Characterization of Bone Metabolism in Hungarian Psoriatic Arthritis Patients: A Case–Control Study.

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Abstract

Background: Skeletal manifestations are predominant in psoriatic arthritis (PsA). The aim of this cross-sectional, case-controlled study is the complex assessment of areal and volumetric bone mineral density (BMD), fracture risk, vitamin D status and bone turnover markers, and its association with disease-related variables.

Methods: Lumbar spine (L1-L4) and femur neck (FN) areal, and distal radius (DR) volumetric BMD, 10-year probability of major and hip osteoporotic fracture as assessed by the fracture risk assessment (FRAX) tool, markers of bone metabolism and disease activity were assessed.

Results: Upon comparison of the disease and age- and sex-matched control groups, there was a statistically significant difference in FN areal (0.955±0.145 g/cm^2 vs. 1.034±0.148 g/cm^2; p=0.001) and DR total volumetric (285.7±61.8 mg/cm^3 vs. 369.6±23.6 mg/cm^3; p<0.001) BMD, 10 year probability for major osteoporotic (5.0% (0.7%-32%) vs. 3.5% (0%-17.5%); p=0.003) and hip (1.1% (0%-16%) vs. 0.5% (0%-6.1%); p=0.002) fracture and 25-hydroxyvitamin D status (53 (10-120) nmol/L vs. 67 (10-137; p<0.001) nmol/L). As compared to areal assessment, volumetric BMD measurements identified a significantly higher number of patients with low bone mass (T-Score £ -1.00) (34% vs. 88%, p<0.001). Upon multiple linear regression analysis, disease activity score, as determined by DAS28 assessment, was an independent predictor of 10-year probability for major osteoporotic fracture (B (95%CI) = 1.351 (0.379–2.323); p = 0.007).

Conclusion: In the studied PsA cohort, disease activity was an independent predictor of 10-year probability for a major osteoporotic fracture, and complemented assessment of volumetric and areal BMD assured better efficacy at identifying those with low bone mass.

Background

The prevalence of psoriasis is estimated at 1–3% of the world's population [1]. It is a common skin disease associated with multiple comorbidities and the most prevalent coexisting condition, psoriatic arthritis (PsA) develops in 19,7% of psoriatic patients [2].

In majority of the patients, arthritis is manifested following psoriasis, and in others, it develops simultaneously or before the appearance of skin lesions [3]. Spinal manifestations resemble those in ankylosing spondylitis, and destructive peripheral joint characteristics resemble those of rheumatoid arthritis [4]. Pathologic *de novo* bone formation, including joint ankylosis, and syndesmophyte formation, characteristically localize to sites of soft-tissue inflammation surrounding the enthesis [5].

Osteoporosis is a systemic skeletal disease characterized by reduced bone mass, microarchitectural damage and increased fragility of bone. Bone loss is a common comorbidity in chronic inflammatory diseases including PsA [6]. A systematic review by Chandran et al, where 21 studies conducted between

2001 and 2014 were included, highlighted the gap in our current knowledge given the non-consensual findings reported on the prevalence of low bone mineral density in PsA [7].

Osteoporosis has been operationally defined on the basis of bone mineral density (BMD) assessment. The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DEXA), and diagnostic criteria based on the T-score for BMD are a recommended criteria for prescription of pharmaceutical interventions in osteoporosis [8]. According to the WHO criteria, osteoporosis is defined as a BMD that lies ≤ 2.5 standard deviations below the average value for young healthy women (T-score ≤-2.5 SD) [9, 10]. A major problem with BMD measurement is that these tests alone are not optimal for the detection of individuals at high risk of fracture [11].

On the other hand, peripheral quantitative computed tomography (pQCT) is excellent at three-dimensional quantification of cortical and trabecular bone at various regions of interest, *albeit*, is not recommended for conventional diagnostic classification [12]. Recent reports have discussed the techniques' utility in patients suffering from inflammatory rheumatic disease [13, 14].

Fragility fractures are defined as fractures that occur spontaneously or following low-trauma and are potential cause of severe disability along with increased mortality risk [9]. Major advance in fragility fracture risk stratification has been achieved by the development of the fracture risk assessment tool (FRAX). The FRAX tool is based on country specific population-based cohorts that assimilate the risks associated with clinical risk factors (age, sex, body mass index, prior fragility fracture, parental history of hip fracture, steroid use, smoking, alcohol intake, disorders strongly associated with osteoporosis and rheumatoid arthritis) and bone mineral density (BMD) at the femoral neck. The percentage output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture) [15]. Given the clinical, social and economic burden of osteoporotic fractures, the FRAX tool is considered ideal in identifying those at risk and advancing timely preventive or therapeutic interventions.

Presently, studies on complex assessment of areal and volumetric bone mineral density, fracture risk with the FRAX tool, vitamin D and markers of bone turnover in the same cohort of PsA patients are unavailable and the aim of the present cross-sectional, case-controlled study is to examine bone metabolism and evaluate its association with disease variables.

Patients And Methods

Patients and controls:

We enrolled a total of 118 patients presenting for regular scheduled follow-up at the Division of Rheumatology, Faculty of Medicine, University of Debrecen, between September 2017 and June 2018. All were diagnosed with PsA as per the Classification Criteria for Psoriatic Arthritis (CASPAR) [16]. Data from patients with psoriatic arthritis was compared to age- and gender-matched healthy volunteers. The age and sex-matched control group was recruited from staff, and escorts of patients presenting for routine

follow-up. Volunteers with the closest dates of birth and with blood drawn in the same meteorological season were selected for pairing with their PsA counterparts. All study participants gave written informed consent. The study was performed according to the Declaration of Helsinki and approved by the Hungarian Scientific Research Council Ethical Committee (approval No. 14804-2/2011/EKU).

Disease activity:

All patients underwent physical examination and disease severity assessment. Disease Activity Score in 28 joints (DAS28), in those with peripheral involvement, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), in those with spinal involvement, and Psoriasis Area and Severity Index (PASI) were calculated [17–19].

Laboratory:

Blood sampling was done after overnight fasting to measure levels of 25-hydroxyvitamin D (25OHD), parathyroid hormone (PTH), osteocalcin (OC), C-terminal telopeptides of type-I collagen (CTx), and procollagen type I amino-terminal propeptide (PINP). Serum 25-OH-D was analyzed using the automated Liaison DiaSorin total 25OHD chemiluminescence immunoassay (CLIA) (DiaSorin Inc., Stillwater, MN, USA). Serum PTH, OC, CTx, and PINP were measured using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). The inter-assay CV was < 7.8% for 25-OH-D (lower detection limit: 10 nmol/L, upper detection limit: 375 nmol/L), < 7% for PTH (lower detection limit: 0.127 pmol/L, upper detection limit: 530 pmol/L), < 4% for OC (lower detection limit: 0.5 µg/L, upper detection limit: 300 µg/L), < 7% for CTx (lower detection limit: 0.010 µg/L, upper detection limit: 6 µg/L), and < 6% for PINP (lower detection limit: 5 µg/L, upper detection limit: 1200 µg/L). Hypovitaminosis D was defined as 25-OH-D levels < 75 nmol/l as suggested by Dawson-Hughes et al [20] The erythrocyte sedimentation rate (ESR) was assessed with the Westergren method [21] and used in the calculation of the DAS28 score.

Dual energy X-ray absorptiometry:

Dual energy X-ray absorptiometry (DEXA) examination was performed using the LUNAR Prodigy (GE-Lunar Corp., Madison, WI, USA) densitometer. Areal BMD was measured at L1–L4 lumbar spine and left femur neck (FN). The coefficient of variation (CV) of the technique at our institute was 0.8% using the anatomical spine phantom measured daily. BMD was expressed as a T score, normalcy, osteopenia and osteoporosis were defined according to the WHO classification [10].

Peripheral quantitative computer tomography (pQCT):

Single-slice pQCT assessments of the ultradistal region of the left forearm were performed using a Stratec XCT-2000 instrument (Stratec Medizintechnik GmbH, Pforzheim, Germany) as described by Juhasz et al [13]. In summary, distal sites at 4% of the radius length mainly contain trabecular bone. pQCT can differentiate between cortical and trabecular bone. Total, trabecular, and cortical BMD values are expressed as mg/cm^3. The applied setting to acquire the image was 0.59 mm voxel. Analysis was

done with the XCT 6.00 B software (Stratec Medizintechnik GmbH, Pforzheim, Germany) with measuring mask set to radius and threshold density to 269 mg/cm^3 to define trabecular bone.

FRAX:

A trained study nurse administered a questionnaire to assess the country-specific FRAX index using the tool available online [15]. The data collected was age, sex, weight, height, non-traumatic fracture in the history, parental history of hip fracture, current smoking and alcohol consumption habits, corticosteroid use, diagnosis of rheumatoid arthritis or any condition known to cause low bone mass and femoral BMD.

Statistical analysis:

Descriptive statistics are presented, as applicable, as mean, range and standard deviation (SD). The Kolmogorov-Smirnov test was used to check for normality of distribution. The Wilcoxon signed ranks test was used to compare the age- and gender-matched pairs. The Spearman's ρ was calculated for correlation analysis. Univariate and multiple regression analysis using the stepwise method was used to determine correlations and independent associations between parameters. DEXA, pQCT and FRAX parameters were the dependent variables and other parameters were independent variables. The β standardized linear coefficients showing linear correlations between two parameters were determined. The B (+ 95% CI) regression coefficient indicated independent association between the dependent and independent variable during changes. *p* values < 0.05 indicated statistical significance. All analyses were performed using the SPSS Statistics software, version 25.0 (IBM Corps., Armonk, NY, USA).

Results

Patients (n = 118) presenting with psoriatic arthritis, confirming to the CASPAR diagnostic criteria, were included in this cross-sectional, analyst blinded, age- and sex-matched, case-control study [16]. The mean age (range) of the patients was 53 (25–85) years, with a women:men ratio of 67:51. The mean (range) disease duration for psoriasis and arthritis was 18.4 (1–72) and 11.2 (0–39) years, respectively. In a small percentage of the patients (n = 14, 12%), the diagnosis of psoriasis was confirmed following the diagnosis of arthritis (on an average within 5 years). Compared to the controls, L1-L4 areal BMD (1.281 ± 0.169 gm/cm^2 vs. 1.192 ± 0.195 gm/cm^2; p < 0.001), FN areal BMD (1.034 ± 0.148 gm/cm^2 vs. 0.955 ± 0.145 gm/cm^2; p = 0.001), distal radius (DR) total volumetric BMD (369.6 ± 23.6 gm/cm^3 vs. 285.7 ± 61.8 gm/cm^3; p < 0.001), DR trabecular volumetric BMD (200.6 ± 19.5 gm/cm^3 vs. 187.6 ± 47.1 gm/cm^3; p = 0.002), DR cortical volumetric BMD (515.9 ± 39.9 gm/cm^3 vs. 361.6 ± 92.3 gm/cm^3; p < 0.001) and 25OHD (67 (10–137) nmol/L vs. 53 (10–120) nmol/L; p < 0.001) was significantly lower, and the 10 year probability for a major osteoporotic fracture (3.5 (0-17.5) % vs. 5.0 (0.7–35) %; p = 0.003) and hip fracture (0.5 (0-6.1) % vs. 1.1 (0–16) %; p = 0.002), CTx (0.223 (0.100–0.511) µg/L vs. 0.302 (0.040–1.090) µg/L; p < 0.001) and PINP (35.6 (8.2–72.5) µg/L vs. 49.3 (11.0-253.7) µg/L; p < 0.001) were significantly higher in the PsA group (Table 1). The frequency of normal, osteopenia and osteoporotic BMD in PsA patients at

different regions of interest is presented in Table 2. Areal and volumetric BMD showed statistically significant correlation with each other (Table 3).

Table 1
Subject characteristics.

Parameters	All patients (n = 118)	All controls (n = 118)	*p* value
Age, years (mean, range)	53 (25–85)	53 (25–85)	1.000
Women:Men	67:51	67:51	1.000
DAS28, % (mean, range) (n = 110)	2.60 (0.49–5.85)	-	-
BASDAI, % (mean, range) (n = 8)	1.51 (0.02–3.08)	-	-
PASI, % (mean, range)	3.22 (0-29.40)	-	-
Arthritis duration, years (mean, range)	11.2 (0–39)	-	-
Psoriasis duration, years (mean, range)	18.4 (1–72)	-	-
FRAX Major, % (mean, range) (n = 100)	5.0 (0.7–32)	3.5 (0-17.5)	0.003
FRAX Hip, % (mean, range) (n = 100)	1.1 (0–16)	0.5 (0-6.1)	0.002
10 year probability of major osteoporotic fracture ≥ 20% (n, %)	1 (1%)	0 (0%)	-
10 year probability of hip fracture ≥ 3% (n, %)	8 (8%)	4 (4%)	-
L1-L4 areal BMD, g/cm^2 (mean ± SD)	1.192 ± 0.195	1.281 ± 0.169	< 0.001
Femur neck areal BMD, g/cm^2 (mean ± SD)	0.955 ± 0.145 (n = 117)	1.034 ± 0.148	0.001
Distal radius total volumetric BMD, mg/cm^3 (mean ± SD)	285.7 ± 61.8	369.6 ± 23.6	< 0.001
Distal radius trabecular volumetric BMD, mg/cm^3 (mean ± SD)	187.6 ± 47.1	200.6 ± 19.5	0.002
Distal radius cortical volumetric BMD, mg/cm^3 (mean ± SD)	361.6 ± 92.3	515.9 ± 39.9	< 0.001
Calcium, mmol/L (mean, range)	2.4 (2.2–2.7)	2.3 (2.1–2.7)	< 0.001
Phosphate, mmol/L (mean, range)	0.96 (0.6–1.6)	1.07 (0.6–1.51)	< 0.001

DAS28: Disease activity Score in 28 joints; BASDAI: Ankylosing spondylitis disease activity index; PASI: Psoriasis area and severity index; FRAX Major: 10-year probability of a major osteoporotic fracture as assessed by the FRAX tool; FRAX Hip: 10-year probability of a hip osteoporotic fracture as assessed by the FRAX tool; BMD: bone mineral density; CTx: C-terminal telopeptides of type-I collagen; PINP: procollagen type I amino-terminal propeptide; PTH: parathyroid hormone; 25OHD: 25-hydroxyvitamin D. *Femur neck BMD assessment was not performed for one patient as she had bilateral total hip replacement.

Parameters	All patients (n = 118)	All controls (n = 118)	*p* value
Osteocalcin, µg/L (mean, range)	19.6 (5–77)	17.9 (8.6–33)	0.186
CTx, µg/L (mean, range)	0.302 (0.040–1.090)	0.223 (0.100–0.510)	< 0.001
PINP, µg/L (mean, range)	49.3 (11.0-253.7)	35.6 (8.2–72.5)	< 0.001
PTH, pmol/L (mean, range)	4.77 (1.43–11.69)	3.78 (1.6–9.6)	< 0.001
25OHD, nmol/L (mean, range)	53 (10–120)	67 (10–137)	< 0.001
25OHD < 75 nmol/L	79% (n = 93)	58% (n = 68)	-
25OHD < 50 nmol/L	49% (n = 58)	28% (n = 33)	-

DAS28: Disease activity Score in 28 joints; BASDAI: Ankylosing spondylitis disease activity index; PASI: Psoriasis area and severity index; FRAX Major: 10-year probability of a major osteoporotic fracture as assessed by the FRAX tool; FRAX Hip: 10-year probability of a hip osteoporotic fracture as assessed by the FRAX tool; BMD: bone mineral density; CTx: C-terminal telopeptides of type-I collagen; PINP: procollagen type I amino-terminal propeptide; PTH: parathyroid hormone; 25OHD: 25-hydroxyvitamin D. *Femur neck BMD assessment was not performed for one patient as she had bilateral total hip replacement.

Table 2

T Score categories based on femur neck and lumbar spine areal bone mineral density (BMD), and distal radius volumetric BMD in PsA patients.

Region of Interest	Normal (n,%)	Osteopenia (n,%)	Osteoporosis (n,%)
Femur neck (n = 117)	77, 66%	35, 30%	5, 4%
L1-L4 lumbar spine	82, 70%	32, 27%	4, 3%
Distal Radius (total)	14, 12%	66, 56%	38, 32%

Normal: T Score ≥ -0.99; Osteopenia: T Score between − 1.00 and − 2.49; Osteoporosis: T Score ≤ -2.50.

Table 3
Correlation analysis between areal and volumetric bone mineral density

			Areal		Volumetric Distal Radius		
	Region of Interest		**Femur Neck**	**L1-L4**	**Total**	**Trabecular**	**Cortical**
Areal	**Femur neck**	Spearman's ρ	1.000	0.526	0.496	0.374	0.422
		p value	-	< 0.001	< 0.001	< 0.001	< 0.001
	L1-L4	Spearman's ρ	0.526		0.488	0.343	0.421
		p value	< 0.001		< 0.001	< 0.001	< 0.001
Volumetric Distal Radius	**Distal Radius (total)**	Spearman's ρ	0.496	0.488		0.601	0.842
		p value	< 0.001	< 0.001		< 0.001	< 0.001
	Trabecular	Spearman's ρ	0.374	0.343	0.601		0.377
		p value	< 0.001	< 0.001	< 0.001		< 0.001
	Cortical	Spearman's ρ	0.422	0.421	0.842	0.377	
		p value	< 0.001	< 0.001	< 0.001	< 0.001	

Fracture risk characteristics used in the FRAX tool are presented in Table 4 for PsA patients (n = 100) between 40 and 90 years of age. A 10 year probability of ≥20% for major osteoporotic fracture and 10 year probability of ≥3% for hip fracture was observed in 1 (1%) and 8 (8%) patients, respectively. One patient had probability above treatment threshold for both fracture types.

Table 4
Patients' fracture risk characteristics used in the FRAX tool.

Risk Factors	Patients between 40 and 90 years of age (n = 100)
Age, years (mean, range)	57 (40–85)
Male:Female	42:58
Weight (kg) (mean, range)	84 (48–125)
Height (cm) (mean, range)	166 (150–188)
Previous Fracture (n, %)	22 (22%)
Parent Fractured Hip (n, %)	4 (4%)
Current Smoking (n, %)	10 (10%)
Glucocorticoids (n, %)	20 (20%)
Rheumatoid Arthritis (n, %)	0 (0%)
Secondary Osteoporosis (n, %)	16 (16%)
Alcohol 3 or more units/day (n, %)	0 (0%)
Femur neck areal BMD, g/cm^2 (mean ± SD) (n = 99)	0.941 ± 0.136
FRAX Major, % (mean, range)	5.0 (0.7–32)
FRAX Hip, % (mean, range)	1.1 (0–16)
10 year probability of major osteoporotic fracture ≥ 20% (n, %)	1 (1%)
10 year probability of hip fracture ≥ 3% (n, %)	8 (8%)

A total of 53 (44.9%) and 62 (52.5%) of the patients were on conventional (Methotrexate, Leflunomide, Hydroxychloroquine or Sulphosalazine) and biologic (Infliximab, Adalimumab, Etanercept, Rituximab, Abatacept, Tocilizumab, Certolizumab, Golimumab or Ustekinumab) disease-modifying anti-rheumatic drugs (DMARD), respectively, either as monotherapy or in a combination. Three (2.5%) PsA patients did not receive therapy as they were suffering from malignant conditions (prostate cancer, breast cancer and malignant melanoma).

Upon univariate analysis of the PsA cohort data, patients with lower FN areal BMD were older, with longer duration of psoriasis and arthritis disease duration, and those with higher FN areal BMD had higher body mass index (BMI) ($p<0.05$); women had significantly lower L1-L4 areal BMD ($p<0.05$); those with lower DR total volumetric BMD were older and had longer menopause duration ($p<0.05$); older patients and women had lower DR trabecular volumetric BMD and those with higher DR trabecular volumetric BMD had longer fertility duration ($p<0.05$); those with lower DR cortical volumetric BMD were older ($p<0.05$); the 10 year

probability of major osteoporosis fracture was higher in patients with more severe disease as evaluated by DAS28, longer psoriasis and arthritis disease duration, and menopause duration ($p<0.05$); and the 10 year probability of hip fracture was higher in patients with longer psoriasis and arthritis disease, and menopause duration, in those on conventional DMARDs and insufficient vitamin D status with 25OHD levels < 75 nmol/L or < 50 nmol/L ($p<0.05$) (Table 5).

Table 5
Comparison of PsA patient subsets by univariable analyses

Dependent variable	Independent variable	Univariate analysis		
		B (95% CI)	β	p value
Femur neck areal BMD	Age	-0.003 (-0.005 - -0.001)	-0.307	0.001
	Psoriasis duration	-0.002 (-0.005– 0.000)	-0.211	<0.001
	Body Mass Index	0.004 (0.000– 0.009)	0.180	0.050
	Arthritis duration	-0.005 (-0.008 – -0.002)	-0.286	0.002
L1-L4 areal BMD	Sex (women vs. men)	-0.068 (-0.139 - -0.001)	-1.174	0.049
Distal radius total volumetric BMD	Age	-1.563 (-2.397 - -0.729)	-0.326	<0.001
	Menopause duration	-2.213 (-4.070 - -0.356)	-0.352	0.021
Distal radius trabecular volumetric BMD	Age	-0.836 (-1.491 - -0.181)	-0.228	0.031
	Sex (women vs. men)	-24.338 (-41.172 - -7.505)	-0.257	0.005
	Fertility duration	2,482 (0.124– 4.480)	0.315	0.040
Distal radius cortical volumetric BMD	Age	-2.116 (-3.376 - -0.857)	-0.295	0.001
10 year probability of major osteoporotic fracture	DAS28	1.351 (0.379– 2.323)	0.277	0.007
	Psoriasis duration	0.085 (0.001– 0.170)	0.198	0.048
	Arthritis duration	0.165 (0.045– 0.286)	0.265	0.008
	Menopause duration	0.348 (0.142– 0.554)	0.470	0.001

BMD: Bone mineral density; DAS28: Disease activity Score in 28 joints; cDMARD: Conventional disease-modifying anti-rheumatic drugs; bDMARD: Biologic disease-modifying anti-rheumatic drugs; 25OHD: 25-hydroxyvitamin D.

Dependent variable	Independent variable	Univariate analysis		
		B (95% CI)	β	p value
	cDMARD vs bDMARD	-2.890 (-5.049 - -0.731)	-0.259	0.009
10 year probability of hip fracture	Psoriasis duration	0.054 (0.008–0.100)	0.230	0.021
	Arthritis duration	0.080 (0.013–0.146)	0.233	0.020
	Menopause duration	0.178 (0.051–0.305)	0.405	0.007
	cDMARD vs bDMARD	-1.664 (-2.841 - -0.487)	-0.273	0.006
	< 75 nmol/L vs ≥75 nmol/L 25OHD	-1.800 (-3.317 - -0.284)	-0.232	0.020
	< 50 nmol/L vs ≥50 nmol/L 25OHD	-1.405 (-2.598 - -0.213)	-0.230	0.021

BMD: Bone mineral density; DAS28: Disease activity Score in 28 joints; cDMARD: Conventional disease-modifying anti-rheumatic drugs; bDMARD: Biologic disease-modifying anti-rheumatic drugs; 25OHD: 25-hydroxyvitamin D.

Multiple linear regression analyses revealed that age was an independent predictor of both areal and volumetric BMD. Additionally, BMI and arthritis disease duration also predicted FN areal BMD, female sex was an independent predictor of DR trabecular volumetric BMD. DAS28 disease activity score predicted the 10 year probability of major osteoporosis fracture and conventional DMARD predicted the 10 year probability of hip fracture (Table 6).

Table 6
Multiple regression analysis of bone mineral density and 10-year fracture probability.

Dependent variable	Independent variable	Multivariable analysis		
		B (95% CI)	β	p value
Femur neck areal BMD	Age	-0.004 (-0.006 - -0.002)	-0.334	<0.001
	Body Mass Index	0.006 (0.002–0.011)	0.266	0.003
	Arthritis duration	-0.003 (-0.006–0.000)	-0.184	0.039
Distal radius total volumetric BMD	Age	-1.563 (-2.397 - -0.729)	-0.326	<0.001
Distal radius trabecular volumetric BMD	Age	-0.905 (-1.538 - -0.272)	-0.247	0.005
	Sex (women vs. men)	-25.947 (-42.333 - -9.560)	-0.274	0.002
Distal radius cortical volumetric BMD	Age	-2.116 (-3.376 - -0.857)	-0.295	0.001
10 year probability of major osteoporotic fracture	DAS28	1.351 (0.379–2.323)	0.277	0.007
10 year probability of hip fracture	cDMARD vs. bDMARD	-1-139 (-2.270 - -0.009)	-0.187	0.048

BMD: Bone mineral density; DAS28: Disease activity Score in 28 joints; cDMARD: Conventional disease-modifying anti-rheumatic drugs; bDMARD: Biologic disease-modifying anti-rheumatic drugs; 25OHD: 25-hydroxyvitamin D.

The prevalence of hypovitaminosis D (25-OH-D < 75 nmol/L) was 79% and 58% in the PsA and control groups, respectively. A significant association was found between hypovitaminosis D and PsA; the odds for PsA patients to suffer with hypovitaminosis D was 2.74 (95%CI 1.54–4.85, p < 0.001).

Discussion

Both areal and volumetric bone mineral density in our patient population was significantly lower than the age and sex-matched controls. This finding is in agreement with a number of studies that have reported PsA patients with an increased risk of low areal bone mineral density [22–27]. But simultaneously is in disagreement with another series of studies that did not report low areal BMD [28–33]. This dichotomy may be due to the non-consistent comparison groups and reported outcomes. Our finding of FN areal BMD significantly correlating with disease duration supports similar previous findings [24, 31, 34].

BMD measured by pQCT have been reported previously by Kocijan et al [35]. Kocijan et al reported that trabecular and not cortical density was significantly lower in the patient population as compared to the controls, this finding is in contrast to our results of decreased trabecular and cortical density in the patient population. A probable explanation for this discrepancy may be due to the fact that our patient cohort is older, with longer psoriasis and arthritis disease duration. The present study is the first where areal BMD has been compared to volumetric BMD in PsA patients, with statistically significant correlation between the two methodologies. This finding is in tally with 2 other studies in patients with inflammatory rheumatic disease [13, 14].

We observed a significantly increased 10-year probability of both major and hip osteoporotic fractures as assessed by the FRAX tool in the studied Hungarian patients with psoriatic arthritis. Probability of fragility fractures has not been reported previously in PsA patients using the FRAX tool. Our probability findings are in concordance with findings where osteoporotic fractures were studied as primary endpoints, reporting higher odds of diagnosis with pathological fractures and elevated risk of all fractures [22, 36, 37]. A cross-sectional study from Spain reported increased prevalence of fragility fractures in postmenopausal PsA patients [28]. A Brazilian study reported longer disease duration as predictor of low-impact fractures [26]. Nonetheless, an Italian study reported no difference in the prevalence of fragility fractures between cases and controls [38].

Beside known predictors of the 10-year probability of fragility fractures, i.e., age and BMD, our findings suggest that in PsA, severe disease activity as assessed by DAS28 is also a noteworthy risk factor.

FRAX assessment and DR volumetric BMD measurement are excellent alternatives when FN BMD cannot be measured, as in our study where one patient had total bilateral hip replacement.

Although patients identified as being osteoporotic with FN areal BMD measurement were also classified as osteoporotic with DR volumetric BMD measurement, volumetric measurements identified a significantly greater number of patients with low bone mass (34% vs. 88%, $p<0.001$). Although manufacturer provided German reference population is used to derive the T-score with both methodologies, the absence of agreement has also been reported by Marshall et al [39].

Fracture risk assessment using the FRAX tool identified more patients deserving anti-osteoporosis treatment as compared to FN areal BMD assessment (n = 8 vs. n = 6). Patients with major osteoporotic or hip fracture probability in the intervention range, i.e, ≥20% (n = 8) and ≥3% (n = 1), respectively, were also osteoporotic when assessed for DR volumetric BMD, nonetheless, a wide discrepancy was noticed as a significant proportion of the cohort with non-intervention level FRAX probability was identified as osteoporotic (n = 28, 24%). The FRAX tool offers optional inclusion of FN areal BMD and its clinical utility in identification of those at increased risk of fragility fractures may be improved were volumetric BMD values and psoriatic arthritis, as a secondary risk factor, also facilitated in the calculation of fracture probability.

The FRAX tool is designed to assess those between 40 and 90 years of age, given this inherent limitation the fracture probability of the young cannot be assessed. Among those under 40 years of age (n = 18), areal FN BMD assessment identified 3 (17%) and DR volumetric BMD examination identified 16 (89%) psoriatic arthritis patient with low bone density (T Score ≤ -1.0). Our observation suggests that volumetric BMD assessment better identifies those at increased fracture probability, and offers opportunity to initiate fracture risk reduction intervention promptly at a younger age. The true burden to osteoporosis may be underestimated with areal BMD measurement alone.

The Hungarian National Healthcare System subsidises antiosteoporotic therapy for those with an osteoporotic T score, based on the WHO classification (T Score ≤-2.5), or with FRAX probability of more than 3% and 20% for hip and major osteoporotic fracture, respectively. Our results suggests that a number of osteoporotic and osteopenic patients deserving fracture risk reducing intervention are missed using areal BMD measurement alone, and as such FRAX assessment.

As compared to the control groups, the studied biochemical markers of bone turnover were significantly elevated suggesting a high bone turnover in the PsA population. This finding is supported by one previous study [40]. Grisar et al reported that CTx levels were significantly higher in the PsA group as compared to the healthy controls [29]. Szentpetery et al reported correlation between the studied bone markers and hand BMD [41]. Borman et al reported correlation between CTx and duration of arthritis and no difference in marker levels comparing patients with and without arthritis [27]. Nonetheless, in our study we found no correlation between the studied parameters and bone markers. The inconsistency in bone marker results in the numerous studies published has been summarized in a review by Jadon et al [42].

Our finding of high hypovitaminosis D prevalence is in concordance with results from quite a few previous studies [40, 43–45]. Although a study has reported that there is no difference in vitamin D levels between patients suffering from psoriasis with and without arthritis, correlation between disease activity and vitamin D levels has also been reported inconsistently [11, 40]. A probable predisposition for hypovitaminosis D in the PsA cohort may be due to the debilitating nature of their condition, and as such, they may not involve in physical activity that may be naturally assumed for a healthy age- and sex-matched counterpart; in addition, patients may shy away from outdoor activity given the psychological burden of their skin condition.

Although not supported by correlation analysis in our study cohort, hypovitaminosis D, high bone turnover and low bone mass may contribute to the increased fragility fracture probability in this population.

There are limitations to our study. Due to difficulties in getting access to the local population register and no commercially available population registers, we employed a method where recruitment of healthy volunteers may have been biased. Validation of our results is deemed mandatory optimally with a substantially larger cohort.

A higher number of study participant could have improved the statistical power of our analyses, nonetheless, we report a high 10-year probability of fragility fractures along with an increased prevalence of hypovitaminosis D in a PsA cohort complemented with low bone mass and high bone turnover; furthermore, the comparison to a systematically selected healthy age- and gender-matched population discards the effect of confounding risk factors.

Although warranting validation, the clinical utility of volumetric BMD examination complemented with traditional DEXA-based areal BMD measurement and FRAX assessment, are readily applicable in the PsA patient population and serve as an inexpensive tool in identifying those at increase fracture risk. Prompt identification, treatment and follow-up of patients at risk would help in reducing the burden of fragility fractures in the PsA patient population.

Conclusion

In the studied PsA cohort, disease activity was an independent predictor of 10-year probability for a major osteoporotic fracture, and complemented assessment of volumetric and areal BMD assured better efficacy at identifying those with low bone mass.

Abbreviations

25OHD 25-hydroxyvitamin D

BASDAI Bath ankylosing spondylitis disease activity index

bDMARD Biologic disease-modifying anti-rheumatic drugs

BMD Bone mineral density

BMI Body mass index

CASPAR Classification criteria for psoriatic arthritis

cDMARD Conventional disease-modifying anti-rheumatic drugs

CLIA Chemiluminescence immunoassay

CTx C-terminal telopeptides of type-I collagen

CV Coefficient of variation

DAS28 Disease activity score in 28 joints

DEXA Dual energy X-ray absorptiometry

DMARD Disease-modifying anti-rheumatic drugs

DR Distal radius

ESR Erythrocyte sedimentation rate

FN Femur neck

FRAX Fracture risk assessment

L1-L4 Lumbar vertebrae L1 to L4

OC osteocalcin

OTKA Hungarian national scientific research fund

PASI Psoriasis area and severity index

PINP Procollagen type I amino-terminal propeptide

pQCT Peripheral quantitative computed tomography

PsA Psoriatic arthritis

PTH Parathyroid hormone

WHO World Health Organization

Declarations

Ethics approval and consent to participate:

All study participants gave written informed consent. The study was performed according to the Declaration of Helsinki and approved by the Hungarian Scientific Research Council Ethical Committee (approval No. 14804-2/2011/EKU).

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

ZP recruited patients, coordinated patient examinations, performed peripheral qCT examinations, administered questionnaires, collected and interpreted data and contributed in writing the manuscript. EK performed the routine laboratory examinations and contributed in writing the manuscript. ZP contributed in data collection and writing the manuscript. KH did the statistical analyses. RF administered questionnaires, contributed in data collection and writing the manuscript, AB conceived the study design and contributed in writing the manuscript. ZS conceived the study design, interpreted data and contributed in writing the manuscript and its critical evaluation. HPB conceived the study design, interpreted data and was a major contributor in writing the manuscript and its critical evaluation.

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