The risk of fracture and prevalence of osteoporosis is elevated in patients with idiopathic inflammatory myopathies: data from a single Hungarian center

CURRENT STATUS: UNDER REVISION

BMC Musculoskeletal Disorders  BMC series

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Abstract

Background: The prevalence of osteoporosis and risk of fractures is elevated in rheumatoid arthritis, but we have little information about the bone mineral density and fracture risk in patients with inflammatory myopathies. We intended to ascertain and compare fracture risk, bone mineral density (BMD) and the prevalence of vertebral fractures in patients with inflammatory myositis and rheumatoid arthritis (RA) and to assess the effect of prevalent fractures on the quality of life and functional capacity.

Methods: Fifty-two patients with myositis and 43 patients with rheumatoid arthritis were included in the study. Fracture Risk was determined using FRAX® Calculation Tool developed by the University of Sheffield. Dual energy X-ray absorptiometry and bidirectional thoracolumbar radiographs were performed to assess BMD and vertebral fractures. Quality of life was measured with Short Form-36 (SF-36) and physical function assessment was performed using Health Assessment Questionnaire (HAQ).

Results: We found a significantly elevated fracture risk in RA compared to myositis patients if the risk assessment was performed without the application of the BMD results. If BMD results and glucocorticoid dose adjustment were taken into account, the differences in fracture risk were no longer significant. The prevalence of osteoporosis was found to be significantly higher in the myositis group (7% vs. 13.5%, p: 0.045), but the fracture prevalence was similar in the two groups (75% vs. 68%). The fractures rates were associated with age in both groups, but not with cumulative dose of steroid and BMD results correlated with fracture prevalence only in the RA patients. The number of prevalent fractures was significantly correlated to poorer physical function in both groups, and poorer health status in the myositis group, but not in the RA group.

Conclusions: Our findings suggest that inflammatory myopathies carry significantly elevated risk for osteoporosis and fractures. This higher risk is comparable to one detected with RA in studies and strongly affects the physical function and quality of life of patients. Therefore further efforts are required to make the fracture risk assessment reliable and to facilitate the use early preventive treatments.
Background
Osteoporosis is a common metabolic skeletal disorder characterized by decreased bone mass and deteriorated bone structure, leading to increased fracture rate [1]. Since the average age and the proportion of elderly persons in the population is increasing continuously, osteoporosis and consecutive fractures have become a global public health problem with enormous socioeconomic consequences [2, 3]. It is widely known that rheumatoid arthritis (RA) is one of the most important causes of secondary osteoporosis. Osteoporotic bone fractures are of crucial importance on the function and quality of life of patients. The pathogenesis of bone loss in autoimmune disorders involves numerous factors. The increased serum and tissue levels of pro-inflammatory mediators (tumor necrosis factor alpha /TNF-α/, prostaglandins, interleukin–1, 6, 8, 15, 17) lead to the increased expressions of: receptor activator of nuclear factor kappa-B ligand (RANKL) by osteoblasts, T-lymphocytes and synovial fibroblasts. The RANKL-RANK binding is the main pathogenetic event of osteoclastogenesis, osteoclast maturation and functioning. Another, not all that negligible reason, is the synergism of several factors that negatively affect the bone mass: dietary factors (decreased calcium /Ca/ and vitamin D3 intake), decreased muscle mass/strength and functional capacity, immobilization, deteriorated intestinal Ca absorption, reduced levels of sexual steroids, avoidance of sunlight and use of sunscreens and last but not least glucocorticoid (GC) use [4, 5, 6, 7, 8, 9, 10]. The chronic GC exposure leads to decreased calcium absorption, increased renal Ca loss, secondary hyperparathyroidism, decreased sexual hormone levels, decreased number and function of osteoblasts and eventually increased bone resorption and reduced bone formation [11, 12]. In patients with RA, systemic osteoporosis coincides with local bone resorption, as a typical consequence of inflammatory synovitis. Vertebral fractures are important but yet under recognized manifestation of osteoporosis. Most of them are asymptomatic, which makes their recognition more difficult, consequently they might remain unnoticed for years. Clinical observations show that 30% of patients taking steroids for more than 3 years suffer from an osteoporotic fracture. Moreover, literature data also demonstrated that patients with polymyositis (PM) or dermatomyositis (DM) had significantly lower BMD in both the hip and lumbar (L) spine compared to the healthy, age- and
gender-matched population [10,13]. The Fracture Risk Assessment Tool (FRAX®) developed and validated by Kanis et al, more than 10 years ago, is the most widely accepted and used method in clinical practice to estimate the 10-year probability of osteoporotic fractures [14]. FRAX score takes into account the relevant risk factors for a bone fracture, e.g., the presence of RA, but not myositis. Our present work is a cross-sectional observational study, whereby we intended to answer the following questions: 1. What is the prevalence of low BMD, vertebral fracture and high fracture risk in our patients with inflammatory myositis and RA? 2. Which factors are associated with fracture rates in myositis and RA patients? 3. How do the vertebral fractures influence the physical function and quality of life of patients?

Methods
This scientific cross-sectional study was conducted on our own initiative, in 52 consecutive patients with myositis and 43 patients with RA under the care of the National Myositis Center, in the Division of Clinical Immunology, Faculty of Medicine, at the University of Debrecen. This study meets, and is in compliance with all ethical standards of medicine. Informed consent was obtained from all of the subjects. This study is ethically compliant and was carried out in compliance with the Declaration of Helsinki. The inclusion criteria were the diagnosis of probable, or definitive idiopathic inflammatory myopathy (IIM) based on the Bohan and Peter criteria [15], and rheumatoid arthritis according to the 2010 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria [16]. The patients with confounders of bone health were excluded from the study: if the patient took any drug affecting bone mineral density (including bisphosphonates, thiazide diuretics, anticoagulants, anticonvulsants, glitazones, etc.) except for vitamin D3 and Ca; secondary osteoporosis and those patients suffering from malignancies.

Laboratory tests included the measurements of calcium, alkaline phosphatase, C-reactive protein (CRP), thyroid-stimulating hormone, serum 25 OH Vitamin D3 and bone turnover markers (BTM): (parathyroid hormone, osteocalcin /OC/, beta-crosslaps / C-terminal telopeptides of type-I collagen:CTX-I/) levels. Blood sampling was done after overnight fasting to measure levels of PTH, OC and CTX-I. Plasma 25-OH-D3 level was analyzed by high pressure liquid chromatography (HPLC) using
a Jasco HPLC system (Jasco, Tokyo, Japan) and Bio-Rad reagent kit (Bio-Rad Laboratories, Hercules, CA, USA). Serum PTH, OC and CTX-I were measured using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). The inter-assay CV was <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) and <7% for CTX-I (lower detection limit: 0.010 µg/L, upper detection limit: 6 µg/L).

We measured the BMD of the lumbar spine (L₁-₄ vertebrae) and the left femoral neck by AP-DXA. The scan was performed with a DPX Pro bone densitometer (GE-Lunar Radiation Corporation, Madison, WI, USA), according to the manufacturer’s protocol. In patients with a history of a previous hip fracture, hip replacement surgery, or severe joint destruction, we measured bone mineral density in the right femoral neck. Osteoporosis was diagnosed according to the criteria proposed by the World Health Organization Study Group, when the BMD was 2.5 or more standard deviations below the young-adult mean, and osteopenia was diagnosed when the BMD was between −1 and −2.5 [17].

The FRAX, Health Assessment Questionnaire (HAQ) and Short Form 36 (SF–36) questionnaires were completed by a personal interviewer. The web-based algorithm at http://www.shef.ac.uk/FRAX® was applied as the FRAX® algorithm (version 3.6) adapted for Hungary [18]. Special risk factors (age, sex, weight, height, previous fracture, parent fractured hip, current smoking, GCs, RA, secondary osteoporosis, alcohol 3 or more units/day, femoral neck BMD) were recorded into this calculator, for every single patient. The output was a 10-year probability of hip fracture and a 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) [18]. We measured quality of life including mental health with the SF–36 questionnaire validated for use in Hungary [19]. The assessment of the patients’ physical function was performed using the HAQ questionnaire [20].

To assess the prevalence of vertebral fractures 40 myositis patients and 35 RA patients underwent a bidirectional (anteroposterior and lateral) X-ray imaging of the thoracic (Th) and lumbar (L) spine on separate cassettes for each picture. The Genant’s semi-quantitative assessment on standard radiographs was used to evaluate vertebral fractures [21]. Vertebral shape (wedge, concave, or
crush) and decreases in anterior, posterior, and/or middle vertebral height (grade 0, no reduction; grade 1, minimal fracture, 20%-25% height decrease; grade 2, moderate fracture, 25%-40% height decrease; and grade 3, severe fracture, greater than 40% height decrease) were determined by two independent assessors (A. V.; O. S.). The differences were resolved by repeated analysis and by consensus.

Statistical analysis was performed with version 20.0 of the SPSS software package (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Normally distributed continuous variables were described by mean and standard deviation values (SD). Categorical variables were described using frequency (case number) and percentage. For comparing the groups we used independent samples t-test or Mann-Whitney test according to the distribution. The connection of two independent variables was analyzed with Spearman’s correlation, Chi² test, and for lower numbers of cases Fisher’s exact test. P values of less than 0.05 were regarded as statistically significant.

Results
Ninety-five patients participated in the study. The myositis group consisted of 52 patients (9 males and 43 females, with a mean age of 57.46 years), while the RA group consisted of 43 patients (2 males and 41 females, with a mean age of 58.58 years). There was no significant difference between the two groups in the basic clinical data (including the mean BMD and 25 OH Vitamin D3 level) as indicated in Table 1. The proportion of patients receiving oral Ca and vitamin D substitution did not differ significantly between the two groups (34 vs. 29 patients). We could not find any significant differences between the two groups in terms of other factors included in the FRAX® tool (previous fracture, parent fractured hip, smoking, glucocorticoids, alcohol consumption) except the presence of rheumatoid arthritis (data not shown). In the myositis and RA groups normal BMD was found in 27% and 53.5% respectively, whilst osteopenia was found in 60% and 39.5% of the patients respectively, and osteoporosis found in 13.5% and 7% of the patients respectively, and the difference in frequency of osteoporosis found to be statistically significant between the two groups (Fisher’s exact test, p = 0.045).
The fracture risk assessment was calculated first without applying the BMD values. Regarding the other major and femoral neck fractures the fracture risk in RA patients was significantly higher than in myositis patients (15.58% vs. 9.68% and 6.23% vs 3.06%; p = 0.008 and p = 0.022). As a second step, the fracture risk calculation was repeated, and this time with the BMD values taken into account, with the earlier significant difference in the fracture probability disappearing (13.25% vs. 9.44% and 3.57% vs. 2.77%; p = 0.053 and p = 0.811). During third step, the fracture risk assessment was performed after adjustment to the dose of glucocorticoids according to Kanis et al [22]. With this correction the magnitude of the difference further decreased: the risk of major osteoporotic and hip fracture were found to be 9.96% vs 9.54% (p = 0.884) and 2.46% vs. 2.87% (p = 0.128) (Figure 1 - Fracture risk in patients with myositis and rheumatoid arthritis).

As previously mentioned 75 patients underwent bidirectional vertebral X-ray examinations, 40 myositis patients (8 males and 32 females, mean age 60.97 years) and 35 RA patients (all female, mean age 59.71 years). Patients with myositis had significantly longer disease duration (14.98 ±7.94 vs. 10.97 ±7.38 years, p = 0.021) and higher cumulative steroid dose (24.82 ±28.16 g vs. 9.85 ±12.745 g, p = 0.009) (Table 2). Overall 194 vertebral fractures were discovered in 54 patients (115 fractures in 30 myositis and 79 fractures in 24 RA patients), with these patients representing 75% of the myositis group and 68% the RA group, and the difference was not statistically significant (Table 2). As a next step the myositis and RA patients were divided into two groups according to the presence of vertebral fractures. The mean age of the fractured patients was significantly higher in both groups (62.83 vs. 55.4; p = 0.034 in the myositis group, and 63.25 vs. 52.0; p = 0.022 in the RA group). In addition significantly lower mean lumbar and femur neck BMD and higher -CTX levels were seen in fractured patients in the RA group (1.02g/cm2 vs 1.17 g/cm and 0.819g/cm2 vs 0.944g/cm2; p = 0.01 and p = 0.012, as well as 0.31µg/L vs. 0.21µg/L; p = 0.018). The mean 25OH Vitamin D3 levels showed no correlation with the presence of vertebral fractures (Table 3, Table 4).

Finally we investigated the influence of vertebral fractures on the patients’ physical function and quality of life using HAQ and SF-36 questionnaires (Figure 2a-b). It was found that the decrease in physical function and quality of life was proportional to the number of vertebral fractures. The
worsening of physical function was more pronounced in the myositis group compared to the RA group (R = 0.457; p = 0.008 vs. R = 0.376; p = 0.041). (Figure 2a - Correlation between number of fractures and the results of a) the functional tests (HAQ)). Surprisingly, we could not detect any significant correlations regarding the SF36 data of patients with RA, but in myositis patients and in the total patient group the number of bone fractures was strongly associated with poor SF36 results (Figure 2/b - Correlation between number of fractures and the results of the patient’s health (SF–36)). The same results were found, if we examined separately the mental and the physical components of the questionnaire (data not shown).

Discussion

To our knowledge this study is the first, which investigates and compares bone fracture risks in IIM and RA, and the first work which correlates BMD, FRAX and vertebral fracture data of myositis patients with rheumatoid arthritis patients. Data from a recent population based study from Taiwan also showed a higher osteoporosis prevalence rate among patients with DM/PM. The increased osteoporosis risk was independent of the corticosteroids and immunosuppressant treatment [9]. Gupta et al recently published a study about prevalence of vertebral deformities in patients with inflammatory myositis and found a high prevalence of asymptomatic vertebral fractures, but they did not examine the fracture risk and the consequences of fracture on physical function and quality of life [23]. Basically, fracture risk assessed without taking BMD into consideration showed greater risk of fracture in patients with rheumatoid arthritis than in myositis patients. If the BMD data were applied as well, there was no longer any significant differences between the values of the two groups. This might support the argument that for the lower BMD—which is more frequent in patients with myositis - counterbalanced the “confounding” effect of RA as a risk factor. With an adjustment of FRAX according to the dose of glucocorticoids, the remaining non-significant differences further decreased. Taking into account the high prevalence of osteoporosis/osteopenia in the myositis group, it seems logical to consider incorporating a factor that modifies the FRAX tool and allows for a more reliable risk calculation in patients with myositis. Of course, this requires studies with larger patient population and with bone fracture endpoints. In addition, it would generate a necessity for multiple,
disease dependent modifying factor development according to other systemic musculoskeletal diseases (lupus, Sjögren’s syndrome, vasculitis, etc). We showed, that the fractured patients were significantly older in both groups, and had higher -CTx levels in RA. The occurrence of vertebral fractures in both myositis and rheumatoid arthritis were very common and seriously affected the patients’ physical function and quality of life, especially in those with multiple fractures. It was interesting to observe that this effect was more pronounced in myositis patients with regard to the HAQ results, and surprisingly, the fractures did not modify significantly the health status of the RA patients. This latter phenomenon could be explained by the frequent joint damage and secondary fibromyalgia seen in RA, which might bias the results of the questionnaire. We found a similar high prevalence rate of vertebral fracture as Gupta et al [22], but in their myositis population the median age and disease duration were shorter than in our population and only patients with myositis were investigated. Despite the longer duration of the disease in our population the prevalence of fractures were not materially more frequent, therefore it is imperative to speculate that the majority of fractures occur in the early phase of the disease, when the administration of higher corticosteroid doses is more frequent. Based on the results of our study, a national patient educational material, a patient warning card has been constructed, which we use regularly to increase the patients’ awareness and adherence to preventive pharmacological and non-pharmacological antiporotic treatments.

The possible limitations of this study should be acknowledged. This work was a single institution study from a national myositis center in Hungary, the number of participants in the study was relatively low and due to the cross sectional nature of the investigation the calculated and the real fracture risk were not comparable.

Conclusions
It can be concluded that osteoporosis and consequential fractures in myositis are common and probably underestimated and that their examination is often neglected. Therefore it would be important to pay greater attention to the recognition of the low BMD and high fracture risk and the use of preventive measures. Our results showed a good agreement with data of groups from other
regions of the world, suggesting that the high fracture prevalence is a global myositis dependent feature. Beyond that, in our opinion, the use of validated, internationally accepted patient warning cards could increase patients’ adherence and will lead to decreased fractures rate. We believe, that through the collaboration of myositis centers we can integrate the myositis into the FRAX calculator as a unique risk factor. This way we can make the risk assessment more reliable worldwide in patients with inflammatory myositis.

List Of Abbreviations

ACR: American College of Rheumatology

β-CTx: beta-crosslaps

BMD: bone mineral density

BMI: body mass index

BTM: bone turnover markers

Ca: calcium

CRP: C-reactive protein

CTX-I: C-terminal telopeptides of type-I collagen

DEXA: dual-energy x-ray absorptiometry

DM: dermatomyositis

EULAR: European League Against Rheumatism

FRAX: Fracture Risk Assessment Tool

GC: glucocorticoid

HAQ: Health Assessment Questionnaire

HPLC: high pressure liquid chromatography

IIM: idiopathic inflammatory myopathy

L: lumbar

OC: osteocalcin

PM: polymyositis

PTH: parathyroid hormone
RA: rheumatoid arthritis
RANK: receptor activator of nuclear factor kappa-B
RANKL: receptor activator of nuclear factor kappa-B ligand
SD: standard deviation
SF–36: Short Form–36
TNF-α: tumor necrosis factor alpha
ug: microgram

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Scientific and Research Ethics Committee of the University of Debrecen under the number of DE RKEB/IKEB 5101.

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
Anett Vincze, Levente Bodoki, Katalin Szabó, Melinda Nagy-Vincze, Orsolya Szalmás, Katalin Dankó, János Gaál and Zoltán Griger declare that they have no conflict of interest.

Funding
This work was supported by the ÚNKP-17-2 New National Excellence Program of the Ministry of Human Capacities “

Authors’ contributions
AV: performed the fracture risk assessment, data capture, statistical analysis, radiographs assessment; LB participated in data capture and manuscript preparation, KS participated in the patients selection and in the organization of the study; MN-V participated in data acquisition and processing, OS: assessment of radiographs; KD participated in the design of the study and helped in
drafting the manuscript. JG and ZG conceived of the study participated in its design and coordination.

All authors read and approved the final manuscript.

JG and ZG equally contributed to this work.

Acknowledgments

We thank Katalin Hodosi for her help with the statistical analysis.

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Tables
Table 1 - Summary of the most relevant clinical data of the patients
|                           | Myositis patients  | RA patients  | P-value |
|---------------------------|--------------------|--------------|---------|
|                           | N=52               | N=43         |         |
| Age (years)               | 57.46±11.168       | 58.58±10.486 | 0.618   |
| Men                       | 9 (17.3%)          | 2 (4.7%)     | 0.104   |
| Women                     | 43 (82.7%)         | 41 (95.3%)   |         |
| Menopause at examination  | 33/43 (76.67%)     | 35/41% (85.3%) | 0.314  |
| Weight (kg)               | 70.88±14.38        | 73.74±13.77  | 0.328   |
| Height (cm)               | 164.12±7.56        | 161.35±17.62 | 0.308   |
| BMI (kg/m²)               | 26.39±5.58         | 27.46±4.56   | 0.318   |
| Vitamin D and calcium supplement | 34 (65.4%)   | 29 (67.4%)    | 0.833  |
| 25 OH Vitamin D3 level (nmol/L) | 59.13±22.12 | 62.82±23.62 | 0.440  |
| BMD L1-4 (g/cm²)          | 1.04±0.238         | 1.07±0.159   | 0.557   |
| BMD femur (g/cm²)         | 0.83±0.108         | 0.85±0.125   | 0.294   |
| Normal                    | 14 (27%)           | 23 (53.5%)   | 0.045   |
| Osteopenia                | 31 (60%)           | 17 (39.5%)   |         |
| Osteoporosis              | 7 (13.5%)          | 3 (7%)       |         |

Table 2 – Basic clinical data of patients available for vertebral X-ray assessments

|                           | Myositis (N=40) | RA (N=35) | P-value |
|---------------------------|-----------------|-----------|---------|
| Age (years)               | 60.97 ±10.09    | 59.71 ±11.16 | 0.795  |
| Female/male (N)           | 32/8            | 35/0      | -       |
| Duration of disease (years) | 14.98 ±7.94   | 10.97 ±7.38 | 0.021  |
| Cumulative steroid dose (g) | 24.82 ±28.16  | 9.85 ±12.745 | 0.009  |
| Patients with vertebral fractures | 30          | 24        | 0.375   |
| Number of all fractures   | 115             | 79        | 0.206   |
### Table 3 – Clinical and laboratory data of myositis patients with and without fractures

|                          | With fracture (N=30) | Without fracture (N=10) | P-value |
|--------------------------|----------------------|-------------------------|---------|
| Age (years)              | 62.83±9.858          | 55.4±9.057              | 0.034   |
| Duration (years)         | 16.03±8.024          | 11.8±7.115              | 0.150   |
| Cumulative steroid (g)   | 25.93±29.85          | 21.46±23.42             | 0.778   |
| BMD L1-4 (g/cm²)         | 1.05±0.285           | 0.99±0.114              | 0.259   |
| BMD femur (g/cm²)        | 0.83±0.111           | 0.84±0.130              | 0.744   |
| 25OH-Vitamin D3 level (nmol/L) | 62.91±28.065     | 70.81±29.305            | 0.365   |
| ß-CTx (ug/L)             | 0.307±0.216          | 0.281±0.124             | 0.988   |

### Table 4 – Clinical and laboratory data of RA patients with and without fractures

|                          | With fracture (N=24) | Without fracture (N=11) | P-value |
|--------------------------|----------------------|-------------------------|---------|
| Age (years)              | 63.25±9.175          | 52±11.610               | 0.022   |
| Duration (years)         | 10.71±6.969          | 11.55±8.537             | 0.957   |
| Cumulative steroid (g)   | 11.34±14.25          | 6.59±8.23               | 0.430   |
| BMD L1-4 (g/cm²)         | 1.02±0.142           | 1.17±0.138              | 0.010   |
| BMD femur (g/cm²)        | 0.819±0.122          | 0.944±0.082             | 0.012   |
| 25OH-Vitamin D3 level (nmol/L) | 71.59±27.35     | 52.25±19.816            | 0.076   |
| ß-CTx (ug/L)             | 0.31±0.139           | 0.21±0.068              | 0.018   |

**Figures**
Figure 1

Fracture risk in patients with myositis and rheumatoid arthritis
Correlation between number of fractures and the results of a) the functional tests (HAQ), b - Correlation between number of fractures and the results of the patient’s health (SF-36)