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ORIGINAL ARTICLE

Bone microstructure and volumetric bone mineral density in patients with hyperuricemia with and without psoriasis

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Abstract

Summary We analyzed volumetric bone mineral density (vBMD) and bone microstructure using HR-pQCT in subjects with normouricemia (NU) and subjects with hyperuricemia (HU) with and without psoriasis (PSO). HU was associated with higher cortical vBMD and thickness. Differences in average and trabecular vBMD were found between patients with PSO + HU and NU.

Introduction Hyperuricemia (HU) and gout are co-conditions of psoriasis and psoriatic arthritis. Current data suggest a positive association between HU and areal bone mineral density (BMD) and a negative influence of psoriasis on local bone, even in the absence of arthritis. However, the influence of the combination of HU and psoriasis on bone is still unclear. The aim of this study was to assess the impact of HU with and without psoriasis on bone microstructure and volumetric BMD (vBMD).

Methods Healthy individuals with uric acid levels within the normal range (NU), with hyperuricemia (HU), patients with hyperuricemia and psoriasis (PSO + HU), and patients with uric acid within the normal range and psoriasis (PSO + NU) were included in our study. Psoriasis patients had no current or past symptoms of arthritis. Average, trabecular, and cortical vBMD (mgHA/cm^3); trabecular number (Tb.N, 1/mm) and thickness (Tb.Th, mm); inhomogeneity of the network (1/N.SD, mm); and cortical thickness (Ct.Th., mm) were carried out at the ultradistal radius using high-resolution peripheral quantitative computed tomography. In addition, bone turnover markers such as DKK-1, sclerostin, and P1NP were analyzed.

Results In total, 130 individuals were included (44 NU participants (34% female), 50 HU (24%), 16 PSO + HU (6%), 20 PSO + NU (60%)). Subjects were aged: NU 54.5 (42.8, 62.1), HU 57.5 (18.6, 65.1), PSO + HU 52.0 (42.3, 57.8), and PSO + NU 42.5 (34.8, 56.8), respectively. After adjusting for age, sex, BMI, and diabetes, patients in the HU group revealed significantly higher values of cortical vBMD ($p < 0.001$) as well as cortical thickness ($p = 0.04$) compared to the NU group. PSO + NU showed no differences to NU, but PSO + HU demonstrated both lower average ($p = 0.03$) and trabecular vBMD ($p = 0.02$). P1NP was associated with average, cortical, and trabecular vBMD as well as cortical thickness while sclerostin levels were related to trabecular vBMD.

Conclusion Hyperuricemia in otherwise healthy subjects was associated with a better cortical vBMD and higher cortical thickness. However, patients with both psoriasis and hyperuricemia revealed a lower vBMD.

Keywords HR-pQCT · Psoriasis · Hyperuricemia · Bone Mineral Density

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Introduction

Hyperuricemia (HU) is a common phenomenon in the western world [1] and is associated with numerous conditions including gouty arthritis, metabolic syndrome, and cardiovascular diseases [2, 3]. When serum uric acid levels reach the solubility limit, the solution is considered supersaturated and monosodium urate (MSU) crystal formation starts. MSU crystals induce the expression of resorptive cytokines such as IL-1, IL-6, and TNFα in monocytes. Moreover, infiltrating T cells promote RANKL and consequently osteoclastogenesis under inflammatory conditions [4].

Clinical data regarding systemic bone loss suggest a beneficial role rather than a risk factor for HU. A positive association for uric acid and areal bone mineral density (aBMD) and an inverse correlation to bone turnover markers was reported [5]. High uric acid levels were found to be associated with a low prevalence and incidence of vertebral and non-vertebral fractures in several studies [6, 7]. A tenable explanation for these findings may be the anti-oxidative capacity of uric acid and therefore a protective effect on systemic bone loss [8]. Regrettably, previous studies focused exclusively on aBMD and no applicable data are available on bone microstructure—one of the main components of bone strength.

Numerous studies have shown the association between chronic inflammatory joint disorders and systemic bone loss. Our study group previously showed that rheumatoid arthritis and psoriatic arthritis are associated with altered bone microstructure [9, 10], and thereby osteoporosis. Deteriorations of bone microstructure measured by high-resolution peripheral quantitative computed tomography (HR-pQCT) were also reported in the pre-stages of rheumatic diseases without clinical signs of inflammation [11, 12]. Skin psoriasis, which usually precedes psoriatic arthritis, appears to be associated with local and systemic bone reaction and subclinical inflammation [13]. In addition, the duration of skin psoriasis was reported to be uniquely associated to trabecular bone loss in patients with psoriatic arthritis [10].

Hyperuricemia and gout are well-known comorbidities of psoriasis and psoriatic arthritis [14, 15]. Patients with psoriasis show higher levels of uric acid due to excessive turnover of keratocytes in psoriatic plaques. Conversely, monosodium urate crystals can induce cell proliferation in skin psoriatic plaques [16]. Consequently, psoriasis is an independent risk factor for gout and hyperuricemia and further supports the development of psoriatic arthritis [17]. This has also been shown in an animal model, where psoriasis-like symptoms were induced when animals were fed food containing uric acid [16]. Interestingly, patients with psoriasis and hyperuricemia showed marked improvement in psoriasis when treated for their elevated uric acid [16].

Typically, psoriasis precedes psoriatic arthritis and hyperuricemia precedes gout. As inflammatory joint diseases are well-known factors for systemic bone loss and psoriasis is often connected to hyperuricemia or gout [18, 19], the hypothesis of this study was to test whether hyperuricemia—with or without psoriasis—is associated with changes in volumetric bone mineral density (vBMD) and bone microstructure.

Accordingly, the primary objectives were to establish and compare vBMD and microstructure measured by HR-pQCT between (i) healthy subjects with normal serum uric acid with (ii) subjects with hyperuricemia without psoriasis, (iii) psoriasis patients with hyperuricemia, and (iv) psoriasis patients with normal serum uric acid.

Secondary objectives were to determine bone turnover markers including Sclerostin and Dickkopf-1 and to evaluate a possible relationship between volumetric bone mineral density, microstructure, and bone turnover markers in patients with hyperuricemia.

Materials and methods

Study participants

In this case-controlled, two-center study, healthy subjects with normal levels of uric acid (NU), subjects with hyperuricemia (HU), psoriasis patients with hyperuricemia (PSO + HU), and psoriasis patients with normal levels of uric acid (PSO + NU) were included. Subjects were seen between 2014 and 2016 in the inpatient and outpatient units of the II. Medical Department for Bone Diseases and Rheumatology of the St. Vincent Hospital Vienna, Austria; in the Dermatology Clinic of the University of Erlangen-Nuremberg, Germany; and in the Department of Internal Medicine 3 for Rheumatology and Immunology of the University of Erlangen-Nuremberg, Germany. Patients of the University of Erlangen-Nuremberg were part of the Erlangen Imaging Cohort (ERIC), which assesses articular and peri-articular bone composition in healthy controls and patients with inflammatory arthritis, respectively [20].

All subjects were interviewed and medical records were reviewed for any obvious exclusion criteria. Healthy controls were matched for age but not for height, weight, or BMI. No special matching algorithm was used.

Subjects were included in the present study if they were male or female, 30–70 years old and had a serum uric acid > 7.0 mg/dl (HU), or suffered from skin psoriasis without any signs of arthritis and had a serum uric acid > 7.0 mg/dl (PSO + HU) or suffered from skin psoriasis without any signs of arthritis and had a serum uric acid < 6 mg/dl (PSO + NU) or had a serum uric acid ≤ 6 mg/dl (NU). Participants in the HU group never showed symptoms of arthritis and did not fulfill the 2015 gout classification criteria [21]. PSO + HU and PSO + NU patients were referred from the Dermatology Clinic with the diagnosis of plaque psoriasis as determined

by an experienced dermatologist (MS). PSO + HU and PSO + NU patients were then examined by an experienced rheumatologist (JR, AK). Individuals with any signs of musculoskeletal involvement or who met the Classification Criteria for Psoriatic Arthritis criteria (CASPAR) [22] were excluded. Subjects were also excluded if they suffered from severe comorbidities or metabolic bone disorders. Subjects were not allowed to take urate-lowering therapy including xanthine oxidase inhibitors (allopurinol, febuxostat), or medication interfering with bone metabolism including bisphosphonates, denosumab, strontium ranelate, teriparatide, or glucocorticoids. Demographic data were recorded for all subjects. All participants included in this study were Caucasian from central Europe and did not receive any financial compensation. The study was approved by the appropriate ethics committees and was conducted in accordance with the Declaration of Helsinki.

Laboratory analyses

Blood sampling was performed in the morning after an overnight fast between 22:00 and 10:00. Samples were immediately cooled, centrifuged, and stored at − 70 °C for later analysis. Venous blood was taken for full blood count, serum uric acid, C reactive protein (CRP), Rheumatoid Factor (RF), antibodies against citrullinated proteins (ACPA), Glomerular Filtration Rate (GFR), creatinine, calcium, phosphate, TSH, and liver function parameters. Bone turnover markers including intact N-terminal type 1 procollagen propeptide (P1NP) and cross-linked C-telopeptide (CTX) were analyzed by electrochemiluminescence immunoassays (ECLIA). All serological parameters were analyzed in local ISO certified laboratories.

HR-pQCT assessment

HR-pQCT scans (XtremeCT, SCANCO Medical, Bruetisellen, Switzerland) were performed in all subjects at the ultradistal radius of the non-dominant hand. Measurements were performed as has been previously described [20, 23]. Cross-calibrations with standardized control phantoms (Moehrendorf, Germany) were conducted daily to validate the measurements. Reproducibility of measurements was not systematically assessed. The precision error for the standard in vivo protocol of the Xtreme-CT scanner was reported to be less than 5% for volumetric bone mineral density as well as trabecular and cortical parameters. [24] The manufacturer's standard protocol was used for the assessment of volumetric bone mineral density (vBMD) and bone microstructure (software version 6.0) [25].

Average vBMD (mgHA/cm^3), trabecular vBMD (Dtrab, mgHA/cm^3), and the cortical vBMD (Dcomp, mgHA/cm^3) were measured. Bone microstructure parameters including trabecular bone volume fraction (BV/TV, %), trabecular number (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), inhomogeneity of the network (standard deviation of 1/trabecular number, Tb.1/N.SD, mm), and cortical thickness (Ct.Th., mm) were performed [23].

Statistical analysis

Measures of central tendency and dispersion were calculated for demographic data, serum markers, vBMD, and bone microstructure, respectively. Group differences of NU subjects and HU, PSO + HU, and PSO + NU patients were carried out using two-sample *t* tests for continuous variables and Fisher's exact tests for dichotomous variables. In order to account for potential confounders, the above-group differences for serum markers, vBMD, and bone microstructure were investigated further by multiple linear regression models with age, sex, BMI, and diabetes status as covariates. Group differences in the multiple regression model are shown in units of the dependent variable as well as relative to mean values of the NU group. The impact of serum markers on vBMD and bone microstructure was examined by multiple linear regression models adjusted for uric acid, age, sex, BMI, and diabetes status. All tests were two-sided and *p* values less than 0.05 were considered statistically significant. Distributional assumptions for *t* tests and multiple linear regression were checked visually by quantile-quantile and residual plots, respectively. All statistical analyses were performed with the statistical software R version 3.50 (R Development Core Team, 2018).

Results

Characteristics of patients and controls

Bone microstructure of 130 individuals was analyzed (44 NU, 50 HU, 16 PSO + HU, 20 PSO + NU). Age distribution was comparable between all groups. BMI values were significantly higher in the HU group compared to the NU group ($p = 0.002$). Smoking and alcohol intake was highest in the PSO + NU group ($p < 0.001$ and $p = 0.002$, respectively). In the NU group, 66% were male (HU 76%, PSO + HU 94%, PSO + NU 40%). All participants were negative for RF and ACPA.

Two subjects in the NU group suffered from diabetes (5%), 16 patients of the HU group (32%), 3 in the PSO + HU group (19%), and none in the PSO + NU group. No subject in the NU, the PSO + HU, and PSO + NU group but seven (14%) of the HU group took diuretics. Detailed information on demographic characteristics is listed in Table 1.

Table 1 Descriptive characteristics, serum parameters, volumetric bone mineral density, and bone microstructure of the study population

	NU	HU	PSO + HU	PSO + NU	HU vs. NU	PSO + HU vs. NU	PSO + NU vs. NU	Reference range
Demographic data								
Number	44	50	16	20	NA	NA	NA	NA
Age (years)	54.5 (42.8, 62.1)	57.5 (18.6, 65.1)	52.0 (42.3, 57.8)	42.5 (34.8, 56.8)	0.190	0.342	0.055	NA
Sex (female, %)	34	24	6	60	0.362	**0.046**	0.062	NA
BMI	25.5 (24.4, 28.4)	29.9 (25.6, 33.2)	27.7 (25.8, 30.7)	28.3 (24.5, 30.7)	**0.002**	0.298	0.440	18.5–25
Diabetes (%)	5	32	19	0	0.098	0.113	1	NA
Alcohol (%)	36.4	22	25	50	0.170	0.451	**0.002**	NA
Nicotine (%)	22.8	28	37.5	50	0.639	0.325	**< 0.001**	NA
Serum markers								
Uric acid (mg/dl)	5.1 (4.0, 5.5)	8.4 (7.7, 8.9)	8.0 (7.2, 8.7)	4.8 (4.13, 5.5)	**< 0.001**	**< 0.001**	0.995	< 6.0
Creatinine (mg/dl)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	**0.001**	0.117	**0.038**	< 1.0
CRP (mg/dl)	2.2 (1.2, 3)	4 (1.8, 10)	2.5 (1.8, 3.5)	2.7 (1.3, 4.0)	**< 0.001**	0.561	0.277	< 5.0
Calcium (mmol/l)	2.3 (2.3, 2.4)	2.3 (2.3, 2.4)	2.4 (2.3, 2.4)	2.4 (2.3, 2.5)	0.788	0.558	0.111	2.10–2.58
CTX (ng/ml)	0.21 (0.19, 0.47)	0.28 (0.21, 0.32)	0.34 (0.26, 0.39)	NA	0.340	0.468	NA	0.115–0.748
Vitamin D (ng/dl)	24.2 (17.7, 29.3)	22.4 (16.2, 28.9)	14.13 (8.18, 22.10)	21.9 (18.0, 28.60)	0.524	0.051	0.775	> 30
P1NP (μg/ml)	43.6 (28.6, 51.9)	42.3 (38.2, 48.3)	53.9 (31.6, 58.8)	NA	0.942	0.568	NA	28–128
DKK-1 (ng/ml)	34.2 (19.3, 44.1)	40.1 (24.4, 52.5)	33.0 (25.9, 38.4)	NA	0.210	0.441	NA	12–20
Sclerostin (ng/ml)	33.8 (27.5, 40.4)	29.4 (24.4, 35.7)	30.8 (23.9, 35.0)	NA	0.587	0.083	NA	22–57
vBMD and bone microstructure								
Average vBMD (mgHA/cm^3)	291.8 (261.3, 349.3)	328.0 (275.7, 382.6)	276.8 (231.1, 317.4)	300.3 (272.4, 343.1)	0.081	0.158	0.658	NA
Tb.vBMD (mgHA/cm^3)	169.4 (149.2, 188.0)	183.6 (148.0, 211.9)	168.9 (138.6, 192.2)	173.1 (149.7, 194.3)	0.306	0.547	0.689	NA
Ct.vBMD (mgHA/cm^3)	799.8 (750.4, 849.5)	857.4 (818.9, 904.0)	802.5 (736.0, 826.6)	830.6 (788.0, 858.2)	**0.005**	0.258	0.346	NA
BV/TV	14.3 (12.5, 16.1)	15.5 (12.3, 17.7)	14.1 (11.5, 16.0)	14.4 (12.5, 16.2)	0.431	0.419	0.850	NA
Tb.number (1/mm)	2.02 (1.87, 2.23)	2.19 (1.92, 2.40)	2.14 (1.80, 2.30)	2.14 (1.96, 2.33)	0.319	0.936	0.320	NA
Tb.thickness (mm)	0.07 (0.06, 0.08)	0.07 (0.06, 0.08)	0.07 (0.06, 0.07)	0.07 (0.06, 0.07)	0.758	0.463	0.711	NA
Inhomogeneity (mm)	0.17 (0.15, 0.20)	0.16 (0.13, 0.20)	0.17 (0.15, 0.19)	0.16 (0.14, 0.17)	0.758	0.420	0.190	NA
Ct.thickness (mm)	0.70 (0.64, 0.79)	0.82 (0.68, 0.95)	0.71 (0.59, 0.82)	0.69 (0.62, 0.78)	**0.030**	0.499	0.998	NA

Results are median (Q1, Q3) and percentage. Bold indicates statistically significant findings

NU normouricemia, *HU* hyperuricemia, *PSO + HU* psoriasis and hyperuricemia, *PSO + NU* psoriasis and normouricemia, *BMI* body mass index, *CRP* C reactive protein, *iPTH* parathyroid hormone, *CTX* cross-linked C-telopeptide, *DKK-1* Dickkopf-1, *PINP* intact N-terminal type 1procollagen propeptide, *vBMD* volumetric bone mineral density, *BV/TV* bone volume fraction, *Tb.* trabecular, *Ct.* cortical

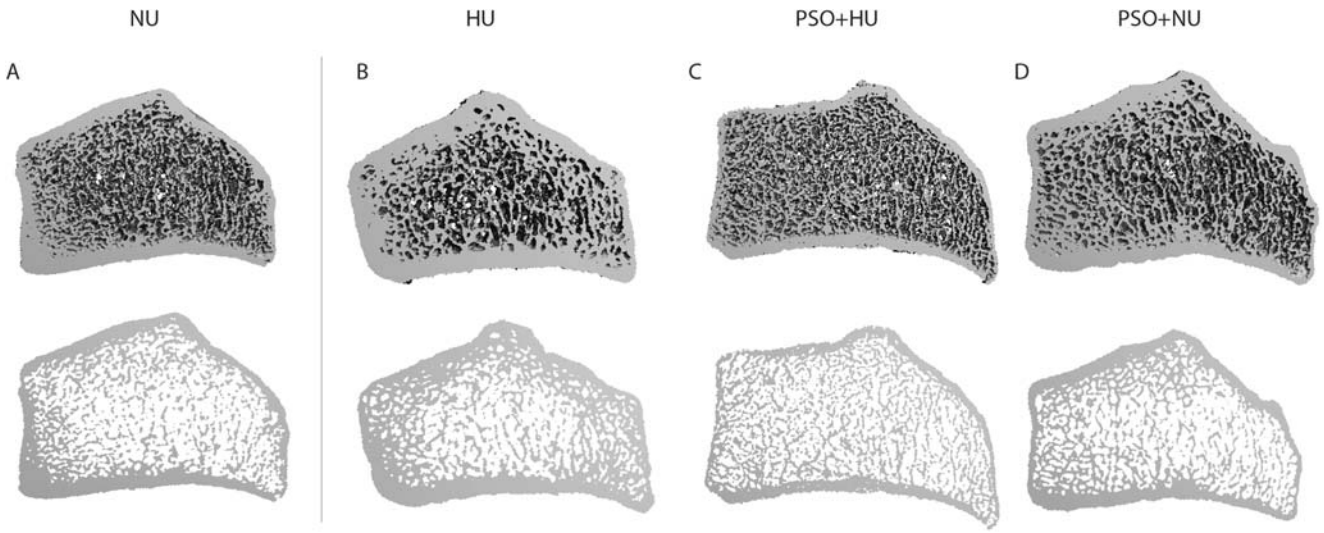

Fig. 1 Bone microstructure assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) in a representative male subject with uric acid levels within the normal range (NU, **a**), with hyperuricemia (HU, **b**), with hyperuricemia and psoriasis (PSO + HU, **c**), and with uric acid within the normal range and psoriasis (PSO + NU, **d**). The figure shows a dense trabecular network and a high cortical thickness (Ct.Th.) in the subject with hyperuricemia and deteriorations of trabecular bone in the patient with hyperuricemia with concomitant psoriasis. Upper row: 3D reconstruction of the radius, 60 slices, axial view, standard images. Lower row: 3D reconstruction of the radius, two slices, axial view

Volumetric BMD and bone microstructure

Volumetric bone mineral density (vBMD) and microstructural parameters for HU, PSO + HU, PSO + NU were first compared to the NU group (reference group). When comparing HU to NU, significantly higher values regarding cortical vBMD and Ct.Th were found for HU. No significant differences were found between PSO + HU and PSO + NU when compared to NU (Table 1, Fig. 1).

In a second step, we compared the abovementioned bone parameters after adjusting for age, sex, BMI, and diabetes. Again, significant differences were found between HU and NU regarding cortical vBMD and Ct.Th.. The regression model for PSO + HU versus NU revealed significant differences in average and trabecular vBMD as well as Tb.N.. Only Tb.N. was significantly different in the model for PSO + NU versus NU (all data are shown in Table 2).

Serum markers

Comparing serum markers in the same manner as bone parameters revealed that uric acid was significantly higher in the HU and PSO + HU groups compared to NU ($p < 0.001$). Creatinine levels were higher in the HU, but lower in the PSO-NU group when compared to NU ($p = 0.001$ and $p = 0.038$, respectively). CRP levels were in the normal range, but highest for HU ($p < 0.001$). Lower levels of vitamin D were found for PSO + HU; however, this comparison did not reach statistical significance ($p = 0.051$). All bone turnover markers including CTX, P1NP, DKK-1, and sclerostin were comparable between the subgroups (Table 1).

After adjusting for age, sex, BMI, and diabetes, significant differences were found for creatinine in HU versus NU and in the PSO + HU versus NU, and for calcium in PSO + NU versus NU (Table 2).

Effect of demographic data and serum parameters on volumetric BMD and bone microstructure

In the regression model for demographic data including the HU total group (HU and PSO + HU), only female gender was associated with low trabecular vBMD. Uric acid, BMI, and age did not show significant effects on vBMD or bone microstructure. A significant impact of diabetes on Tb.N. was found (Table 3).

After calibrating for uric acid, age, sex, diabetes, and BMI, effects of serum parameters on volumetric bone mineral density and bone microstructure were tested in the HU total group (HU and PSO + HU). Significant associations of vitamin D, sclerostin, and P1NP on trabecular vBMD were found. Moreover, significant associations were observed between P1NP and average vBMD and cortical vBMD as well as Ct.Th. (Table 4 and Fig. 2).

Discussion

In the present study, hyperuricemia was associated to higher cortical vBMD and cortical bone microstructure. In contrast, the combination of both hyperuricemia and skin psoriasis was linked to low vBMD.

Table 2 Group comparison for serum parameters, volumetric bone mineral density and bone microstructure adjusted for age, sex, BMI and diabetes

	HU vs. NU					PSO + HU vs. NU					PSO + NU vs. NU				
		(%)	CI_low	CI_up	*p* value		(%)	CI_low	CI_up	*p* value		(%)	CI_low	CI_up	*p* value
Creatinine (mg/dl)	0.10	0.12	0.04	0.17	**< 0.001**	− 0.12	− 0.14	− 0.19	− 0.06	**< 0.001**	− 0.03	− 0.03	− 0.09	0.04	0.38
Calcium (mmol/l)	− 0.01	0.00	− 0.07	0.05	0.77	− 0.01	0.00	− 0.08	0.07	0.89	0.07	0.03	0.01	0.14	**0.03**
CTX (ng/ml)	0.03	0.09	− 0.10	0.17	0.64	0.04	0.12	− 0.22	0.31	0.74	NA	NA	NA	NA	NA
Vitamin D (ng/dl)	0.61	0.02	− 4.53	5.75	0.81	− 7.85	− 0.30	− 16.71	1.02	0.08	2.72	0.11	− 7.29	12.73	0.59
DKK-1 (ng/ml)	5.50	0.15	− 5.98	16.98	0.34	0.87	0.02	− 14.01	15.76	0.91	NA	NA	NA	NA	NA
Sclerostin (ng/ml)	− 3.98	− 0.12	− 10.56	2.60	0.23	− 6.79	− 0.20	− 14.74	1.16	0.09	NA	NA	NA	NA	NA
P1NP (µg/ml)	5.90	0.13	− 2.95	14.76	0.19	10.16	0.22	− 4.07	24.39	0.16	NA	NA	NA	NA	NA
Average vBMD (mgHA/cm^3)	28.47	0.09	− 3.73	60.67	0.08	− 45.32	− 0.15	− 86.17	− 4.48	**0.03**	6.30	0.02	− 31.62	44.21	0.74
Tb.vBMD (mgHA/cm^3)	9.06	0.05	− 9.20	27.32	0.33	− 29.12	− 0.17	− 52.74	− 5.50	**0.02**	17.84	0.11	− 2.39	38.07	0.08
Ct.vBMD (mgHA/cm^3)	57.55	0.07	23.06	92.05	**< 0.001**	− 27.37	− 0.03	− 76.39	21.64	0.27	− 1.69	0.00	− 42.92	39.54	0.93
Tb.number (1/mm)	0.08	0.04	− 0.07	0.23	0.29	− 0.21	− 0.10	− 0.40	− 0.01	**0.04**	0.20	0.10	0.03	0.36	**0.02**
Ct.thickness (mm)	0.11	0.15	0.00	0.21	**0.04**	− 0.09	− 0.12	− 0.21	0.04	0.16	− 0.01	− 0.01	− 0.12	0.11	0.93

Bold indicates statistically significant findings ($p < 0.05$)

CTX cross-linked C-telopeptide, *DKK-1* Dickkopf-1, *PINP* intact N-terminal type 1procollagen propeptide, *vBMD* volumetric bone mineral density, *Tb.* trabecular, *Ct.* cortical

The lowest absolute vBMD values were found in patients with psoriasis and concomitant hyperuricemia. After adjusting for age, sex, BMI, and diabetes, significantly lower levels for average and trabecular vBMD as well as a lower trabecular number were found in patients with skin psoriasis and concomitant hyperuricemia when compared to otherwise healthy subjects with normal uric acid. Parameters of trabecular bone were markedly decreased. The combination of both psoriasis and hyperuricemia seems to promote systemic bone loss. However, patients with psoriasis without elevated levels of uric acid showed comparable vBMD and bone microstructure to healthy subjects with normal uric acid levels. These findings indicate that chronic inflammation in psoriasis in combination with hyperuricemia influences bone microarchitecture. Consequently, in the treatment of psoriasis patients with hyperuricemia, it should be kept in mind that a reduced bone microstructure may be present and that this may also increase the risk of fracture.

In our previous study, patients with skin psoriasis without arthritis showed comparable bone microstructure and vBMD when compared to healthy controls [10]. Among patients with psoriatic arthritis, the duration of skin disease appeared to negatively influence bone quality [10]. Alterations in local bone were previously reported for psoriasis patients. Enthesiophyte formation as well as osteitis, two typical features of psoriatic arthritis, were also found in patients with psoriasis in the absence of joint disease [11, 13].

Interestingly, otherwise healthy subjects with hyperuricemia showed significantly better cortical vBMD and a higher cortical thickness when compared to subjects with normal uric acid, even after adjusting for co-factors. A positive influence of high uric acid on areal BMD, measured by two-dimensional DXA, in men

Table 3 Regression model including all patients with hyperuricemia (HU and PSO + HU). Effects of demographic data on vBMD and bone microstructure

	Average vBMD	Tb.vBMD	Ct.vBMD	Tb.Number	Ct.Thickness
Uric acid	− 3.66 [− 19.53–12.20]	− 0.80 [− 10.2–8.41]	− 11.29 [− 29.08–6.51]	− 0.01 [− 0.09–0.07]	− 0.02 [− 0.07–0.04]
Age	− 0.66 [− 2.16–0.84]	− 0.23 [− 1.10–0.64]	− 0.96 [− 2.65–0.72]	− 0.00 [− 0.01–0.00]	− 0.00 [− 0.01–0.00]
Sex	− 20.98 [− 71.82–29.87]	**− 37.98 [− 67.52–− 8.44]**	28.98 [− 28.07–86.03]	− 0.20 [− 0.45–0.05]	− 0.09 [− 0.26–0.08]
BMI	1.66 [− 1.82–5.13]	1.17 [− 0.85–3.19]	0.66 [− 3.23–4.56]	0.01 [− 0.00–0.03]	0.00 [− 0.01–0.02]
Diabetes	− 25.87 [− 77.33–25.59]	− 30.33 [− 60.23–− 0.43]	14.22 [− 43.52–71.96]	**− 0.26 [− 0.51–− 0.01]**	− 0.02 [− 0.19–0.15]

Bold indicates statistically significant findings ($p < 0.05$)

vBMD volumetric bone mineral density, *Tb.* trabecular, *Ct.* cortical

Table 4 Effect of serum parameters on volumetric bone mineral density and bone microstructure adjusted for uric acid, age, sex, BMI, and diabetes in patients with hyperuricemia (HU) and patients with skin psoriasis with hyperuricemia (PSO + HU)

	Average vBMD	Tb.vBMD	Ct.vBMD	Tb.Number	Ct.Thickness
Creatinine	76.3 [− 33.9–186.6]	62.8 [− 0.01–125.6]	65.0 [− 59.7–189.7]	0.48 [− 0.05–1.02]	0.12 [− 0.25–0.51]
Calcium	− 15.5 [− 151.7–182.8]	38.0 [− 57.9–133.8]	− 91.5 [− 275.6–92.7]	0.70 [− 0.11–1.51]	− 0.03 [− 0.60–0.53]
CTX	− 135.5 [− 287.5–16.4]	− 48.0 [− 137.2–41.2]	− 104.5 [− 280.7–71.7]	− 0.16 [− 0.87–0.56]	− 0.44 [− 0.96–0.07]
Vitamin D	1.12 [− 0.61–2.85]	**1.16 [0.22–2.10]**	0.35 [− 1.56–2.25]	0.01 [− 0.00–0.01]	0.00 [− 0.01–0.01]
DKK1	0.97 [− 0.51–2.45]	0.82 [− 0.06–1.71]	0.85 [− 0.80–2.50]	0.00 [− 0.00–0.01]	0.00 [− 0.00–0.01]
Sclerostin	1.44 [− 0.77–3.64]	**1.66 [0.41–2.91]**	0.69 [− 1.80–3.17]	0.01 [0.00–0.02]	0.00 [− 0.01–0.01]
PINP	***− 2.48 [− 3.85–− 1.12]***	**− 0.97 [− 1.82–0.13]**	***− 2.45 [− 4.05–− 0.84]***	− 0.00 [− 0.01–0.01]	***− 0.01 [− 0.01–− 0.00]***

Bold indicates statistically significant findings, $p < 0.05$; bold and italic indicates statistically significant findings, $p < 0.01$

vBMD volumetric bone mineral density, *Tb*. trabecular, *Ct*. cortical, *CTX* cross-linked C-telopeptide, *DKK-1* Dickkopf-1, *PINP* intact N-terminal type 1 procollagen propeptide

and women at different measuring sites has been proposed repeatedly [26–28]. Moreover, a significantly higher risk for osteoporosis was reported in subjects with low uric acid compared to those with high levels [5]. Valuable explanations are potentially protective, antioxidant effects of uric acid [8]. Dalbeth et al. confirmed the positive association between serum uric acid and areal BMD in their cohort. However, using a weighted genetic urate score, a causal effect was not provided [29]. Thus, high serum uric acid does not seem to cause increased BMD. Other likely explanations for high areal BMD in individuals with hyperuricemia include high body weight, fat, and muscle mass. Serum uric acid levels were positively associated with all indices of adiposity including as fat mass, waist circumference and abdominal visceral fat area in the study of Pirro et al. [27]. Fat accumulation was linked to both serum uric acid and areal BMD. Uric acid was also positively correlated to a greater muscle mass, at least partly

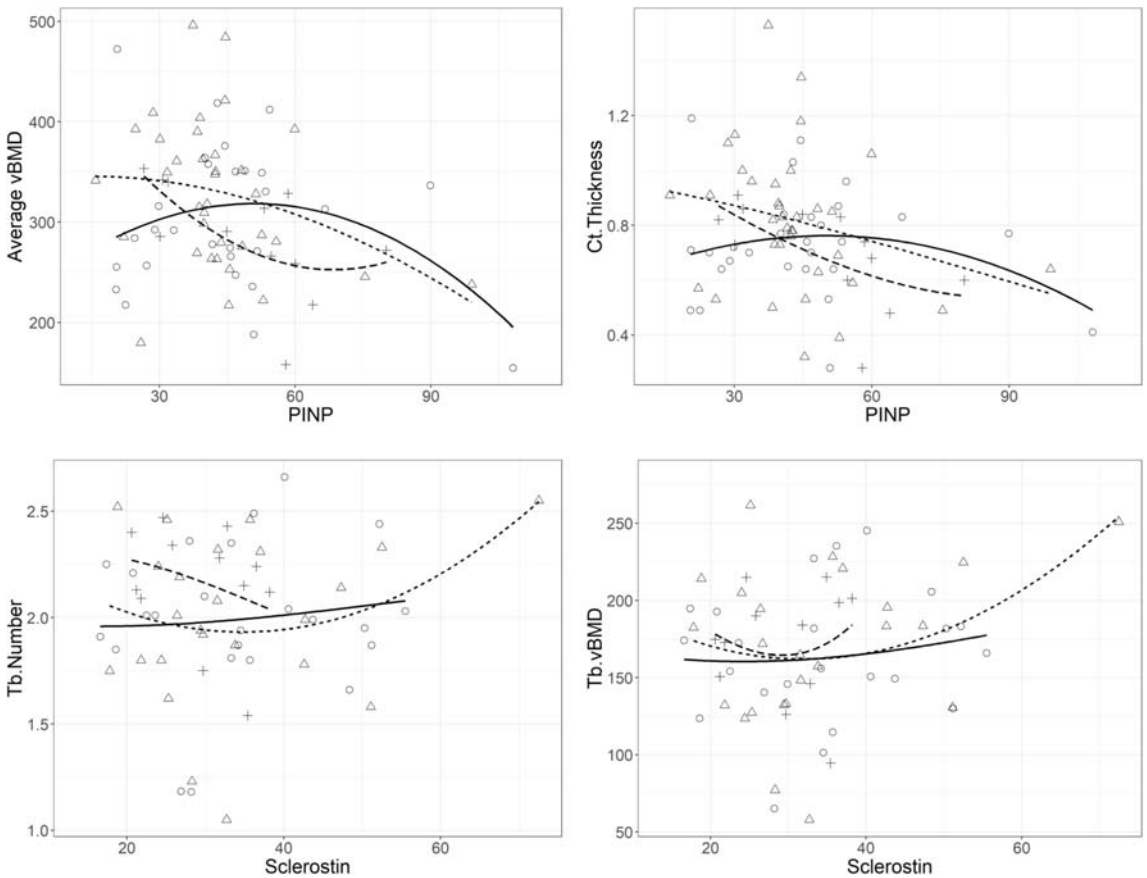

Fig. 2 Visual presentation of associations between bone turnover markers and bone microstructure in subjects with normal uric acid (NU, solid line, circles), hyperuricemia (HU, small dashes, triangles), and patients with psoriasis and hyperuricemia (PSO + HU, large dashes, crosses)

explaining the uric acid-areal BMD association in another study [26]. However, in the present study, BMI was not associated to vBMD, nor to bone microstructure in subjects with hyperuricemia.

Data regarding fracture risk in patients with hyperuricemia and gout are conflicting. An increased risk of vertebral, non-vertebral, and hip fractures in patients with high serum uric acid levels or gout was reported previously [8, 30, 31]. In addition, the utilization of uric acid-lowering therapy significantly reduced the risk of fractures compared to non-users [30]. In contrast, in a longitudinal study over 2 years among patients with gout, serum uric acid was not associated with fracture risk [32] and others suggested a positive effect on fracture risk in patients with hyperuricemia [6, 7, 28, 33].

No differences in established bone turnover markers were found between hyperuricemia and normouricemia in the present study. However, Sclerostin, an inhibitor of the canonical wnt-signaling-pathway and thereby osteoblasts, and P1NP, reflecting osteoblast activity and bone formation were significantly related to vBMD and bone microstructure. Low P1NP and high sclerostin levels were related to better vBMD and bone microstructure.

One limitation of this study is the small number of cases in the subgroups and that we have no information on prevalent fractures for all patients. Lamentably, the sample size of our subgroups would not be sufficient to provide a reliable conclusion about fracture risk. Future studies with larger groups would be helpful to substantiate our findings and clarify the fracture risk. Another constraint of our study is that DXA scans were not available in our patients. However, DXA data in psoriasis are conflicting, because areal BMD can be low, normal, or even high [34–36]. We report for the first time the influence of hyperuricemia with and without skin psoriasis on vBMD and bone microstructure as assessed by a high-resolution technique.

In conclusion, hyperuricemia in combination with skin psoriasis is a risk factor for low trabecular volumetric bone mineral density and impaired bone microstructure—even in the absence of gouty or psoriatic arthritis. Hyperuricemia in otherwise healthy individuals is associated to higher bone mass, assessed by HR-pQCT.

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Compliance with ethical standards

The study was approved by the appropriate ethics committees and was conducted in accordance with the Declaration of Helsinki.

Conflicts of interest None.

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