		DISH (<i>n</i> = 30)		<i>P</i> -value
			Mean	(s.d.)	Mean	(s.d.)	
Radius	4	BMC, g/cm	1.41	(0.39)	1.31	(0.38)	0.328
		Total CSA, mm ²	415.8	(83.7)	404.2	(110.5)	0.648
		Total BMD, mg/cm ³	339.4	(70.9)	329.0	(64.1)	0.553
		Trab. BMD, mg/cm ³	202.9	(53.0)	187.2	(55.1)	0.265
	66	BMC, g/cm	1.15	(0.26)	1.10	(0.29)	0.431
		Total CSA, mm ²	169.3	(36.2)	176.1	(52.4)	0.573
		Cort. CSA, mm ²	86.6	(21.8)	78.0	(20.8)	0.139
		Cort. BMD, mg/cm ³	1110.1	(45.3)	1085.1	(56.8)	0.078
Tibia	4	Cort. thickness, mm	2.20	(0.44)	1.96	(0.48)	0.061
		BMC ^a , g/cm	3.62	(0.73)	3.39	(0.71)	0.233
		Total CSA ^a , mm ²	1264.4	(159.2)	1228.4	(178.6)	0.429
		Total BMD, mg/cm ³	287.3	(48.3)	276.9	(50.1)	0.434
	66	Trab. BMD, mg/cm ³	227.3	(38.2)	211.8	(44.4)	0.168
		BMC ^a , g/cm	4.21	(0.61)	4.05	(0.73)	0.387
		Total CSA, mm ²	633.2	(114.1)	647.0	(137.0)	0.686
		Cort. CSA ^a , mm ²	326.4	(49.4)	311.0	(61.0)	0.306
MCP3	4	Cort. BMD ^a , mg/cm ³	1115.2	(36.9)	1102.5	(32.9)	0.187
		Cort. thickness ^a , mm	4.33	(0.50)	4.01	(0.75)	0.083
		BMC, mg/mm	50.11	(10.92)	49.37	(9.79)	0.783
		Total CSA, mm ²	145.6	(20.7)	144.9	(27.6)	0.909
	50	Total BMD, mg/cm ³	340.9	(45.1)	343.2	(44.2)	0.84
		Trab. BMD, mg/cm ³	293.8	(48.8)	287.8	(56.1)	0.664
		BMC, mg/mm	56.44	(11.86)	56.21	(11.99)	0.941
		Total CSA, mm ²	72.65	(12.22)	74.41	(18.24)	0.671
		Cort. CSA, mm ²	42.26	(9.57)	41.13	(9.28)	0.652
		Cort. BMD, mg/cm ³	1158.1	(34.4)	1144.7	(60.9)	0.316
		Cort. thickness, mm	1.70	(0.32)	1.66	(0.37)	0.641
		MI, cort. CSA/total CSA	0.58	(0.07)	0.57	(0.11)	0.614

^aAccording to Levene's test group, variances were not equal for this parameter. Hence, individual variances were used for the *t*-test.

Rheumatology key messages

- DISH patients do not have increased vBMD and bone geometric properties at peripheral bones.
- Ossification at tendon/ligament insertion sites in DISH patients may lead to overestimation of aBMD.

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