Myostatin and Markers of Bone Metabolism in Dermatomyositis

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Abstract

Background: In dermatomyostis (DM) patients, inflammation, reduced activity, and medication have a negative impact on the musculoskeletal system. Several endocrine factors are involved in muscle growth and bone turnover.

Objective: We aimed to investigate factors regulating myogenesis and bone metabolism and to evaluate possible associations between these endocrine factors, muscle strength, and functional tests in DM patients.

Methods: We conducted a cross-sectional study in 18 dermatomyositis patients. Serum levels of myostatin (MSTN), follistatin (FSTN), dickkopf 1 (Dkk1), sclerostin (SOST), periostin (PSTN), the receptor activator nuclear factor kB ligand (RANKL):osteoprotegerin (OPG) ratio and fibroblast growth factor 23 (FGF23) were determined. Physical function was evaluated by hand-held strength measurement, chair rising test, timed up and go test and the 3-minute walking test.

Results: Serum MSTN and FGF23 levels were significantly higher in DM patients than in controls. Dkk1 was significantly lower. Muscle strength and physical function tests correlated with each other.

Conclusion: In DM patients, biochemical musculo-skeletal markers are altered and physical function shows deficits. All these tests reflect independent of each other different deficits in long-term DM patients which is important to know for the assessment of DM patients as well as planning of therapeutic interventions in clinical routine.

Background

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by chronic skeletal muscle inflammation and weakness; proximal muscles are the ones which are mostly affected. The skin manifestation is expressed as rashes [1]. The aetiology of muscle weakness is not fully understood but besides inflammation, corticosteroid treatment, and disuse, a switch of muscle fibre type as well as decreases of adenosine monophosphate deaminase (AMPD1) may contribute to skeletal muscle weakness in inflammatory myopathy [2, 3]. Inflammation, corticosteroid treatment, and low body weight may also be factors responsible for the elevated susceptibility to osteoporosis and fragility fractures in DM patients [4, 5].

Throughout life muscle metabolism is influenced by several endocrine factors, including cytokines like myostatin (MSTN), a negative regulator of muscle mass and function [6]. MSTN levels have been shown to be increased in subjects with muscle atrophy due to sarcopenia or cachexia [7]. Another member of the transforming growth factor-ß (TGF-ß) superfamily is follistatin (FSTN) which is able to block signal transduction of MSTN [8] and, thus, has the capability of ameliorating muscle growth reduction. Just like muscle metabolism, bone homeostasis also depends on the balance between positive and negative regulators. Sclerostin (SOST) and dickkopf-1 (Dkk 1), inhibitors of the Wnt/ß-catenin signaling pathway

reduce bone formation and regeneration [9]. Another regulator of bone metabolism is the osteoblast-specific factor 2, periostin (PSTN) which is supposed to be associated with bone strength [10]. The RANKL (receptor activator of nuclear factor-kB ligand) /OPG (osteoprotegerin) system plays an important role in osteoclastogenesis as well [11]. The fact that the overexpression of fibroblast growth factor 23 (FGF23) leads to phosphaturia whereas the deletion of FGF23 causes hyperphosphatemia, established FGF23 as a regulating factor of phosphate homeostasis [12] which is involved in skeletal metabolism.

Inflammation has a negative impact on muscle and bone metabolism. Nevertheless, none of the above-mentioned regulators of muscle growth or bone turnover have been investigated in DM patients so far. Thus, the aim of this study was to investigate factors regulating myogenesis and bone metabolism in patients with DM and to evaluate possible associations between these endocrine factors and physical function.

Methods

Study population

Patients with dermatomyositis according to the Bohan and Peter criteria [13, 14] and regular follow-up at the Department of Dermatology, Medical University of Vienna were invited to participate in this cross-sectional study if the diagnosis was verified by muscle biopsy and if the patients were at least 18 years of age. To be eligible, participants had to be able to follow the study protocol. Excluded were patients who had a malignant disease within the previous five years, had to undergo surgery within the past three months, were immobilized, or had renal or liver insufficiency. Ethical approval was provided by the Medical University of Vienna Ethics Committee and all participants gave written informed consent to this study after the procedure of the study was explained to them.

Procedures

Anthropometric measures of patients with DM either on standard therapy (glucocorticoids and methotrexate) or intravenous immunoglobulin (IVIG) treatment were performed. Standing height was measured in stocking feet to the nearest centimeter using a stadiometer, and weight was measured using a balance beam scale, recalibrated monthly. Afterwards venous blood samples were drawn. To eliminate diurnal variations in biochemical variables sample collection was performed in the morning. After centrifugation of the whole blood serum was immediately frozen and stored at -70 degrees until assayed. All samples were handled in a single batch run. Additionally, muscle strength was measured and patients conducted three different functional tests.

Biochemistry

Serum levels of C-reactive protein (CRP), creatinine kinase (CK), and aldolase were measured to give information on disease activity. Basic serum chemistry included calcium, phosphate, creatinine, parathyroid hormone, and 25-hydroxvitamin D (25OHD). Analysed bone formation markers were bone

specific alkaline phosphatase (BAP; Liaison Analyzer, DiaSorin Inc., USA, detection limit: 0.1 µg/L; intra-assay coefficient of variation: 3.3 – 4.3 %, inter-assay coefficient of variation: 6.1 – 8.1 %), osteocalcin (Oc; Cobas 8000 Analyzer, Roche Diagnostics, Switzerland, detection limit: 0.01 ng/mL; intra-assay coefficient of variation: 0.9 – 1.3 %, inter-assay coefficient of variation: 1.2 – 2.3 %), and N-terminal propeptide of type I collagen (P1NP; Cobas 8000 Roche Analyzer, Roche Diagnostics, Switzerland, detection limit: 5 ng/mL; intra-assay coefficient of variation: 1.6 – 3.5 %; inter-assay coefficient of variation: 2.0 – 3.8 %). Cross-linked-C-telopeptide of type I collagen (CTX; Cobas 8000 Roche Analyzer, Roche Diagnostics, Switzerland, detection limit: 0.5 ng/mL; intra-assay coefficient of variation: 1.2 – 4.7 %, inter-assay coefficient of variation: 1.5 – 5.7 %) was the determined bone resorption marker. All analyses were conducted according to standard procedures.

Additionally, the following musculoskeletal markers were evaluated: *myostatin* (MSTN, colorimetric competitive immunoassay, Immundiagnostik, Bensheim, Germany, limit of blank LoB: 0.370 ng/ml; intra-assay coefficient of variation: <12 %, inter-assay coefficient of variation: <14%, according to manufacturer's data), *follistatin* (FSTN, colorimetric sandwich immunoassay, R&D Systems, Minneapolis, USA, MDD range 0.005-0.068 ng/mL; mean MDD 0.016 ng/mL; intra-assay coefficient of variation: <3 %, inter-assay coefficient of variation: <10%, according to manufacturer's data), *sclerostin* (SOST, BI-20492, colorimetric sandwich immunoassays, Biomedica, Vienna, Austria; detection limit: 3.2 pmol/l; intra-assay coefficient of variation: ≤7 %, inter-assay coefficient of variation: ≤10%, according to manufacturer's data), dickkopf 1 (Dkk 1; BI-20412, colorimetric sandwich immunoassays, Biomedica, Vienna, Austria; detection limit: 0.38 pmol/l; intra-assay coefficient of variation: ≤8.0 %, inter-assay coefficient of variation: ≤12.0 %, according to manufacturer's data), and *periostin* (PSTN; SEH339Hu, colorimetric sandwich immunoassays, Cloud-Clone-Corp, Houston, USA; detection limit: 0.068 ng/ml; intra-assay coefficient of variation: ≤10 %, inter-assay coefficient of variation: ≤12%, according to manufacturer's data). *Receptor activator nuclear factor kB ligand* (RANKL) and *osteoprotegerin* (OPG) were measured using a commercially available immunoassay from Biomedica, Austria (OPG detection limit: 0.14 pmol/l; intra-assay CV: 4-10%, inter-assay coefficient of variation: 7-8%; RANKL detection limit: 0.08 pmol/l; intra-assay CV: 3-5%, inter-assay coefficient of variation: 6-9%). Serum levels of *fibroblast growth factor 23* (FGF23) were determined by an ELISA targeting the C-terminal end of the molecule (Biomedica, Vienna, Austria). The detection limit of the assay is 0.08 pmol/L with an intra-assay coefficient of variation of ≤12%.

The biomarkers were also assessed in a healthy age matched control group. All subjects of the control group were part of a previously published population-based cohort [15].

Muscle strength

Hand-held muscle strength measurement has been shown to be a feasible and reliable method for evaluation of muscle strength in dermatomyositis patients with an intraclass correlation coefficient between 0.88 and 0.98 as well as excellent internal reliability (r=0.91-0.98) and consistency (Cronbach's alpha 0.78-0.97) [16, 17]. Thus, maximal isometric muscle strength of shoulder abduction (SAb), elbow

flexion (EF), elbow extension (EE), hip flexion (HF), and knee extension (KE) was evaluated with the handheld dynamometer Hoggan microFET2 ® (Hoggan Scientific, LLC, Salt Lake City UT, USA). Stabilization specifics used for each muscle action were similar to those performed by Andrews and coauthors [18]. Within 2 seconds the patient tried to reach maximal isometric strength and held that level for another 4-5 seconds. The mean value of the left and right sided maximal strength was used for statistical analysis.

Functional assessment

Physical examination included three different functional tests. The chair rising test (CRT) was used to assess leg power; it measures the time an individual needs to stand up and sit down five times as quickly as possible from a chair of standard height (46 cm seat height) with his/ her arms fold across the chest [19]. Mobility performance was evaluated by the timed up and go test (TUG), a test which measures, in seconds, the time it takes the individual to stand up from a chair, walk a distance of 3m, turn around, walk back to the chair, and sit down again [20]. Completion of both tasks was timed from the beginning of the manoeuvre until the patient was re-seated. To assess functional exercise capacity the distance covered within 3 minutes of walking at self-selected speed corresponding a perceived exertion rate of 13 (“somewhat hard”) on a level course was collected (3-minute walking test; 3MWT) [21].

Statistical analysis

Data are presented as medians and quartiles. Statistical analysis of between group differences concerning the serum levels of the biochemical markers as well as the parameters of physical function was performed with the Mann Whitney U test. Spearman’s rank correlation coefficient was used to identify potential associations between FGF23 and biochemical markers, between MSTN and muscle strength as well as physical function, and between maximal muscle strength and physical function. Significance was set at p-values less than 0.05. Statistical analyses were done using the software packages GraphPad Prism 5 (Prism 5 für Windows, Version 5.00, 2007) and SPSS Statistics V21 (SPSS Inc., Chicago, IL, USA, 2012).

Results

Eighteen female and two male DM patients with a median age of 66 [55; 76] years participated in this study. Their disease duration was 6.5 [4.25; 12.5] years. Eight patients were on the traditional medical regimen of glucocorticoid therapy (12.5 [4.7; 15.6] mg/day); 12 patients received intravenous immunoglobulins (IVIG) on a regular basis (2 g/kg for 2–5 days every 4 weeks) but five of these 12 patients additionally needed glucocorticoids. Three patients of the glucocorticoid group and four patients of the IVIG group took bisphosphonates on a regular basis. Twenty healthy controls with a median age of 61 [56; 68] years were included for comparison of musculoskeletal markers. There was no significant difference between the DM and control group with respect to age.

Serum 25OHD levels were reduced. All other basic chemistry parameters as well as bone turnover markers were within the normal range (Table 1). Maximal isometric muscle strength was lower than published reference values for healthy controls of comparable age. The median time needed to perform the CRT was higher than published reference values. Patients needed 9 seconds for the TUG test and managed to cover a distance of 240 meters within the 3 minutes' walk (Table 2).

Table 1
DM patients' demographic data and biochemical parameters

	n = 18	**Normative values**
Age	66 [55; 76]	-
BMI	26 [23; 30]	-
CRP [mg/dl]	0.3 [0.1; 0.6]	< 0.5
CK [U/l]	133 [63; 173]	< 170
Aldolase [U/l]	3.8 [2.5; 5.4]	0-7.6
Ca [mmol/l]	2.3 [2.3; 2.4]	2.15–2.50
Phosphate [mmol/l]	1.04 [0.94; 1.19]	0.81–1.45
Creatinine [mg/dl]	0.74 [0.64; 0.87]	0.50–0.90
PTH [pg/ml]	43.2 [33.0; 69.5]	15–65
25OHD [nmol/l]	66.7 [50.4; 87.0]	75–250
BAP [U/l]	8.8 [5.9; 12.4]	5.2–24.4
OC [ng/ml]	18.8 [10.0; 27.8]	14–46
P1NP [ng/ml]	42.0 [29.5; 80.5]	16–52
CTX [ng/ml]	0.22 [0.11; 0.50]	0.09–0.44

CK: creatinine kinase; CRP: C-reactive protein; PTH: parathyroid hormone; 25OHD: 25-OH-Vitamin D; BAP: bone-specific alkaline phosphatase; OC: osteocalcin; P1NP: N-terminal propeptide of type I collagen ; CTX: cross-linked-C-telopeptide of type I collagen; median [quartiles]

Table 2
DM patients' physical function

	n = 18	Normative values
Shoulder abduction N [N]	80 [71; 107]	114.1 ± 20.2 [18]*
Shoulder abduction D [N]	92 [70; 108]	125.0 ± 25.8 [18]*
Elbow flexion N [N]	110 [72; 147]	150.8 ± 26.5 [18]*
Elbow flexion D [N]	115 [73; 137]	156.7 ± 29.4 [18]*
Elbow extension N [N]	86 [66; 122]	96.6 ± 24.2 [18]*
Elbow extension D [N]	81 [62; 113]	96.1 ± 22.9 [18]*
Hip flexion N [N]	87 [50; 115]	121.2 ± 21.2 [18*]
Hip flexion D [N]	88 [59; 113]	122.7 ± 23.2 [18]*
Knee extension N [N]	203 [99; 288]	248.0 ± 66.4 [18]*
Knee extension D [N]	207 [77; 281]	257.2 ± 58.0 [18]*
CRT [s]	11.8 [7.2; 17.6]	≤ 10 [19]
TUG test [s]	9.0 [5.4; 10.0]	< 10 [20]
3MWT [m]	240 [183; 277]	n.a.

N: nondominant; D: dominant; CRT: chair rising test; TUG timed up and go test; 3MWT: 3 minute walking test; n.a.: not applicable; median [quartiles]; * decade and gender-specific data are given as mean ± SD

Group comparison of musculoskeletal markers is shown in Table 3. Serum MSTN und FGF23 levels were significantly higher in DM patients than in controls. DKK 1 was significantly lower in DM patients. Concerning FSTN, SOST, PSTN, and the RANKL:OPG ratio no group-specific differences could be detected.

Table 3
Musculoskeletal markers of DM patients and controls

	DM (n = 18)	Controls (n = 18)	p-value
MSTN [ng/ml]	2.5 [1.9; 3.2]	1.9 [1.6; 2.3]	< 0.05
FSTN [pg/ml]	1343 [929; 1856]	1232 [1093; 1433]	n.s.
SOST [pmol/l]	28.9 [23.3; 34.4]	28.3 [24.4; 35.7]	n.s.
Dkk 1 [pmol/l]	11.4 [6.9; 20.0]	31.8 [14.3; 50.6]	< 0.01
PSTN [ng/ml]	3.2 [2.0; 5.8]	3.6 [2.6; 7.0]	n.s.
RANKL/OPG	0.017 [0.005; 0.055]	0.030 [0.020; 0.048]	n.s.
FGF23 [pmol/l]	2.17 [1.45; 3.26]	1.28 [0.79; 1.96]	< 0.05

MSTN: myostatin, FSTN: follistatin, SOST: sclerostin. Dkk 1: dickkopf 1, PSTN: periostin; RANKL: receptor activator nuclear factor kB; OPG: osteoprotegerin; FGF23: fibroblast growth factor 23

Correlation analyses revealed a significant positive association between serum levels of FGF23 and aldolase ($r = 0.563$; $p < 0.05$), phosphate ($r = 0.572$; $p < 0.05$), as well as 25OHD ($r = 0.553$; $p < 0.05$). No association could be detected with creatinine kinase. No statistically significant correlations were found between MSTN on one side and muscle strength and physical function on the other side (r ranged from −0.426 to 0.194). Correlations between maximal muscle strength obtained by manual muscle testing and functional tests are shown in Table 4.

Table 4
Correlations – muscle strength and physical function in DM patients

	SAb	EF	EE	HF	KE	CRT	TUG	3MWT
SAb	1	0.791**	0.464*	0.707**	0.739**	-0.572*	-0.583*	0.529*
EF		1	0.782**	0.648**	0.815**	-0.513	-0.513*	0.604*
EE			1	0.565**	0.699**	-0.366	-0.408	0.482*
HF				1	0.788**	-0.729**	-0.748**	0.788**
KE					1	-0.651**	-0.680**	0.633**
CRT						1	0.910**	-0.841**
TUG							1	-0.868**
3MWT								1

SAb: shoulder abduction; EF: elbow flexion; EE: elbow extension: HF: hip flexion; KE: knee extension; 3MWT: 3 minute walking test; CRT: chair rising time; TUG: timed up and go test; * $p < 0.05$; ** $p < 0.01$

Discussion

This is the first study evaluating musculoskeletal parameters of DM patients. It revealed elevated MSTN and FGF23 serum levels as well as reduced levels of DKK 1.

Compared to the control group DM patients had higher MSTN levels. Up to now serum levels of MSTN have not been investigated in DM patients. In rheumatoid arthritis patients in remission, we found decreased serum levels of myostatin which may be caused by disease-modifying anti-rheumatic drugs (DMARDs) suppressing disease activity and thus reducing inflammation [22]. This study's patients had a relatively low level of inflammation indicated by median values of CRP, CK, and aldolase within the normal range. However, even chronic low-grade inflammation is associated with loss of muscle mass and reduced ability to carry out physical activities. Muscle atrophy is known to be associated with increased serum levels of the negative regulator of muscle mass MSTN [23]. Glucocorticoid-induced myopathy may play an important role as well. The median glucocorticoid dose of the GC group was 12.5 mg per day and almost half of the IVIG patients additionally needed glucocorticoids. It is known that glucocorticoids stimulate muscles' production of MSTN [24]. Thus, increased MSTN levels in long-term DM patients may be caused by irreversible muscle damage and/or reduced muscle mass. Interestingly FSTN, the antagonist of MSTN was alike to the control group. That emphasizes the relevance of MSTN.

This study's results of lowered DKK 1 levels and no group-specific difference of SOST are in accordance with our previous study on RA patients in remission [22]. The reduced and normal levels of the Wnt inhibitors, respectively, foreclose a reduction of bone formation. This assumption is corroborated by the fact that the markers of bone formation were in the normal range. It should also be mentioned that Dkk1 is not as bone-specific as SOST because it is expressed in other tissues as well.

Since PSTN levels were similar to the control group one can assume that these long-term DM patients were well treated and did not have an elevated risk of fragility fractures. This is underlined by normal values of the BTMs and vitamin D. Additionally, some patients took a bone-specific medication.

The RANKL:OPG ratio did not show a significant difference between DM patients and controls. At the time of diagnosis children with juvenile DM had an increased RANKL:OPG ratio [25]. However, another study investigating juvenile DM patients on glucocorticoid therapy with a mean disease duration of 46 months could not detect a difference of the RANKL:OPG ratio compared to healthy controls [26]. Patients participating in this study received IVIG and/ or glucocorticoids - treatments with contrary effects on bone metabolism. Glucocorticoids suppress OPG and increase RANKL expression [27] whereas IVIG is supposed to inhibit osteoclastogenesis by supressing RANKL signalling [28].

We for the first time evaluated serum FGF-23 in dermatomyositis and related the serum levels to parameters of clinical chemistry and disease activity. Normal values of the clinical chemistry parameters indicated that there was no disturbance in our patients' phosphate metabolism or renal function. The positive correlation between aldolase and FGF23 indicates that despite the fact of relatively low serum markers of current disease activity, prevalent residual activity of the disease influenced the expression of

FGF23. In vitro and experimental studies have shown that pro-inflammatory stimuli increase serum levels of FGF23 [29, 30]. Correlations with inflammatory markers have also been reported in several different inflammatory diseases (for review see [31]) including rheumatoid arthritis - in one of two studies investigating such patients [32, 33]. Therefore, elevated FGF23 levels detected in this study may be caused by DM associated inflammation. Since this study's patients did not show a highly active disease, patients' intake of glucocorticoids may also be relevant for the changes in FGF 23 expression. In their investigation Sato and co-authors could not detect a correlation of FGF23 with glucocorticoid doses [32] in rheumatoid arthritis. Nevertheless, an experimental study showed that the release of FGF23 is upregulated by the exposure to deoxycorticosterone acetate [34]. Correlation analyses showed a positive association with serum levels of phosphate, and 25OHD. That fits well with the central role of FGF23 in the regulation of phosphate balance. No data on a potential effect of IVIG therapy on FGF23 exist.

Compared to the mean normative values published by Andrews et al (1996) [18] median maximal isometric muscle strength in our long-term DM patients was reduced. That is in line with two of three previous studies [35–37] and is most likely caused by the disease associated muscle damage. We have shown that this low muscle strength can be improved by exercise without a negative effect on inflammation [38]. The increased time needed for the CRT for sure is an expression of the reduced leg power caused by muscle damage as well. As our patients managed the TUG test within the normal time limit, they performed better than juvenile DM patients investigated by Berntsen et al [39]. The median distance covered during the 3MWT was 240 m. Unfortunately, no reference values exist for this test which is related to maximal oxygen uptake [21] but results obtained in this study were better than in a study investigating clinically stable patients with chronic obstructive pulmonary disease (COPD) [40]. A lack of difference in the 6MWT in inactive inflammatory myopathies [41] and inactive juvenile DM [39] has been shown. All muscle strength tests showed a positive moderate to high correlation with each other. As expected the CRT and the TUG test correlated negatively whereas the 3 MWT correlated positively with the muscle strength measurements. Physical function tests were highly to very highly associated with each other.

Conclusion

This first investigation of myostatin in DM patients revealed the negative regulator of muscle mass as an interesting marker of muscle damage and/ or muscle loss. The study also showed that biochemical musculo-skeletal markers as well as functional tests reflect independent of each other different deficits in long-term DM patients. Our findings are important for the appraisal of studies and for assessment as well as planning of therapeutic interventions in clinical routine.

Abbreviations

DM: dermatomyositis; CK: creatinine kinase; CRP: C-reactive protein; PTH: parathyroid hormone; 25OHD: 25-OH-Vitamin D; BAP: bone-specific alkaline phosphatase; OC: osteocalcin; P1NP: N-terminal propeptide of type I collagen; CTX: cross-linked-C-telopeptide of type I collagen; MSTN: myostatin, FSTN: follistatin,

SOST: sclerostin. Dkk 1: dickkopf 1, PSTN: periostin; RANKL: receptor activator nuclear factor kB; OPG: osteoprotegerin; FGF23: fibroblast growth factor 23; N: nondominant; D: dominant; CRT: chair rising test; TUG timed up and go test; 3MWT: 3 minute walking test; n.a.: not applicable; SAb: shoulder abduction; EF: elbow flexion; EE: elbow extension: HF: hip flexion; KE: knee extension

Declarations

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Authors' contributions

Authors KKS, WG, CB, PP had a substantial contribution to study conception and design. All authors had a substantial contribution to analysis and interpretation of data, and drafting the article or revising it critically. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets of the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the regional ethics review board and written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Competing interests

Peter Pietschmann has received research support and/or honoraria from Amgen GmbH, Biomedica GmbH, DePuySynthes, Eli Lilly GmbH, Fresenius Kabi Austria, Meda Pharma/Mylan GmbH, Shire Austria GmbH, TAmiRNA GmbH and UCB Pharma. All other authors have no conflicts of interest.

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