Chapter 5

Bone turnover and hip bone mineral density in patients with sarcoidosis

AC Heijckmann, MSP Huijberts, J De Vries, PPCA Menheere, E van der Veer, AC Nieuwenhuijzen Kruseman, BHR Wolffenbuttel, P Geusens, M Drent

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Abstract

Background
Sarcoidosis is a chronic inflammatory T-cell-driven disease that can also affect bone. We evaluated bone remodelling and bone mineral density (BMD) in patients with sarcoidosis and their dependency of disease-related and treatment-related factors.

Methods
In 124 patients BMD of the hip (DXA) and markers of bone resorption (ICTP) and formation (PINP) were evaluated. Furthermore a lateral DXA of the spine for morphometric assessment of vertebral deformities was performed in 87 patients. Potential predictors of bone markers, BMD and determinants of prevalent vertebral deformities were assessed using multiple and logistic regression analysis.

Results
The population studied comprised untreated patients (n=51), patients that previously used glucocorticoids (n=31) and patients currently using glucocorticoids (n=42). In all these groups the age- and gender corrected Z-scores of the hip were normal, except in untreated patients, which revealed an increased Z-score at the trochanter ($p=0.004$). In all but the patients currently on glucocorticoids the Z-scores for PINP and ICTP were increased ($p<0.05$). In patients currently on glucocorticoids the Z-ICTP was also increased ($p<0.05$), but the Z-PINP decreased ($p<0.01$ compared to untreated patients). In 20.6% of patients one or more morphometric vertebral deformities were found.

Conclusions
Hip BMD is normal in patients with sarcoidosis, despite an increased bone turnover. This may imply that in sarcoidosis mechanisms are involved that compensate for the well-known effects of cytokines in inflammatory diseases on osteoclastogenesis and bone resorption. Nonetheless, vertebral deformities suggestive of fracture were found in a significant number of patients which indicates that patients with sarcoidosis still have a relevant fracture risk.

Introduction

Sarcoidosis is a multiorgan, inflammatory, granulomatous disorder of unknown origin that can affect almost any organ of the body, including bone.[1-5] In addition to localized bone lesions of sarcoid granulomas,[6] increased bone mineral density (BMD)[7] as well as generalized bone loss have been described in longstanding sarcoidosis.[8]

There are a number of mechanisms that may be involved in bone changes in sarcoidosis. Due to overproduction of 1,25 dihydroxyvitamin D ($1,25(OH)_2D_3$) by sarcoid granulomas, intestinal absorption of calcium is enhanced and bone turnover can be increased.[5,9] As sarcoidosis is a chronic T-cell-driven inflammatory disease, cytokines such as interleukin 6 (IL-6) and tumour necrosis factor are increased. These cytokines play a pivotal role in the pathogenesis of granulomatous diseases,[10,11] and can also influence bone turnover.[12,13] Finally, prolonged treatment with glucocorticoids and decreased physical activity may also negatively affect bone.

Up till now, only a limited number of studies on BMD measurements in untreated sarcoidosis are published.[7,14,15] All these studies are of small size and reveal predominantly an unchanged BMD with only mild trabecular bone loss in longstanding sarcoidosis.[14] This is in contrast with what can be expected in a chronic inflammatory disorder. In addition, in only one study bone turnover parameters were determined[16] and no data are available of fracture risk in patients with sarcoidosis. For that reason we studied a large and well-characterized sarcoidosis population, consisting of a group of untreated subjects, subjects that were previously treated with glucocorticoids and subjects that were currently on glucocorticoids. In addition to measurement of bone turnover parameters and BMD, morphometry of the spine was done to identify vertebral deformities suggestive of non-clinical fractures and to substantiate the fracture risk in sarcoidosis.

Patients and methods

Patients

Between January 2002 and July 2003, all 167 sarcoidosis patients with a disease duration of at least one year attending the outpatient clinic of the Sarcoidosis Management Center of the University Hospital Maastricht, were asked to participate in this cross-sectional study. Hundred and thirty-eight patients (82%) agreed to participate. All patients were Caucasians and diagnosed with sarcoidosis according to the WASOG guidelines,[1] based on consistent clinical features and results of an analysis of bronchoalveolar lavage

fluid.[17] In 71% a biopsy confirmed the diagnosis. None of the patients had any significant co-morbidity. Known causes of bone mass abnormalities, such as renal failure, thyroid dysfunction, alcoholism and long-term anticoagulant use were exclusion criteria, but no patient was excluded on the basis of these factors. Fourteen patients were excluded because of the use of bisphosphonates or hormone replacement therapy. Finally, 124 patients were included in this study. This group consisted of 43 pre-menopausal women, 19 post-menopausal women, and 62 men. The patients were grouped according to the way of treatment, e.g. no treatment, previously treated with glucocorticoids and currently on glucocorticoids.
The clinical records of all patients were reviewed. Demographic, clinical and treatment data of these patients are summarized in Table 5.1. Patients were evaluated according to a standard protocol that included questionnaires related to risk factors for osteoporosis, calcium intake, physical activity and health status, measurement of height and weight, lung function, measurement of BMD, and collection of a blood sample and morning urine. Informed consent was obtained from all participants and this study was approved by the medical ethics committee. None of the patients who declined to participate or were excluded had impaired mobility or a history of vertebral fractures. Mean age of this group was 43 years and there were seven postmenopausal women in this group.

Pulmonary evaluation

Lung function, including forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), was measured with a pneumotachograph. The diffusion capacity for carbon monoxide (DLCO) was measured using the single-breath method (both Masterlab, Jaeger, Würzburg, Germany). Values were expressed as a percentage of those predicted.[18]
Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV, the end stage of lung fibrosis.[1,19] All interpretations were made by a radiologist who was blinded to the patient's history.

Bone Mineral Density

In all 124 patients bone mineral density (BMD) of the hip was measured by dual X-ray absorptiometry (DXA) (Hologic QDR 4500). As reference group the NHANES III database was used. A standard protocol as described previously was used for measurement of BMD.[20] Furthermore a lateral DXA of the thoracic and lumbar spine for assessment of vertebral fractures (morphometric X-ray absorptiometry (MXA))[21] was performed in 87 patients. All these morphometric analyses were done twice by one trained operator using the

quantitative technique of Genant.[22] On the basis of the average score of these morphometric measurements prevalent vertebral deformity suggestive of fracture was defined as a reduction of height of 20% or more.[22]

Table 5.1 Demographic, clinical, and treatment variables in the study patients (n=124).

Variable	Never GC use (n=51)	Previous GC use (n=31)	Current GC use (n=42)	p[a]	p[b]
Demographic variables					
Female sex	36 (71)	13 (39)	14 (33)	<0.001	<0.001
Postmenopausal (% of group)	8 (16)	4 (13)	7 (17)		
Age years	42 (20-67)	45 (25-66)	49 (28-70)		
Body mass index (kg/m^2)	26.9 ± 5.9	26.6 ± 4.8	27.4 ± 5.8		
Smoking	8 (16)	3 (10)	5 (12)		
Daily dietary calcium intake (mg)	736 ± 355	880 ± 549	750 ± 347		
Clinical variables					
Disease duration, median (range) yrs	3 (1-39)	4 (1-20)	3,5 (1-36)		
Chest X-ray stage (0-I-II-III-IV)	15/10/16/10/0	6/4/9/9/3	4/6/9/16/7		0.002
FEV1 (% of predicted ± SD)	98 ± 15	83 ± 24	77 ± 25	<0.001	<0.001
DLCO (% of predicted ± SD)	93 ± 14	79 ± 16	77 ± 21	<0.001	<0.001
Laboratory values (in serum)					
Calcium (mmol/l)	2.4 ± 0.1	2.4 ± 0.2	2.4 ± 0.1		
1,25(OH)2D3 (nmol/l)	0.16 ± 0.05	0.14 ± 0.03	0.15 ± 0.04		
ACE (U/l)	21.4 ± 7.9	21.5 ± 11.2	26.5 ± 13.9		
sIL-2R (kU/l)	695 (216-2636)	638 (264-4546)	715 (188-4315)		
Hs-CRP (mg/l)	2.3 (0.2-79)	3.4 (0.2-58)	4.4 (0.2-191)		
Treatment variables					
Lifetime glucocorticoid dose (mg)	-	7200 (200-54000)	13125 (1650-189000)		
Daily dose (mg)	-	17.4 ± 7.9	18.1 ± 9.0		
Clinical risk factors for osteoporosis					
Fracture >50 years	0	1 of 11 (9)	2 of 20 (10)		
Vertebral fracture by DXA	8 of 36 (22)	4 of 19 (21)	6 of 32 (19)		
Low body weight (<60 kg)	8 (16)	4 (13)	2 (5)		
Severe immobilization	0	0	0		
Low physical activity index ≤5	10 (20)	9 (29)	17 (41)		
Mother with hip fracture	2 (4)	1(3)	3 (7)		

Data are given as mean ± SD, median (range) or number (%); Reference parameters: Calcium: 2.1-2.6 mmol/l; 1,25(OH)2D3 0.040-0.200 nmol/l; ACE: 9-25 U/l; sIL-2R: 241-846 KU/l; hs-CRP: 0-10 mg/l; Abbreviations: GC, glucocorticoid; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity for carbon monoxide; 1,25(OH)2D3, 1,25 dihydroxyvitamin D; ACE, angiotensin converting enzyme; sIL-2R, soluble interleukin-2 receptor; Hs-CRP, high-sensitivity C-reactive protein. [a] p value never GC use versus previous + current; [b] p value never versus current

Laboratory assays

As a marker for bone formation, serum procollagen type I amino-terminal propeptide (PINP) was measured. As a marker for bone resorption, serum carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) was assessed. Both PINP [interassay coefficient of variation (IE-CV) 3.2%, intra-assay CV (IA-CV) 2.5%, lowest detectable concentration 0.4 µg/l] and ICTP (IE-CV 3.5%, IA-CV 2.3%, lowest detectable concentration <0.1 µg/l) were measured using commercial RIA kits (Orion Diagnostica Oy, Espoo, Finland).

The Z-score for these bone markers was obtained using a Dutch reference group (300 women, 150 men), checked for normal BMD of the lumbar spine and femur and normal 25-hydroxyvitamin-D levels.[23] Serum 1,25-dihydroxy-vitamin D concentration was determined by radioimmuno-assay using a commercially available kit (IDS Ltd, Boldon, England, IE-CV 18%, IA-CV 15%). High-sensitivity C-reactive protein (hs-CRP) was measured by particle-enhanced immunonephelometry on the BN Prospec (Dade Behring). The detection limit is 0.175 mg/l and the measuring range is 0.175-1100 mg/l. Soluble IL-2 receptor (sIL-2R) was determined on the IMMULITE automated analyzer, by means of a two–site chemiluminescent enzyme immunometric assay with a measuring range of 50-7500 kU/l (Diagnostic Product Corporation, Los Angeles, CA, cat no LKIP1). Serum angiotensin converting enzyme (ACE) was measured using a colorimetric method. The precision of the ACE assay was <5.6% and the reference interval for ACE was 9-25 U/l.

Questionnaires

Known clinical risk factors for osteoporosis were evaluated (weight below 60 kg, hip fracture in the mother, history of fractures after age 50, menopausal status, severe immobilization and use of glucocorticoids) and physical activity was scored on a scale between 0 and 18.[24] Calcium intake was evaluated via an extensive dietary list and dosing and duration of glucocorticoid therapy was evaluated by means of a patient questionnaire and verified using all the records of the patient's pharmacist.

Statistics

Student t-tests, chi-square tests, and one-way ANOVAs were used, depending on the variables and subgroups tested. Z-score analyses were performed to correct for age and gender when comparing subgroups. One-sample t-tests were used to compare patient scores with norm scores. Z-scores for BMD were evaluated by univariate analysis in relation to risk factors and clinical variables using bivariate correlations for continuous and ANOVA for dichotomous variables. Bone markers were expressed as Z-scores. Factors associated ($p<0.10$) with a low BMD and bone turnover were entered as independent variables in a multiple regression analysis (method: stepwise) with BMD and bone turnover as outcome measures. A logistic regression analysis (method: enter) was performed to examine the determinants of morphometric vertebral deformities. For the comparison of subgroups with various glucocorticoid status, a Bonferroni correction was applied, resulting in a $p<0.002$ being considered significant. For the remaining analyses, the level of significance was set at $p<0.05$.

Results

Bone Mineral Density

The results of BMD measurements are shown in Table 5.2 and Figure 5.1. In all groups the Z-scores of the hip were normal, except the Z-scores of patients that never used glucocorticoids, which revealed an increased Z-score at the trochanter (0.45, 95% confidence interval (CI): 0.15- 0.76, p=0.004, Figure 5.1). This Z-score was also higher than that of subjects using glucocorticoids when the data of patients currently on glucocorticoids were taken together with patients that previously used glucocorticoids (0.01 (CI: 0.06- 0.84), p<0.05, not shown in figure).

Table 5.2 BMD variables and bone markers.

Variable	Never GC use (n=51)	Previous GC use (n=31)	Current GC use (n=42)
BMD (gm/cm^2)			
Femoral neck	0.84 ± 0.13	0.79 ± 0.09	0.80 ± 0.18
Trochanter	0.76 ± 0.12	0.71 ± 0.10	0.71 ± 0.18
Z-score			
Femoral neck	0.1 ± 1.2	-0.4 ± 0.9	0.0 ± 1.0
Trochanter	0.5 ± 1.1[a]	-0.1 ± 1.0	0.1 ± 1.1
T-score			
Femoral neck	-0.5 ± 1.2[a]	-1.1 ± 0.9[a]	-0.8 ± 1.0[a]
Trochanter	0.1 ± 1.1	-0.4 ± 0.9[a]	-0.3 ± 1.0
Bone markers in serum			
ICTP (µg/l)	4.1 ± 1.6	4.4 ± 1.7	3.7 ± 1.5
Z-score ICTP	1.2 ± 2.0[a]	1.3 ± 1.9[a]	0.7 ± 2.0[a]
PINP (µg/l)	43.8 ± 19.7	42.9 ± 19.7	35.6 ± 20.4
Z-score PINP	0.4 ± 1.1[a]	0.3 ± 1.4	-0.4 ± 1.3

Data are given as mean ± SD; [a] p value <0.05 one-sample t-test compared to norm scores; Abbreviations: BMD, bone mineral density, ICTP, carboxy-terminal cross-linked telopeptide of type I collagen; PINP, procollagen type I amino-terminal propeptide.

Multiple regression analysis, including factors that correlated in the univariate analysis, revealed only a positive relation between the Z-scores of the femoral neck and trochanter with body mass index (BMI). Z-scores for BMD were unrelated to 1,25$(OH)_2D_3$, radiographic stage of sarcoidosis (0/I versus II/III/IV), lifetime glucocorticoid dose, daily glucocorticoid dose, and duration of glucocorticoid use. In the subgroups we found nevertheless a significant negative correlation in the current glucocorticoid users between Z-score at the trochanter and 1,25$(OH)_2D_3$ (r=-0.38, p=0.02) and between Z-score at the femoral neck and this vitamin D (r=-0.35, p=0.03). The Z-scores for BMD were furthermore also unrelated to life-style factors (smoking, physical activity and calcium intake) or to a family history of osteoporosis. There was also no relation between physical activity scores and BMD.

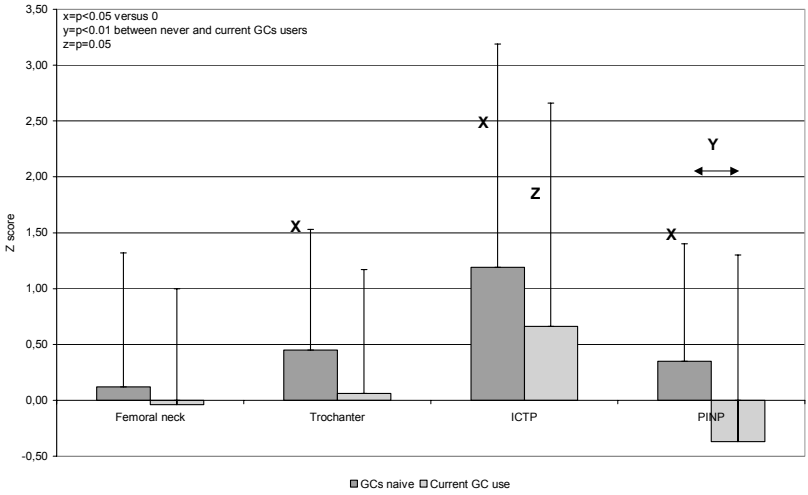

Figure 5.1 Z-scores (± SD) in the untreated group (n=51) versus current glucocorticoid users (n=42); Abbreviations: ICTP, carboxy-terminal cross-linked telopeptide of type I collagen; PINP, procollagen type I amino-terminal propeptide; GC, glucocorticoid.

Bone turnover parameters

ICTP and PINP levels and their Z-scores for the different groups are shown in Table 5.2 and Figure 5.1. Z-scores for ICTP (Z-ICTP) as well as PINP (Z-PINP) were increased in the group of patients not using glucocorticoids (1.2 (CI: 0.6, 1.8), p<0.001 and 0.4 (CI: 0.0, 0.7, p<0.05 respectively). In the group of patients currently on glucocorticoids the Z-ICTP was also increased (0.7 (CI: 0.0-1.3), p=0.05), but the Z-PINP decreased (-0.4 (CI: –0.8, 0.0), p<0.01 compared to glucocorticoid naïve patients).
Z-ICTP was positively related to sIL-2R (r=0.22, p<0.05), ACE (r=0.26, p<0.01), and negatively to DLCO (r=-0.21, p<0.05) and these correlations were even stronger in patients with current glucocorticoid use (r=0.57 (p<0.001), 0.42 (p=0.009) and -0.46 (p=0.005) respectively). The Z-PINP revealed no relation with these parameters. Bone turnover parameters were also not related to BMD, $1.25(OH)_2D_3$ values or fracture rate.

Clinical fractures and vertebral deformities

Three symptomatic, non-vertebral fractures were found in patients older than 50 years (3 out of 51 patients, 6%), one of which appeared to be a fracture of the thumb due to a sarcoid granuloma. When the fracture occurred, these patients suffered from sarcoidosis for eight, 22 and 23 years, respectively. In 18 out of the 87 (20.6%) patients of which DXA images were available for morphometric analysis one or more vertebral deformities (24 vertebrae in total)

were found. None of these had been symptomatic. All but one of the deformities revealed a mild or moderate vertebral height loss of less than 40%. When comparing the group with and without vertebral deformities (threshold value of one of the ratios of <0.8), no significant difference was found between Z-scores of BMD of the trochanter or femoral neck, nor in Z-ICTP or PINP. Using T-scores, a lower BMD at the femoral neck was found in subjects with vertebral deformities compared to those without deformities (-1.2 (CI: -1.5, -0.9) and -0.3 (CI: -0.6, -0.1), p=0.001). The BMD at the trochanter was not different. Furthermore, the group with deformities appeared to be older (42 years (CI: 40, 45) versus 52 years (CI: 48, 56), p=0.001) and contained more males (p=0.01). No differences were seen in other clinical risk factors, glucocorticoid use, daily glucocorticoid dose and disease duration.
Logistic regression analysis revealed that higher T-score for femoral neck was associated with a lower prevalence of vertebral deformities (OR=0.225 (CI: 0.083-0.607), p=0.003). In addition, determinants of higher prevalence of these deformities were male gender (OR=6.34 (CI: 1.355-32.518), p=0.020) and older age (OR=1.120 (CI: 1.039-1.206)).

Discussion

In our series of a large group of sarcoidosis patients the BMD measured with DXA at the hip was not different from the reference population, even if currently or previously treated with glucocorticoids. Surprisingly, in untreated patients the BMD at the trochanter appeared even increased. As sarcoidosis is a T-cell driven disease one would expect a decreased BMD, like in other inflammatory conditions.[25] Our observations are, however, in line with the few clinical studies reported on BMD in sarcoidosis.[7,14,15] Tervonen et al.[7] reported in 14 patients with a disease duration of less than two years an increased BMD. Two other studies of small size involve BMD in untreated patients.[14,15] These studies also found a normal BMD relative to age and sex-matched controls, except for five postmenopausal women in which the BMD was moderately decreased at the spine in longstanding sarcoidosis only.
In contrast to a normal BMD, untreated patients had increased values for the bone resorption marker ICTP and the bone formation marker PINP, which is suggestive of increased bone turnover.
In patients currently on glucocorticoids the bone resorption marker ICTP was also increased, although slightly less than in subjects not using glucocorticoids. PINP, however, was decreased in these patients. As this is in line with the well known effects of glucocorticoids on bone turnover,[26,27] one would expect in such a situation a decreased BMD as well. This discrepancy and the finding of

a normal BMD in untreated patients in spite of increased bone turnover is suggestive of a protective effect of sarcoidosis on bone metabolism.
It is well known that chronic inflammatory diseases affect bone physiology by the production of cytokines.[28,29] Cytokines enhance RANKL expression in osteoblasts. RANKL is the receptor activator of the nuclear receptor-κB ligand that induces osteoclast differentiation by binding to the receptor activator of the nuclear factor-κB (RANK) on the surface of osteoclasts. In addition, cytokines involved in chronic inflammatory diseases can suppress osteoprotegerin (OPG) expression in osteoblasts. OPG is a decoy receptor for RANKL and prevents binding of RANKL to its osteoclast receptor and thereby inhibits osteoclast differentiation. Although there are no data on changes in the RANKL/OPG ratio in sarcoidosis, enhanced activation of nuclear receptor kappa beta (NF-κB), the downstream transcription factor of this pathway, has been reported previously in patients with sarcoidosis.[30,31] The consequence of the influence of cytokines on bone mass in chronic inflammation is usually increased bone resorption rather than increased bone formation,[25] which contrasts with our finding of normal BMD in sarcoidosis. Recent data, however, indicate that a cytokine as interleukin-6 may influence osteoblast proliferation and differentiation as well.[32] It may well be that these dual functions of cytokines on bone physiology are responsible for the normal BMD in untreated sarcoid subjects, despite increased bone turnover.
We found a positive relation between sIL-2R and ACE and the bone resorption marker ICTP, but not between the bone formation marker PINP. No relation was found between hs-CRP and bone turnover markers. All these factors can be used as markers for disease activity in sarcoidosis. Of these, in particular sIL-2R is suitable to monitor the activity of the T-cell component in sarcoidosis.[33,34] Studies on circulating hs-CRP in several immune and inflammatory diseases have shown that increased levels of this parameter are associated with decreased BMD.[35] Our finding of no such an association and a positive relation of sIL-2R and ACE with ICTP but without consequent decrease of BMD supports our suggestion that in sarcoidosis a dual mechanism different from other chronic inflammatory conditions is involved in bone metabolism.
One of the factors responsible for this possible dual mechanism in sarcoidosis may be vitamin D. Vitamin D receptors are identified on macrophages and activated T-lymphocytes,[36] which is suggestive for a potential role for vitamin D in regulating the immune system. Sarcoid granulomas can induce production of the active compound of vitamin D, $1,25(OH)_2D3$.[5,9] Several studies have shown that this hormone can regulate osteoblastogenesis and osteoclastogenesis, the latter partly via regulation of the OPG and RANKL expression of osteoblasts.[37] As we found no differences of $1,25(OH)_2D3$ levels between the groups of patients studied besides a weak negative correlation in the current glucocorticoid users with Z-scores of BMD and no relation with bone turnover

parameters, our findings are not indicative for such an influence of vitamin D on bone turnover on sarcoidosis, neither precludes such an effect.

As fracture risk is not only determined by loss of bone mass, but also by loss of bone micro architecture and consequent bone strength,[38,39] a BMD not different from a reference population does not preclude increased fracture risk. In our series, only three clinical fractures were observed. With quantitative morphometric X-ray absorptiometry (MXA), however, vertebral deformities, which may be suggestive of vertebral fractures, were found in 21% of the 87 patients studied. It is uncertain whether or not this prevalence differs from subjects without sarcoidosis, as no data on non-clinical deformities in healthy young and premenopausal individuals are available. The best comparison with healthy subjects for the present study stems from the EVOS (European Vertebral Osteoporosis Study) study, in which in a very large cross-sectional population based study European subjects aged 50 to 79 years were investigated. The prevalence of vertebral deformities on X-rays in this study was 12% (range 6-21%) in males and females.[40] The investigators of this study used the methodology of McCloskey and Eastell and co-workers.[41,42] Following this methodology measurements are corrected for normal variations in vertebral shape. Relative to the more simple and practical method of Genant we used,[43] the method of Eastell may result in lower prevalences of vertebral deformities. Presumably, the prevalence of vertebral deformities we found in patients with sarcoidosis is not different or perhaps slightly more than what can be found in a reference population. To what extent these vertebral deformities are indeed related to vertebral fractures is ambiguous too in the absence of a gold standard, but may implicate that the occurrence of non-clinical vertebral fractures in patients with sarcoidosis is not rare despite a normal BMD.

One of the limitations of our study is the cross-sectional design. Longitudinal studies are necessary to determine whether or not sarcoidosis may result in substantial bone loss on long term, despite the protective mechanisms suggested before. Another limitation is the measurement of BMD at the hip only, although recently was demonstrated that hip measurements were superior to the spine in overall fracture prediction.[44] This may have contributed to an underestimation of osteopenia and it can not be excluded that more differences would have been found if DXA of the spine was also performed. Despite this drawback of the study, we found an even increased BMD of the trabecular bone of the trochanter in untreated patients. Therefore, it is highly unlikely that measuring the BMD of the trabecular bone of the spine would have revealed a decreased BMD compared to the reference population. In addition, the morphometric assessment of vertebral fractures in a subset of patients may have underestimated the prevalence of fractures as well.

In conclusion, we found that in patients with sarcoidosis hip BMD is normal, even if currently or previously treated with glucocorticoid, despite an increased

bone turnover. As the increased bone resorption was found to be related to ACE and sIL-2R, we suggest that this is - at least partly - the result of disease activity. The increased bone formation, which apparently neutralizes the increased bone resorption, may imply that in sarcoidosis mechanisms are involved that compensate for the well-known effects of cytokines in inflammatory diseases on osteoclastogenesis and bone resorption. Nonetheless, vertebral deformities suggestive of fracture were found in a significant number of patients which indicates that patients with sarcoidosis still have a relevant fracture risk.

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