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Osteoporotic bone fracture risk assessment in Latvian patients with newly diagnosed sarcoidosis

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Abstract *Background and aim:* Increased calcitriol synthesis in sarcoid granulomas with subsequent hypercalcaemia and hypercalciuria can affect bone metabolism in patients with sarcoidosis. Multiple factors can increase the fracture risk in patients with sarcoidosis. This study aimed to evaluate a 10-year osteoporotic and a 10-year hip fracture risk and to analyse factors affecting fracture risk for patients with newly diagnosed sarcoidosis compared to an age- and gender-matched control group from a real-world setting. *Methods:* The cross-sectional study included 171 patients with a histologically verified diagnosis of sarcoidosis who were hospitalised due to suspected sarcoidosis within two years and an age- and gender-matched control group of 178 hospitalised individuals. QFracture algorithm questions were asked during interviews. *Results:* A cohort of 349 subjects was analysed. The median age in the patient group was 40 years (IQR:20), and 60.2% were female. 21.6% of patients with sarcoidosis had at least one comorbidity that could potentially influence the osteoporotic fracture risk. Both the median 10-year osteoporotic fracture risk (0.9% (IQR:2) vs 1.3% (IQR:2.3), p=0.005; U=12394) and a 10-year hip fracture risk (0.1% (IQR:0.3) vs 0.2% (IQR:0.5), p=0.003; U=12368.5) was lower in patients with sarcoidosis compared to control group subjects. As compared to the control group, individuals with sarcoidosis exhibited a lower frequency of both osteoporotic (2.4% vs 11.2%, OR=0.189 (95% CI:0.063-0.566), p=0.003) and low-energy trauma fractures (2.9% vs 11.8%, OR=0.225 (95% CI:0.083-0.612), p=0.003) in personal medical history. *Conclusions*: This was the first study to investigate osteoporotic fracture risk and related factors in Latvian patients with newly diagnosed sarcoidosis. Our data show a lower risk of a 10-year osteoporotic and a 10-year hip fracture risk in patients with sarcoidosis compared to age- and gender-matched control group subjects from a real-world setting.

Key words: osteoporosis, sarcoidosis, vitamin D, calcium, bone, bone fracture risk, fracture risk assessment, fractures, hypercalcaemia, hypercalciuria

Introduction

Sarcoidosis is a granulomatous disease of unknown aetiology with clinical manifestations varying from spontaneously regressive localised forms to a chronic disease with multiorgan involvement, most commonly in the lungs (1-4). In North Europe, the incidence of sarcoidosis is 11.5/100 000 in Sweden and 6.9-9.2/100 000 in Latvia (White population) (5,6). In the USA, the incidence of sarcoidosis is 8-11/100 000 in the White and 17.8/100 000 in the Black population (5,7,8). The most commonly impacted age group is 30 to 50 years of age, and it affects both genders equally, the second peak of incidence is in women aged 50-60 (2,3).

Altered calcium and vitamin D metabolism is a well-known feature of this disease. In sarcoid

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granulomas, INF-gamma and INF-alpha enhance the 1-alpha hydroxylase enzyme in alveolar macrophages. This leads to the conversion of 25-hydroxyvitamin D (calcidiol) to its active form – 1,25-dihydroxyvitamin D (calcitriol), which can result in hypercalcaemia and hypercalciuria (9-12). Although severe hypercalcaemia is uncommon in sarcoidosis, it can have clinical implications (13). Hypercalciuria is the most common defect in calcium metabolism, the prevalence among patients with sarcoidosis is 18.8 to 62% (13-15). This can lead to renal calculi, calcium deposits in the renal parenchyma, and chronic kidney disease (16). Hypercalciuria has been associated with a worse clinical status and could be a marker of sarcoidosis activity (15).

Altered calcium and vitamin D metabolism can affect bone health, potentially leading to changes in bone mineral density (BMD) and an increased risk of fractures in patients with sarcoidosis, whether or not they are receiving glucocorticoid therapy (15,17,18,19). It is recommended for patients on glucocorticoid treatment to take supplements with vitamin D and calcium to prevent glucocorticoid-induced osteoporosis (20). According to some authors, additional intake of vitamin D and calcium could increase the risk of hypercalcaemia in patients with sarcoidosis and should be restricted (11,21). Although 25-hydroxyvitamin D insufficiency is common in sarcoidosis, the great majority of the patients have normal or elevated levels of calcitriol, a marker associated with disease activity, which can result in hypercalcaemia and hypercalciuria (22). For this reason, it has been recommended to control the levels of serum and urine calcium if supplementation is taken to prevent glucocorticoid-induced osteoporosis (4). Two studies showed no increased risk of hypercalcaemia or hypercalciuria with calcium and vitamin D supplementation in patients with sarcoidosis compared to those who did not take supplements (23,24).

Bone mineral density can be influenced directly or indirectly (19,25). Some studies relate sarcoidosis with decreased BMD (18,21). The aetiology of these changes can be multifactorial – due to glucocorticoid use, hypercalcaemia and hypercalciuria, decreased daily calcium and vitamin D intake and decreased physical activity (18,26). However, most patients with sarcoidosis are relatively young, glucocorticoid-free remission periods can be prolonged, and this could outweigh other risk factors for decreased BMD (25). A study in Italy analysed 252 patients with sarcoidosis and found that bone fragility may be related to the degree of severity of the disease (18). A high prevalence of osteoporosis and osteopaenia was found among patients newly diagnosed with interstitial lung disease (27). Other chronic diseases characterised by systemic inflammation, like rheumatoid arthritis or Crohn's disease are known predisposing factors for bone fragility (28,29). Bone resorption and formation markers can be altered in the case of sarcoidosis (30). In a Dutch study that investigated BMD and bone resorption and formation markers in 124 patients with sarcoidosis, increased values were found despite unchanged BMD (except for patients who received glucocorticoid therapy), which could indicate an increased bone remodulation process (30). Some studies have also demonstrated an increased risk of fracture even with normal BMD (31).

Data from multiple studies report varying results on the risk and prevalence of fractures in patients with sarcoidosis (18,25,30-34)

A retrospective cohort study with 5722 British patients showed an increased risk of clinical vertebral fractures, however, the risk of non-vertebral fractures was decreased (33). A meta-analysis of ten studies found no increased risk of fractures or changes in BMD in patients with sarcoidosis compared to controls (25).

All available studies investigated patients with established sarcoidosis, with or without glucocorticoid treatment, no studies have been performed with newly diagnosed patients before any disease-modifying therapy.

This is the first study to investigate bone fracture risk in patients with sarcoidosis in the Latvian population. We aimed to evaluate a 10-year osteoporotic and a 10-year hip fracture risk and to analyse factors and comorbidities affecting fracture risk for patients with newly diagnosed sarcoidosis compared to an age- and gender-matched control group from a real-world setting.

As sarcoidosis is more common in younger age groups, the QFracture algorithm, which has been validated for individuals aged 33 years or above, was selected to evaluate fracture risk during interviews (35).

Methods

Study population

The single-centre cross-sectional study was conducted at a tertiary referral centre (Riga East

Clinical University Hospital's Centre of Tuberculosis and Lung Disease). It included all patients who were hospitalised due to suspected sarcoidosis and treated within two years. Out of 280 patients with histologically verified sarcoidosis, 171 met the inclusion criteria (had a histologically confirmed diagnosis, were at least 33 years old, and provided consent to participate in the study). An age- and gender-matched control group of 178 hospitalised individuals without sarcoidosis and severely decompensated chronic conditions or altered mental status was assembled from a real-world setting.

QFracture risk calculator

All patients were interviewed using questions from the QFracture algorithm. QFracture has been developed and validated in the United Kingdom and is used to determine a 10-year risk of developing any osteoporotic fracture or a 10-year risk of hip fracture alone. The algorithm includes 26 questions and is available free of charge online at www.qfracture.org (35,36). QFracture risk score was designed to be based on readily available risk factors recorded in patients' health records or those that patients themselves are likely to know (self-reported ones) (36). A tool includes a question about the history of low-energy or major osteoporotic fractures (wrist, spine, hip, or shoulder). It is developed for use in the age group 30 to 99 years of age. The age range was increased to 33 years in 2016. The cut-off for the top 10% at the highest 10-year risk was 11.1% for women and 2.6% for men. In comparison to other internationally available instruments developed for the assessment of osteoporotic fracture risk, for example, FRAX (Fracture Risk Assessment Tool) or GARVAN (Garvan Institute's Fracture Risk Calculator), it had the highest accuracy. The AUROC (area under the receiver operating characteristics) curve for the model developed for the prediction of hip fracture was 0.89 in women and 0.86 in men but for the model for the prediction of any osteoporotic fracture – 0.82 in women and 0.74 in men (35).

In addition to QFracture algorithm questions, patients were asked about the use of medications, vitamin D supplementation, and menopausal status in women.

Statistical analysis

The Shapiro–Wilk test was used to determine the normality of data distribution. Means with standard deviations (SD) and parametric tests were used in data presentation and subsequent analysis if data were normally distributed. Medians with interquartile ranges (IQRs) and nonparametric statistical methods were used if the data did not follow the normal distribution. The differences in categorical variables were examined using the chi-square and Fisher exact tests. The Student's t-test (or Mann–Whitney U test) or Anova (or Kruskal–Wallis test) was used to compare continuous variables between two or more groups, respectively. Binominal regression analysis was employed to estimate the odds ratios. Statistical significance was set at p-value <0.05. Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM, New York, NY, USA). Graphs were generated using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA).

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review board of the Ethics Committee of Riga Stradins University (IRB no. 8/24.09.2015). Patients gave consent before participating in this study.

Results

Study population

In the present study, a cohort of 349 subjects (171 patients and 178 age- and gender-matched controls) were analysed to assess a 10-year osteoporotic or a 10-year hip fracture risk. The median age in the patient group was 40 years (IQR:20) and 60.2% were female. In the control group, the median age was 41 years (IQR:20) and 63.5% were female.

A 10-year osteoporotic fracture risk and fractures in personal medical history

The median 10-year osteoporotic fracture risk was lower in patients with sarcoidosis (0.9% (IQR:2), compared to control group subjects (1.3% (IQR:2.3), p=0.005; U=12394)), as well as a 10-year hip fracture risk (in sarcoidosis group, median 0.1% (IQR:0.3)

vs 0.2% (IQR:0.5) in the control group (p=0.003; U=12368.5)) (Figure 1).

A 10-year risk of any osteoporotic fracture above the cut-off for the top 10% at the highest risk (11.1% in women and 2.6% in men) was found in 4.7% in patients with sarcoidosis and 7.3% in the control group. Although patients with sarcoidosis exhibited a lower odds ratio (OR=0.623 (95% CI:0.242–1.543)), this association did not achieve statistical significance (p=0.306).

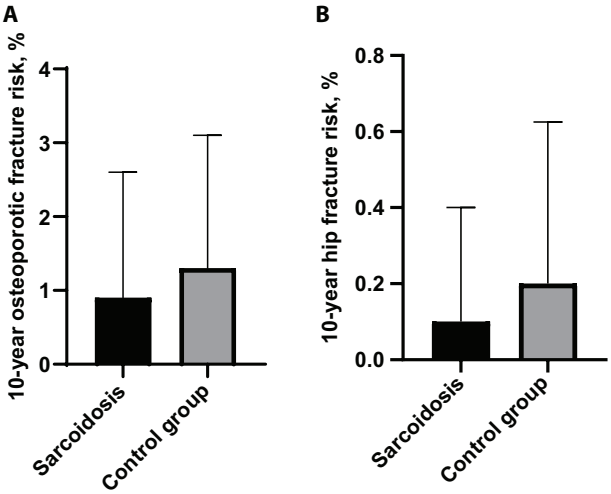

Figure 1. A 10-year osteoporotic and a 10-year hip fracture risk in patients with sarcoidosis and control group: (a) a 10-year osteoporotic fracture risk (n=349) (b) a 10-year hip fracture risk (n=349).

As compared to the control group, individuals with sarcoidosis exhibited a lower frequency of both osteoporotic (2.4% vs 11.2%, OR=0.189 (95% CI:0.063-0.566), p=0.003) and low-energy trauma fractures (2.9% vs 11.8%, OR=0.225 (95% CI:0.083-0.612), p=0.003) in personal medical history.

Comorbidities and factors influencing osteoporotic fracture risk

Differences between clinical parameters and comorbidities in both groups are presented in Table 1. There were statistically fewer current or former smokers among patients with newly diagnosed sarcoidosis (31.6% vs 48.3% in the control group, p<0.001). 21.6% of patients with sarcoidosis had at least one comorbidity that could potentially influence the osteoporotic fracture risk, compared to 44.3% in the control group (p<0.001). The most common comorbidities in

Table 1. Factors influencing osteoporotic fracture risk in patients with sarcoidosis and control group subjects.

Parameter	Patients with sarcoidosis	Control group	p-value
BMI, median, kg/m^2 (IQR)	27.6 (IQR:6.9)	26.1 (IQR:6.5)	0.004
Smoking status, % of smokers/ex-smokers	31.6	48.3	<0.001
Osteoporosis/hip fracture in either of parents, %	1.7	7.6	0.002
History of falls, %	1.2	5.1	0.062
Malignancy, %	4.5	2.3	0.381
Diabetes, %	4.1	14.6	<0.001
Asthma or COPD, %	8.2	6.7	0.685
Myocardial infarction, angina, stroke or TIA, %	6.4	10.7	0.185
Chronic liver disease, %	3.5	9.6	0.030
Chronic kidney disease (stage 4 or 5), %	0.6	1.1	0.520
Rheumatoid arthritis, %	2.9	2.8	0.532
Malabsorption, %	0.6	4.5	0.037
Endocrine disease, %	4.1	17.4	<0.01
Epilepsy or taking anticonvulsants, %	1.2	1.7	0.524
Regular use of antidepressants, %	0	10.1	<0.001
Regular use of glucocorticoids, %	6.4	1.7	0.028
Hormone replacement therapy, %	0.6	3.4	0.112
Regular use of vitamin D, %	33.9	64.0	<0.001

the sarcoidosis group were asthma or COPD (8.2%), followed by coronary artery disease (6.4%).

If comparing particular comorbidities, there were statistically significantly less diabetes mellitus (4.1% vs 14.6%, p<0.001), other endocrine disease (4.1% vs 17.4%, p<0.01), chronic liver disease (3.5% vs 9.6%, p=0.03), and malabsorption (0.6% vs 4.5%, p=0.037) in patients with newly diagnosed sarcoidosis than in the control group. Differences between other conditions did not reach statistical significance.

Patients with newly diagnosed sarcoidosis reported statistically more regular use of glucocorticoids (6.4% vs 1.7%, p=0.028) and less frequent recent use of antidepressants (0 vs 10.1%, p<0.001). They also reported less regular vitamin D intake (33.9% vs 64.0% in the control group, p<0.001).

Discussion

This was the first study to assess osteoporotic fracture risk and related factors in patients with newly diagnosed sarcoidosis (at the time of diagnosis), and the first one in the Latvian population.

Fracture risks

Our data show a statistically significantly lower risk of a 10-year osteoporotic and a 10-year hip fracture risk in patients with newly diagnosed sarcoidosis compared to age- and gender-matched control group subjects from a real-world setting.

It was rather surprising to find that patients with sarcoidosis had lower fracture risk compared to controls in our study. We ensured homogeneity by matching both groups in terms of age and gender, and excluding severely decompensated or mentally altered hospitalised patients who may have been unable to answer survey questions during interviews. The data should be interpreted with caution due to differences in assessment timing, self-reported comorbidities, and other influencing factors between groups.

Time matters

The degree of disease severity reportedly influences bone fragility in sarcoidosis (18). However, our study only included patients with newly diagnosed sarcoidosis. Most studies are conducted with patients with already established and treated sarcoidosis (17,18,32,33). A population-based cohort study in the USA with 345 patients examined the cumulative incidence of fragility fractures during a mean follow-up period of 12.9 years in the sarcoidosis group (32). A study in France included 142 patients with a mean disease duration of 9.5±7.1 years (17).

Multiple studies report varying results on the risk and prevalence of fractures in patients with sarcoidosis.

In previous studies, patients with sarcoidosis have been documented to exhibit a higher prevalence of reduced BMD, including in the lumbar spine (18), as well as an increased occurrence of spinal fractures and deformities (31). A study in the USA of 345 patients with sarcoidosis concluded that the cumulative incidence of fragility fractures was higher among patients with sarcoidosis compared to age- and gender-matched control group subjects (HR 2.18) (32). In a study that included 66 patients with sarcoidosis, the prevalence of spinal column deformations increased from 20 to 32%, in 26% of patients new or progressive vertebral deformities were diagnosed after 45 months of follow-up, although the BMD of the total group was unchanged after follow-up (31). In addition, in a cross-sectional analysis of 142 consecutive patients with histologically proven sarcoidosis, fragility fractures occurred in 23.5% of patients, despite normal mean BMD in the study population (17).

A Danish case-control study concluded that for both, patients with and without sarcoidosis, exposure to glucocorticoids was associated with an increased risk of major osteoporotic fractures, with no between-group difference (22).

A retrospective cohort study of 5722 British patients with sarcoidosis concluded that they had an increased risk of clinical vertebral fractures (RR 1.77) and also an increased risk of any fractures and osteoporotic fractures (RR 1.50) when on recent treatment with oral glucocorticoids. However, the risk of non-vertebral fractures was decreased (33).

A meta-analysis of ten studies including 6448 patients with sarcoidosis and 77857 controls demonstrated neither significantly increased fracture risk nor BMD changes in patients with sarcoidosis compared to controls, despite considerable heterogeneity between available studies (25).

Despite the differences between the two groups, our findings are in line with previous studies (25,33).

Comorbidities

In our study, patients with sarcoidosis had fewer comorbidities compared to the control group.

A population-based cohort study of 345 patients with sarcoidosis showed that patients with sarcoidosis had a significantly higher cumulative incidence rate of developing additional comorbidities and multimorbidity over time compared to age- and gender-matched controls (HR 1.60) (34). Our study only included patients with newly diagnosed sarcoidosis.

While we recognise that some reported comorbidities are associated with a higher risk of fractures, it was important to perform a comparative study instead of a descriptive one. To establish causality and draw more confident conclusions, we randomly selected hospitalised people from a real-world setting as the comparator group, not healthy controls.

Vitamin D supplementation

In our study, patients with newly diagnosed sarcoidosis reported less regular vitamin D intake (33.9% vs 64.0% in the control group, p<0.001).

Three reasons can be proposed. In the early stages before confirming sarcoidosis diagnosis, healthcare professionals advised patients with suspected sarcoidosis to reduce calcium intake and avoid vitamin D supplementation. Some patients were interviewed at a later time point after diagnosis, so they may report not using vitamin D anymore. Subjects in the control group were interviewed at a later time frame when the role of vitamin D had become better established and substitution therapy had become more popular in the general population.

Vitamin D supplementation is controversial for patients with sarcoidosis (21). In Latvia (Northern latitude 56°), vitamin D deficiency is prevalent (37). As previously discussed, if there are low levels of vitamin D in the general population, it is important to assess individual risks and monitor the levels of vitamin D and calcium in the serum and urine of patients with sarcoidosis before administering replacement therapy and determining the appropriate dosage (14,21).

Other influencing factors

In patients with sarcoidosis, low dietary calcium, high glucocorticoid dose, and low creatinine clearance increase fracture risk in addition to comorbidities (17).

In our study, patients with newly diagnosed sarcoidosis reported statistically more regular use of glucocorticoids (6.4% vs 1.7%, p=0.028). This could be explained by the fact that some patients were interviewed at a later time point after the diagnosis was established but not more than a year. Therefore, they reported the therapy that was started after the diagnosis, not beforehand. It is plausible that certain patients may have received glucocorticoid treatment prior to the final confirmation. Some patients with sarcoidosis reported the use of inhaled glucocorticoids but no detailed data were obtained during interviews.

In the study in France, at the time of the incident, 88 out of 142 (62%) patients had received glucocorticoid therapy and 46 out of 142 (32%) had received bisphosphonate therapy (17). In the study in Italy, 160 out of 252 (63%) patients were on glucocorticoid or disease-modifying anti-rheumatic drug treatment. The control group consisted of healthy individuals (18).

When creating a patient care plan for patients with sarcoidosis, it is crucial to consider various factors that may affect BMD and fracture risk. The risk assessment should be comprehensive and tailored to the individual, considering all potential risk factors. This includes not only the commonly described factors such as the use of glucocorticoids, but also altered calcium and vitamin D metabolism. It is recommended to implement multiple preventative measures that address several factors simultaneously.

Strengths and weaknesses

The strength of our study is a relatively large patient sample, a homogenous cohort (white population, a country-level tertiary referral centre), and a control group from a real-world setting. As discussed earlier, our findings are in line with previous studies (25,33). To our knowledge, this is the first study with patients with newly diagnosed sarcoidosis (at the time of diagnosis). Most studies are conducted with patients with already established and treated sarcoidosis (17,18,32,33).

It is important to acknowledge the limitations of this study. First, the QFracture algorithm was utilised to assess the osteoporotic fracture risk, but it was originally validated in the UK general

population for individuals aged 33 years or older. As sarcoidosis is more common in younger age groups, QFracture was used in Latvia due to the lack of other validated scores for assessing osteoporotic fracture risk. In comparison to other internationally available instruments developed for the assessment of osteoporotic fracture risk, such as FRAX or GARVAN, QFracture not only includes the younger population but also displays the highest accuracy (35). A very recent validation study from the UK reported that the CFracture algorithm has similar discrimination to QFracture but is overall better calibrated and applicable in younger people (38,39).

Recall bias may occur as the QFracture algorithm is based on risk factors that are readily available or self-reported by patients (36). Some patients may not discriminate low- vs high-energy fractures during interviews. QFracture under-estimated fracture risk in the whole population but over-estimation was considerable in older age groups and people with more comorbidities and at high risk of death from other causes (40).

Second, due to the current study design, we were unable to collect clinical data from the patients we interviewed. In our previous publication, we reported hypercalcaemia (9.9%) and hypercalciuria (22.7%) rates in Latvian patients with newly diagnosed sarcoidosis (14). However, we could not gather details on the calcium and vitamin D levels, calcium intake (through supplements or meals), and dietary and physical exercise habits of the patients interviewed in the current study. Hence, we could not calculate any association or correlation.

Third, since the data were collected through interviews, there is a possibility of recall bias for events and conditions. Despite providing careful instructions, there could be interviewer bias, as the control group was surveyed by three additional colleagues.

Conclusions

This was the first study investigating osteoporotic fracture risk and related factors in patients with newly diagnosed sarcoidosis (at the time of diagnosis), it was the first one in Latvia, a Northern European country. Data revealed that patients with newly diagnosed sarcoidosis have a statistically significantly lower 10-year osteoporotic (0.9% vs 1.3%) and a 10-year hip fracture risk (0.1% vs 0.2%) compared to age and gender-matched control group subjects from a real-world setting.

Patients with newly diagnosed sarcoidosis had statistically significantly fewer comorbidities that could potentially influence osteoporotic fracture risk (21.6% vs 44.3% in the control group, p<0.001). Despite these discrepancies, our findings are in line with several previous studies. Patients with sarcoidosis reported less smoking (31.6% vs 48.3%, p<0.001) and less regular vitamin D intake (33.9% vs 64.0% in the control group, p<0.001) compared to controls.

Additional research is necessary to measure BMD in patients with newly diagnosed sarcoidosis without therapy and determine the correlation between clinical findings and fracture risk.

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