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# Risk factors for osteoporosis, falls and fractures in hereditary myopathies and sporadic inclusion body myositis — A cross sectional survey ☆

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ABSTRACT

*Background*: The risk of osteoporosis is known in myopathies requiring long-term steroid treatment and Pompe disease, but not in other hereditary myopathies or sporadic inclusion body myositis (sIBM).

*Methods*: Risk factors of osteoporosis, laboratory parameters of bone metabolism, frequency of falls and fractures, walking ability, and pain were surveyed using questionnaires in 89 patients with sIBM and genetically confirmed myopathies facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy types 1 and 2 (DM1, DM2), limb girdle muscular dystrophies (LGMD2A, LGMD2B, LGMD2I), *MATR3* myopathy, and oculopharyngeal muscular dystrophy (OPMD). Additionally laboratory parameters of bone metabolism were determined.

*Results*: The mean age at examination per disease group ranged from 32 years in LGMD2A to 70 years in sIBM. Myopathies with a higher degree of walking impairment had a higher risk of falls (sIBM, LGMD2A, LGMD2B). At the time of examination 3.4% had a history of osteoporosis. The 25-OH D3 level was decreased in 20% of patients (and in 55% of patients with LGMDs), 57% of them were ambulatory. The 25-OH D3 level was significantly lower in patients with myopathies than in other neurological disorders ($p < 0.001$). 2.7 falls per year per person occurred. Fractures were reported in 6.8% of patients within the last year. They involved frequently the tibia bone. The pain score didn't correlate with either the walking disability (WGMS) score or the 25-OH D3 level.



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*Conclusion*: The risk for osteoporosis and reduced 25-OH D3 level seems to be increased in wheelchair-bound patients with myopathy but also in patients with DM1 and autosomal-recessive myopathies.


## 1. Introduction

Osteoporosis has been described in the past decade in several chronic neurological conditions, most of them associated with severe walking impairment [1–11]. A reduced bone density increases the risk of fractures and is associated with pain; hence this might contribute to an increased comorbidity in patients who also have neuromuscular disorders. Established risk factors for low bone mineral density are increased age, low body mass index (BMI), post-menopause in women, current smoking, chronic corticosteroid use, history of prior fractures and falls [12,13]. In men, hypogonadism and excessive alcohol intake further contribute to an increased risk for osteoporosis [12]. The diagnosis of osteoporosis is confirmed by bone densitometry using dual-energy X-ray absorptiometry (DXA) technology [14,15].

The frequency, complications and management of reduced bone mineral density have been extensively described in boys with Duchenne muscular dystrophy and both juvenile and adult patients with dermatomyositis and polymyositis [1–6]. In these conditions long-term steroid treatment regimens and wheelchair dependence were main predisposing factors. Recently, bone mineral density was assessed in children and adults with Pompe disease, an inherited metabolic myopathy. Most of them were receiving enzyme replacement therapy. In these studies osteoporosis was more frequent in patients who were wheelchair-bound, but was also observed in ambulant patients. There was also a correlation between proximal muscle strength and total body bone mineral density [9–11]. However, there is no data about either the frequency or the risk of decreased bone mineral density in other hereditary myopathies and sporadic inclusion body myositis (sIBM).

The objectives of this study were to systematically analyze risk factors for decreased bone mineral density, the frequency of falls and fractures, and to correlate them with pain, walking ability, and markers of bone metabolism in different hereditary myopathies and sIBM.

## 2. Patients and methods

### 2.1. Patients

The study was performed at the Neuromuscular Clinic at the Department of Neurology at Martin-Luther-University Halle-Wittenberg, Germany. The Ethics Committee of Martin-Luther-University Halle-Wittenberg approved the study protocol. Written informed consent was obtained from all patients. Adult patients with a genetically confirmed myopathy or histopathologically-defined sporadic inclusion body myositis [16] were enrolled in the one-time survey between January 2011 and March 2013. Patients with genetically confirmed Pompe disease were excluded from the analysis; their data will be presented elsewhere.

### 2.2. Questionnaires

A questionnaire was designed to capture the onset of the myopathy (paresis as the initial symptom), the frequency of falls during the last twelve months, the history of fractures and osteoporosis, and factors influencing the occurrence of osteoporosis (gender, age, body mass index (BMI), cigarette smoking, use of steroids and other medication, onset of menopause) (Supplemental Fig. 1).

The short form of the Brief Pain Inventory (BPI) is a self-administered 9-item questionnaire and was used to assess the presence and severity of current pain (pain within the previous 24 h) and its interference with daily activities. Four specific questions asked patients to rate the worst, least, and average pain experienced in the previous 24 h, and also to rate current pain. Patients were asked to rate pain on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). The average of these 4 questions

was used to generate a Pain Severity Score (PSS). The design of the BPI minimizes recall bias. Finally, the BPI was used to assess the sites of pain and its treatment [17,18]. The BPI is widely used to evaluate pain in osteoporosis [19–21], but also myopathies [18].

The PSS was compared with the scores from 45 normal age and gender matched volunteers.

The Walton–Gardner–Medwin Scale (WGMS) was completed by the neurologist (F.H.), to asses the degree of walking disability [22].

### 2.3. Laboratory analysis

We analyzed non-fasting blood samples for serum concentrations of calcium (normal values: male <2.81 mmol/L, female <2.41 mmol/L), 25-hydroxyvitamin D (25-OH D3, normal values: in summer 50–300 nmol/L, in winter: 25–125 nmol/L, mild deficiency 25–30 nmol/L, moderate deficiency 10–25 nmol/L, severe deficiency <10 nmol/L), parathyroid hormone (PTH, normal values: 12–88 pg/ml), creatinine (normal value: <88 μmol/L), alkaline phosphatase (normal values: 0.60–1.75 μmol/L * s). Analysis was done using electrochemoluminiscence (Roche, Switzerland). Calcium and 25-OH D3 values were compared with those in 72 age and gender matched patients with a neurological non-myopathic disorder, who were not on long-term therapy with steroids, treated on a neurological ward (diagnoses: cephalalgia n = 19, cerebrovascular disorder n = 11, chronic pain n = 8, multiple sclerosis n = 8, amyotrophic lateral sclerosis n = 8, movement disorders n = 7, multiple sclerosis n = 7, infections of the central nervous system n = 6, epileptic seizures n = 3, tumors of the central nervous system n = 2).

### 2.4. Statistics

Descriptive statistics are presented as mean ± 1 standard deviation, median (Interquartile range) and number (percentage). All variables were analyzed to evaluate their normality using the Kolmogorov–Smirnov test. Differences between groups were analyzed using unpaired Student's *t*-test, $chi^2$ test, and Kruskal–Wallis One Way Analysis of Variance on Ranks, post-hoc analysis was done using all pairwise multiple comparison procedures (Holm–Sidak method). Spearman's rank correlation coefficient was determined to investigate correlations (SPSS 17, IBM Software Group, USA).

## 3. Results

Eighty nine patients with the following diseases participated in the study: myotonic dystrophy type 1 (DM1, n = 9) and type 2 (DM2, n = 23), limb girdle muscular dystrophy type 2A (LGMD2A, n = 5), LGMD2B (n = 3), LGMD2I (n = 5), facioscapulohumeral muscular dystrophy (FSHD, n = 22), *MATR3* myopathy (n = 10), oculopharyngeal muscular dystrophy (OPMD, n = 4), and sIBM, (n = 8). The details of the underlying genetic defects are shown in Table 1.

**Table 1**
Details of the underlying genetic defect in the patients with LGMD2A, LGMD2B, LGMD2I, *MATR3* myopathy.

| Disorder | Pat. nr. | 1st allele | 2nd allele |
|---|---|---|---|
| LGMD2A | 1 | p.Arg489Trp | p.Arg490Trp |
| | 2 | p.Gly445Arg | c.1746-20C > G |
| | 3 | c.550delA | p.Arg490Trp |
| | 4 | c.550delA | n.d.* |
| | 5 | p.Arg572Pro | p.Arg572Pro |
| LGMD2B | 1 | c.247dupG | c.763delC |
| | 2 | p.Arg1607Stop | p.Arg1607Stop |
| | 3 | c.757C > T, c.5212C > T. | c.3059insC |
| LGMD2I | 1…5 | p.L276I | p.L276I |
| *MATR3* myopathy | 1…10 | p.S85C | – |

n.d. not detectable.
* Reduction in intensity of 30, 60, and/or 90 kDa calpain bands in western blot.

**Table 2**
Demographic and clinical data, and data on risk factors of osteoporosis. Three patients had a BMI of 18 g/cm$^2$ (i.e. underweight), but none below. There are two outliers with an extremely high frequency of falls within the last year (one patient with LGMD2A: 200 falls per year, one patient with LGMD2B: 80 falls per year). Data are given as mean ± 1 standard deviation (SD), median (interquartile range, IQR) and number (percentage). The percentage (%) refers to all patients in the disease group, in the column menopause to all women (W). * Differences between groups were analyzed using Kruskal–Wallis One Way Analysis of Variance on Ranks, post-hoc analysis was done using all pairwise multiple comparison procedures (Holm–Sidak method).

| Disease | Sex (f/m) | Age (years) | Disease duration (years) | Distribution paresis | BMI (g/cm$^2$) | WGMS | Wheel-chair-bound | Falls/year | Patients with fractures | Number of fractures | Menopause | Cigarette smoking |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (n) | Mean ± 1SD | Median (IQR) | | Median (IQR) | Median (IQR) | n(%) | Median (IQR) | n(%) | n | *n* (%*W*) | *n*(%) |
| DM1 (n = 9) | 2/7 | 41.7 ± 10.4 | 9.0 (6.75–13.25) | Distal > proximal | 24.0 (19.75–27.25) | 2.0 (0–6.5) | 2 (22) | 0.0 (0–4.5) | 2(22.2) | 6 | 0 (0) | 1 (11.1) |
| DM2 (n = 23) | 20/3 | 62.1 ± 10.5 | 13.5 (7.0–23.0) | LGMD | 25.0 (19.75–28.75) | 4.0 (1.25–6.0) | 1 (4.3) | 0.0 (0–3.0) | 2 (8.7) | 2 | 19 (95) | 1 (4.5) |
| OPMD (n = 4) | 1/3 | 65.3 ± 10.2 | 12.5 (6.5–22.5) | LGMD | 24.0 (22.0–24.5) | 2.0 (0.5–5.0) | 1 (25) | 0.0 (0–1.0) | 0 (0) | 0 | 1 (100) | 0 (0) |
| LGMD2A (n = 5) | 3/2 | 31.0 ± 8.9 | 14.0 (6.5–15.5) | LGMD | 20.0 (19.0–26.25) | 6.0 (3.0–7.0) | 3 (60) | 4.0 (0–57.5) | 2 (40) | 3 | 0 (0) | 2 (40) |
| LGMD2B (n = 3) | 1/2 | 57.3 ± 15.6 | 18.0 (15.75–33.75) | LGMD, distal | 23.0 (22.25–26.75) | 6.0 (4.5–6.0) | 2 (66.6) | 6.0 (2.25–39.0) | 1 (33.3) | 1 | 1 (50) | 1 (33.3) |
| LGMD2I (n = 5) | 4/1 | 47.0 ± 15.6 | 8.0 (2.75–14.75) | LGMD | 24.0 (21.75–26.0) | 3.0 (2.25–5.25) | 0 (0) | 1.0 (0–7.25) | 1 (20) | 1 | 2 (40) | 0 (0) |
| FSHD (n = 22) | 14/8 | 50.0 ± 14,2 | 18.5 (11.5–26.0) | LGMD | 24.0 (23.0–28.0) | 3.0 (2.0–3.0) | 2 (9.5) | 1.0 (0–4.0) | 1 (4.5) | 1 | 7 (53) | 7 (33) |
| MATR3 (n = 10) | 6/4 | 52.8 ± 7.6 | 5.5 (4.5–7.0) | Distal > proximal | 24.5 (21.5–28.5) | 3.0 (3.0–3.5) | 0 (0) | 1.5 (0–6.0) | 1 (11.1) | 1 | 5 (83.3) | 2 (22.2) |
| sIBM (n = 8) | 4/4 | 69.5 ± 4.3 | 9.5 (8.0–12.0) | Distal > proximal | 24.0 (23.0–28.0) | 6.0 (5.5–8.0) | 3 (37.5) | 2.5 (0–6.5) | 3 (37.5) | 6 | 4 (50) | 0 (0) |
| P | | <0.001[a] | p = 0.021[b] | | n.s. (p = 0.825) | n.s. (p = 0.067) | | n.s. (p = 0.545) | | | | |

BMI Body Mass Index, DM myotonic dystrophy, F female, FSHD facioscapulohumeral dystrophy, LGMD limb girdle muscular dystrophy, M male, n.s. non-significantly, OPMD oculopharyngeal muscular dystrophy, sIBM sporadic inclusion body myositis, WGMS Walton–Gardner–Medwin Scale.

[a] Post-hoc analysis using Holm–Sidak method: DM2, OPMD, sIBM vs. DM1, LGMD2A, LGMD2I, FSHD, *MATR3* myopathy ($p < 0.05$).

[b] No differences between the groups.

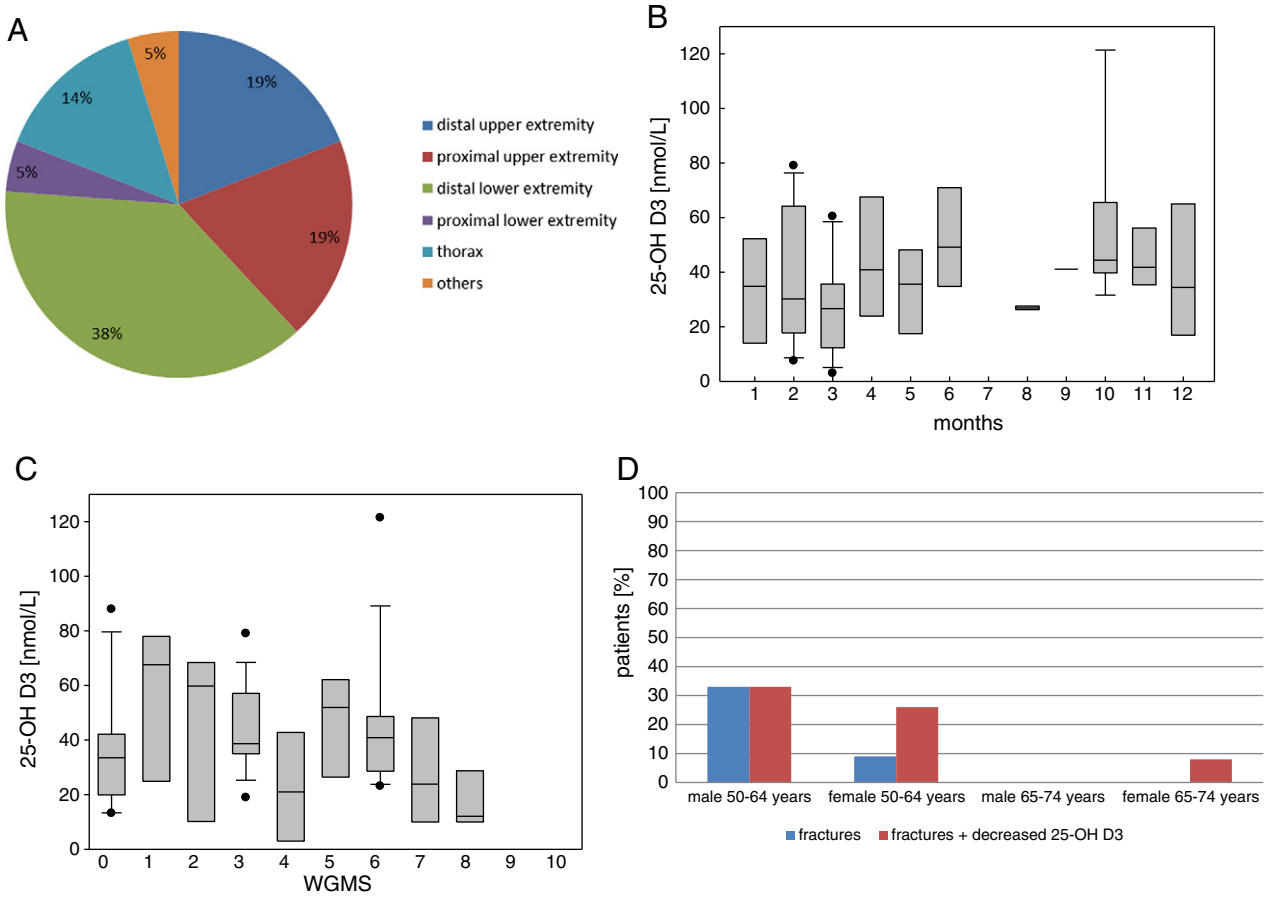


**Fig. 1.** A. Distribution of total number of fractures (n = 21) in all patients with myopathies. B. Serum 25-OH D3 level in all myopathies in relation to the months of the year. C. Serum 25-OH D3 level and WGMS in all myopathies. D. Frequency of fractures and decreased 25-OH D3 level (<30 nmol/L) among the elderly (>50 years, stratified for the age group 50–64 years and 65–74 years, respectively) men and women.

The demographic and clinical data as well as the risk factors for reduced bone density are shown in detail in Table 2. The mean age at examination ranged from 31.0 years ± 8.9 in LGMD2A to 69.5 years ± 4.3 in sIBM. Forty five patients were ≥50 years (30 women, 15 men). The mean age of the >50 year olds was 62 years ± 8.5. The median duration of disease ranged from 5.5 years (7.0–4.5) in *MATR3* myopathy to 18.0 years (33.75–15.75) in LGMD2B. In patients with DM1 and *MATR3* myopathy, and in one patient with LGMD2B, the pareses were predominantly distally located. In the other patients predominantly proximal muscles were affected. The total cohort included 13 wheelchair-bound patients (15.7%). Patients with LGMD2A, LGMD2B and sIBM were most frequently wheelchair-bound. Only 4 out of 39 post-menopausal women were wheelchair-bound (10%). Patients with sIBM had the most severe walking impairment (median WGMS 6.0) followed by patients with LGMDs (mean WGMS from 3.0 to 6.0).

### 3.1. Falls and fractures

Correlating with their severe walking impairment, patients with sIBM and LGMDs experienced the highest frequency of falls within the last 12 months (medians were 2.5–6.0, Table 2). Patients with myotonic dystrophies, OPMD, and *MATR3* myopathy, who had rather mild walking impairment, had the least number of falls (medians were 0.0–1.5). In the total cohort the mean number of falls per person per year was 5.5. If the two outliers (one each of LGMD2A and LGMD2B) were excluded, the mean rate was 2.7 falls per person per year. The incidence rate was between 3524 and 7623 falls per 1000 patients at risk.

**Table 3**
Pain severity score (PSS), localization, and pain medication in all myopathies. Data are given as mean ± 1 standard deviation (SD) or median (interquartile range, IQR) or number (percentage). The percentage (%) refers to all patients who described pain in a certain part of a body or who took a certain pain medication. * Differences between groups were analyzed using Kruskal–Wallis One Way Analysis of Variance on Ranks, post-hoc analysis was done using all pairwise multiple comparison procedures (Holm–Sidak method).

| Disease | PSS | Current pain | Localization: | | Pain medication: | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Shoulder/ upper arm | Lumbar/ lower leg | Non steroidal analgesics | Opioids | Antidepressants | Antiepileptics |
| | Mean ± 1SD | Median (IQR) | (n(%)) | (n(%)) | (n(%)) | (n(%)) | (n(%)) | (n(%)) |
| DM1 (n = 9) | 1.2 ± 1.6 | 0 (0–1.25) | 0(0) | 3(33.3) | 0(0) | 0(0) | 0(0) | 0(0) |
| DM2 (n = 23) | 2.9 ± 2.5 | 2 (0–3.75) | 11(47.8) | 14(65.2) | 7 (30.4) | 4 (17.4) | 0(0) | 1 (4.3) |
| OPMD (n = 4) | 0.7 ± 1.1 | 0 (0–1.0) | 0(0) | 1(25) | 0(0) | 0(0) | 0(0) | 0(0) |
| LGMD2A (n = 5) | 2.4 ± 1.7 | 2 (0–4.25) | 2(40) | 1(20) | 1 (20) | 0(0) | 0(0) | 1 (20) |
| LGMD2B (n = 3) | 2.7 ± 2.3 | 0 (0) | 2(66.7) | 1(33.3) | 0(0) | 0(0) | 0(0) | 0(0) |
| LGMD2I (n = 5) | 2.5 ± 2.7 | 3 (0–4.25) | 1(20) | 3(60) | 1 (20) | 0(0) | 0(0) | 0(0) |
| FSHD (n = 22) | 2.9 ± 2.1 | 3 (1.0–4.25) | 14(63.6) | 13(61.9) | 7 (31.8) | 1(4.5) | 1(4.5) | 0(0) |
| MATR3 (n = 10) | 2.5 ± 2.4 | 2 (0–4.25) | 3(30) | 4(40) | 1 (10) | 2 (20) | 2(20) | 0(0) |
| sIBM (n = 8) | 1.1 ± 1.6 | 0 (0–0.5) | 2(25) | 1(12.5) | 2 (25) | 0(0) | 0(0) | 0(0) |
| P | n.s. (p = 0.241) | n.s. (p = 0.066) | | | | | | |

DM myotonic dystrophy, FSHD facioscapulohumeral dystrophy, LGMD limb girdle muscular dystrophy, n.s. non-significantly, OPMD oculopharyngeal muscular dystrophy, PSS pain severity score, sIBM sporadic inclusion body myositis, WGMS Walton–Gardner–Medwin Scale.

**Table 4**
Serum markers of bone metabolism, frequency of diagnosed osteoporosis, and osteoporosis medication at the time of survey. Data are given as median ± 1 standard deviation (SD) or median (interquartile range, IQR) or number (percentage). The percentage (%) refers to all patients in the disease group. * Differences between groups were analysed using Kruskal–Wallis One Way Analysis of Variance on Ranks, post-hoc analysis was done using all pairwise multiple comparison procedure (Holm–Sidak method).

| Disease | $Ca^{2+}$(mmol/L) | Decreased $Ca^{2+}$ | 25-OH D3 (nmol/L) | Decreased 25-OH D3 | PTH (pg/ml) | AP (μmol/L) | Osteoporosis at visit | Osteoporosis medication at visit |
|---|---|---|---|---|---|---|---|---|
| | mean ± 1SD | (n (%)) | median (IQR) | (n (%)) | median (IQR) | median (IQR) | (n (%)) | (n (%)) |
| DM1 (n = 9) | 2.4 ± 0.1 | 0/9 (0) | 42 (16.3–60.9) | 1/9 (11.1) | 33.3 (24.3–49.9) | 1.1 (0.9–1.9) | 0/9 (0) | 0/9 (0) |
| DM2 (n = 23) | 2.4 ± 0.1 | 0/21 (0) | 39.5 (29.6–53.5) | 1/19 (5.2) | 37.1 (31.7–43.8) | 1.3 (1.1–1.5) | 1/23 (4.3)21 | 1/23 (4.3) |
| OPMD (n = 4) | 2.4 ± 0.1 | 0/4 (0) | 36 (22.2–58.4) | 1/3 (33.3) | n.a. | 0.8 (0.7–1.1) | 0/4 (0) | 0/4 (0) |
| LGMD2A (n = 5) | 2.4 ± 0.1 | 0/5 (0) | 31.7 (17.1–48.2) | 2/4 (50) | 42.3 (41.2–46.6) | 0.9 (0.7–0.9) | 0/5 (0) | 0/5 (0) |
| LGMD2B (n = 3) | 2.4 ± 0.1 | 0/3 (0) | 24.1 (8.3–42.2) | 2/3 (66.6) | 103.8 (41.7–165.8) | 1.2 (1.1–1.3) | 0/3 (0) | 1/3 (50) Dekristol |
| LGMD2I (n = 5) | 2.4 ± 0.1 | 0/4 (0) | 28.9 (18.4–41.5) | 2/4 (50) | 40.8 (28.7–47.9) | 1.1 (1.0–1.2) | 1/5 (20) | 0/5 (0) |
| FSHD (n = 22) | 2.4 ± 0.1 | 1/20 (5) | 38.8 (27.6–58.3) | 4/16 (25) | 29.1 (26.3–35.0) | 1.1 (0.9–1.2) | 0/22 (0) | 2/22 (9.1) Dekristol Calcium |
| MATR3 (n = 10) | 2.3 ± 0.1 | 2/10 (20) | 55.6 (29.9–69.0) | 1/7 (14.3) | 53.4 (35.5–57.2) | 1.1 (0.9–1.3) | 0/10 (0) | 1/10 (10) Calcium |
| sIBM (n = 8) | 2.3 ± 0.1 | 1/8 (12.5) | 28.8 (26.8–30.6) | 0/5 (0) | n.a. | 1.1 (1.0–1.3) | 1/8 (12.5) | 1/8 (12.5) Dekristol |
| Total cohort (n = 89) | 2.4 ± 0.1 | 4/84 (4.8) | 36.1 (26.6–55.9) | 14/70 (20) | 37.2 (29.0–45.9) | 1.1 (0.9–1.3) | 3/89 (3.4) | 6/89 (6.7) |
| P | n.s. (p = 0.241) | | n.s. (p = 0.544) | | n.s. (p = 0.271) | n.s. (p = 0.069) | | |

AP was normal in all patients, PTH was only increased in 1 patient with LGMD2B.
DM myotonic dystrophy, FSHD facioscapulohumeral dystrophy, LGMD limb girdle muscular dystrophy, n.s. non-significantly, OPMD oculopharyngeal muscular dystrophy, sIBM sporadic inclusion body myositis. 25-OH D3 25-hydroxyvitamin D, AP alkaline phosphatase, $Ca^{2+}$ calcium, n.a. not available, PTH parathyroid hormone.

In the total cohort, 13 patients (15%) reported ever experiencing a total of 21 fractures, among them were 8 patients ≥50 years (i.e. 8/45 patients ≥50 years, 18%). The rate of fractures in the total cohort within the year investigated by the survey was 6.8% (i.e. n = 6). In total 14 out of 21 fractures happened after the onset of myopathy. The distribution of fractures is given in Fig. 1A and involves fractures of the lower extremity in 43% and the upper extremity in 38%. Fractures occurred most frequently in patients with disorders associated with a severe walking impairment (n = 6), i.e. LGMD2A, LGMD2B, sIBM, but also myotonic dystrophies (n = 4). Wheelchair-bound patients with fractures had the following disorders: sIBM (n = 2), LGMD2A (n = 1), LGMD2B (n = 1). In the myotonic dystrophies all 4 patients who reported previous fractures were ambulatory (DM1 n = 2, DM2 n = 2) (Table 1). Six out of eight fractures located at a lower limb involved the tibia bone. Four of the tibial fractures occurred in wheelchair-bound patients.

The frequency of fractures and of decreased 25-OH D3 levels (i.e. <30 nmol/L) among the elderly (> 50 years, stratified for gender and the age groups 50–64 years and 65–74 years, respectively) is seen in Fig. 1D. There was no significant difference in the number of fractures or 25-OH D3 level between the two age groups but this may have been due to small sample size in each cohort.

### 3.1.1. Other risk factors

Only 3/89 patients (3.3%) were slightly underweight and had a BMI of 18 kg/m$^2$. Thirty nine out of 51 women were post-menopausal (76.5%). Thirteen patients were current smokers (14.6%), seven of them were women, but only one was a post-menopausal women. Only one woman with *MATR3* myopathy was on long-term cortisone treatment for 15 years due to rheumatoid arthritis. She took calcium as prophylaxis, but had no previous history of osteoporosis.

### 3.1.2. BPI

The PSS was highest in FSHD, DM2, LGMD2B, and LGMD2I with mean scores between 2.5 and 2.9 (Table 2). In these disorders more than 50% reported pain in the shoulder girdle, the limb girdle or both. One third of the patients with DM2 and FSHD took non-steroidal analgesics. The PSS did not correlate with either the walking disability (WGMS) score, or the 25-OH D3 level. The PSS was statistically significantly higher in patients with myopathy than normal controls ($p < 0.029$, Table 5).

## 3.2. Laboratory results

Creatine and alkaline phosphatase levels were normal in all participants. PTH was increased in only one patient with LGMB2B, indicating secondary hyperparathyroidism. The serum calcium level was decreased in four patients (4.8%) without a history of osteoporosis or fractures. One was a wheelchair-bound pre-menopausal smoker with FSHD, one a wheelchair-bound elderly non-smoking male with sIBM, and two were non-smoking ambulant women with *MATR3* myopathy (one pre-menopausal, one post-menopausal).

25-OH D3 levels were available for 70/89 patients. In total 14 of 70 patients (20%) had decreased serum 25-OH D3 levels (mildly n = 4, moderately n = 7, severely n = 3), eight of these were ambulatory

**Table 5**
Characteristics of pain using pain severity score (PSS) in total cohort of patients with myopathies, and in age and gender matched controls (i.e. accompanying spouses and partners). Data is given as median ± 1standard deviation (SD). Groups were compared using unpaired Student's *t*-test.

| | Myopathy patients (n = 85) | Normal controls (n = 43) | p |
|---|---|---|---|
| PSS (range) | 1.73 ± 2.22 (10–0) | 0.63 ± 1.88 (10–0) | 0.029 |
| *PSS subgroups* | | | |
| –No pain (0) (n (%)) | 28 (33) | 25 (57) | |
| –Mild pain (1–3) (n (%)) | 34 (40) | 13 (30) | |
| –Moderate pain (4–6) (n (%)) | 16 (19) | 5 (11) | |
| –Severe pain (7–10) (n (%)) | 7 (8) | 1 (2) | |

**Table 6**
Comparison of walking ability, calcium and 25-OH D3 levels in patients with myopathies and gender- and age matched neurological, non-myopathic controls (i.e. diseased controls). Data are given as mean ± 1SD (range).

| | Myopathy patients (n = 72) | Diseased controls (N = 72) | p |
|---|---|---|---|
| Gender (F/M) | 44/28 | 42/30 | |
| Age (years) | 53.5 ± 15.4 (19–79) | 53.1 ± 18.8 (21–85) | 0.982 |
| WGMS | 3.8 ± 2.4 (9–8) | 1.1 + 2.0 (0–9) | <0.001 |
| $Ca^{2+}$ (mmol/L) | 2.38 ± 0.55 (2.23–5.00) | 2.36 ± 0.11 (2.17–3.0) | 0.297 |
| Decreased $Ca^{2+}$ [n(%)] | 3 (4.2) | 9 (12.5) | |
| 25-OH D3 (nmol/L) | 35.7 ± 24.1 (7.5–121) | 58.7 ± 33.5 (7.5–173) | <0.001 |
| Decreased 25-OH D3 [n(%)] | 15 (20.8) | 11 (15.3) | |

(Table 4). Of the patients who were >50 years and for whom the 25-OH D3 level was available, five out of the 39 patients (12.8%) had decreased 25-OH D3 levels. In total six out of 13 (46%) wheelchair-bound patients had decreased 25-OH D3 levels. The median value in patients with LGMDs and sIBM were at the lower end of the normal range (Table 3). The 25-OH D3 level was decreased in 55% of patients with LGMDs, in 25% of patients with FSHD and in 11% of patients with DM1. There was no correlation between the 25-OH D3 level and the walking ability assessed using the WGMS score (figure 2C). The 25-OH D3 level was non-significantly lower in the winter months than in the summer months. However, the number of measurements during the summer months was quite low (Fig. 1B).

At the time of examination four ambulant non-smoking patients had been diagnosed with osteoporosis using DXA scan (one each with sIBM, LGMD2B, DM2, *MATR3*). The male patient with LGMD2B had serum calcium and 25-OH D3 levels in the lower normal range and was receiving vitamin D3. The two post-menopausal women with DM2 myopathy and sIBM were receiving calcium and vitamin D3 supplements. Their calcium and 25-OH D3 levels were both at the lower end of the normal range. The post-menopausal women with *MATR3* myopathy had slightly decreased 25-OH D3 and took calcium.

Two more patients took calcium for prophylaxis (one ambulant man with FSHD, one wheelchair-bound woman with FSHD).

When aged- and gender matched cohorts of patients with myopathies and those with other neurological disorders were compared, there was no difference in the serum calcium levels, but the myopathy patients had significantly lower 25-OH D3 levels and the number of patients with decreased 25-OH D3 levels was slightly higher in that cohort than in the diseased controls (Table 5). Furthermore, patients of the diseased control group had a significantly lower WGMS score, i.e. had less severe walking difficulties. (See Table 6.)

## 4. Discussion

Apart from studies on Pompe disease, this is the first study to describe risk factors for osteoporosis and serum bone markers in adult patients with myopathies who are not being treated with steroids. Patients with myopathies that caused a high level of walking disability showed an increased risk of falls, fractures and decreased 25-OH D3. In the present study patients with LGMDs and sIBM were most frequently affected. Androgen insufficiency might contribute to the occurrence of fractures and low 25-OH D3 levels in male patients with DM1.

### *4.1. Calcium and 25-OH D3 levels*

The gold standard in the diagnosis of osteoporosis and its precursor osteopenia is the DXA scan [14,15]. However, in the present pilot study we confined the design to the collection of data on classical risk factors of reduced bone mineral density, serum levels of 25-OH D3, calcium, and the bone formation marker ALPs. However, some more specific bone formation (e.g. bone-specific alkaline phosphate (BAP), type 1

procollagen-N-peptide (PINP)) and bone resorption markers (type 2 collagen cross-linked C-telopeptide (CTX) and N-telopeptide (NTX)), became available [40].

The importance of 25-OH D3 supplements in the treatment of reduced bone mineral density is well established and there are guidelines available for recommended 25-OH D3 serum levels and daily intake [12,13]. In contrast the role of 25-OH D3 as a surrogate marker for osteoporosis is controversial. The existing primary literature shows no clear relationship between vitamin D concentrations and fracture risk in people unaffected by neuromuscular disease [23,24]. In the present study there was a correlation between severely reduced walking ability and decreased 25-OH D3 levels, which mainly affected patients with LGMDs and sIBM. Additionally, myopathy patients with a higher degree of walking difficulties had significantly lower 25-OH D3 levels than patients with other neurological disorders, who had better functional abilities. However, the high percentage of patients with decreased 25-OH D3 levels in patients with other neurological disorders in the present study might suggests that 25-OH D3 deficiency is frequent in the general population, too.

Fractures in two ambulant male patients with DM1 (one with repetitive fractures in different locations) and a reduced 25-OH D3 level in three male patients (two wheelchair-bound) in our study might suggest a relationship to androgen insufficiency in this disorder. In contrast, none of the DM1 patients of our cohort had evidence of hyperparathyroidism with increased PTH, which had been previously reported in 19% of patients with DM1 [25].

### *4.2. Falls and fractures*

The frequency of falls within the period of one year is higher in our total cohort of myopathy patients than in a cohort of patients with rheumatoid arthritis (mean age: 62 years, 1.1 falls per person per year), of patients prior to a fall leading to a hip fracture (1.7 falls per person per year) and of the elderly (mean age: 84 years, 1.8 falls per person per year) [26–28]. Our results might be biased by the retrospective nature of the survey in contrast to other studies where falls were recorded on a monthly basis [28]. But the retrospective design is generally considered to lead to an underestimation of falls rather than an overestimation.

In addition the rate of fractures within the year covered by the questionnaire survey was higher in our total cohort of myopathy patients than in cohorts of patients with rheumatoid arthritis (4.3%) and elderly people (2.8%) [26,28]. The most common fracture in the elderly is hip fracture [26,29]. In patients with osteoporosis fractures of the spine, the hip and distal radius occur frequently [30]. In our myopathy cohort 43% of fractures were located at the lower extremity, too. Most of these fractures affected the tibia, and 60% of patients with tibial fracture were wheelchair-bound. This is consistent with the finding in patients with spinal cord injury that fractures in wheelchair-bound patients most frequently involve the tibia bone [31].

The prevalence of osteoporosis in Germany in people >50 years old is estimated to be 5.2–6% in men, 24–39% in women, overall 11.9–14% [32]. In our study, the prevalence was 4% in men and 17% in women aged 50–64 years, rising to 8% in men and 32% in women among 65 to 74-year olds. In the present study 10% of the cohort aged ≥50 years had fractures and a further 12% had decreased 25-OH D3 levels. Using these criteria, 26% of men ≥50 years old and 20% of women ≥50 years old in the present cohort were at a high risk of osteoporosis.

Apart from walking disability and immobility we could not identify any other “classical” risk factors associated with reduced bone mineral density. In conclusion those patients with an impaired walking ability were more frequently prone/at risk of having a fall, and hence having a traumatic fracture. This applied foremost to the LGMDs (LGMD2A, LGMD2B, LGMD2I) and sIBM. Thus, loss of walking ability and a history of (frequent) falls and recent fractures might best serve to identify those myopathy patients at risk of osteoporosis.

### *4.3. Analysis of pain*

The BPI has previously been used to study both a variety of myopathies and also osteoporosis [18–21]. The present study reproduces previous findings that FSHD, DM2, and LGMD2I are frequently associated with moderate pain, resulting in higher pain severity scores than other myopathies [18,33,34]. The pain

scores in our study were also comparably high in patients with other LGMDs (LGMD2A, LGMD2B) with a high level of walking disability, but this relationship between high pain and high walking disability was not found in patients with sIBM. Patients with osteoporosis frequently report low back pain or pain located in the lumbosacrogluteal area due to the high occurrence of vertebral fractures [35,36]. Pain in our total cohort of patients with myopathies was localized in 39% in the shoulder girdle and in 46% in the hip girdle. The distribution of the pain areas was similar in the different myopathies. In previous studies moderate and severe pains were associated with poor vitamin D status, independent of other covariates [37]. We found no correlation between pain severity score (PSS) and serum levels of 25-OH D3 or calcium, which may have been due to the range of different types of myopathies studied. In conclusion, the BPI data suggest that pain in our cohort was myopathic (i.e. myalgia) due to the underlying disorder and intensified by immobility and inappropriate posture, rather than due to bone damage. Although the BPI is not an appropriate instrument to define different types of pain, it has the advantage of a minimized recall-bias since pain during the last 24 h is evaluated.

Due to the heterogeneous cohort of patients with myopathies there was no positive correlation between the PSS and walking ability expressed in the WGMS score.

### *4.4. Summary*

The current study is the first to focus specifically on risk factors of decreased bone mineral density in hereditary myopathies and sIBM. However, some results might be skewed by the low number of participants with the different myopathies, and both its one time-point cross-sectional design and retrospective nature of questions regarding falls. Due to the design of the study, another disadvantage is the missing confirmation of decreased bone mineral density by DXA scan. A larger multicenter study specifically of patients with LGMDs and sIBM seems to be warranted. Physicians should be aware of a potentially increased risk for osteoporosis in non-ambulatory patients with myopathy and those with frequent falls, recent fractures, and newly occurring pain. Patients should undergo DXA scan and if the reduced bone density is confirmed, should be treated for osteoporosis according to the guidelines [38,39].

In conclusion the data presented here suggest an increased risk of osteoporosis in non-ambulatory patients with myopathies. A severe walking disability in combination with a history of fractures and frequent falls and lumbar pain in patients with myopathies should prompt the physician to screen for and to exclude osteoporosis.

## Conflict of interest

F. H. received lecturer honoraria and travel fees from Biomarin, Astellas, and Genzyme Inc. N. K. received lecturer honoraria and travel fees from Genzyme Inc. F. D. received travel grants from the Deutsche Gesellschaft für Neurologie (DGN). A. P. has no financial disclosure.

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