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Functional and Structural Adaptations of Skeletal Muscle in Long-Term Juvenile Dermatomyositis: A Controlled Cross-Sectional Study

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Objective. To compare muscle strength and endurance of the knee extensors between patients with long-term juvenile dermatomyositis (DM) and controls and between patients with active disease and those with inactive disease, and to explore associations between strength/endurance and 1) clinical parameters, 2) physical activity, and 3) humoral/structural adaptation in the skeletal muscle of patients.

Methods. In a cross-sectional study (44 patients and 44 age- and sex-matched controls), we tested isometric muscle strength (peak torque, in Nm) and dynamic muscle endurance (total work, in Joules) of the knee extensors, physical activity (measured by accelerometer), and serum myokine levels (by enzyme-linked immunosorbent assay). Patients were examined with validated tools (clinical muscle tests and measures of disease activity/damage and inactive disease) and using magnetic resonance imaging of the thigh muscles, which included evaluation of the quadriceps cross-sectional area (CSA). Needle biopsy samples of the vastus lateralis muscle (obtained from 12 patients ages ≥18 years) were assessed by histochemistry.

Results. After a mean ± SD disease duration of 21.8 ± 11.8 years, peak torque was lower in patients with juvenile DM compared to controls (mean difference 29 Nm, 95% confidence interval 13–46; $P = 0.001$). Similarly, total work of the knee extensors was lower in patients compared to controls (median 738J [interquartile range 565–1,155] versus 1,249J [interquartile range 815–1,665]; $P < 0.001$). Both peak torque and total work were lower in patients with active juvenile DM compared to those with inactive disease (both $P < 0.019$); in analyses controlled for quadriceps CSA, only total work remained lower in patients with active disease. Moreover, peak torque and total work correlated with findings from clinical muscle tests in patients with active disease (r = 0.57–0.84). Muscle biopsy results indicated that the fiber type composition was different, but capillary density was similar, between patients with active disease and those with inactive disease.

Conclusion. In patients with long-term juvenile DM, both muscle strength and endurance of the knee extensors were lower when compared to matched controls, and also lower in patients with active disease compared to those with inactive disease. Our results indicate a need for more sensitive muscle tests in this clinical setting. We hypothesize that impaired muscle endurance in patients with active juvenile DM may be influenced by structural/functional adaptations of muscle tissue independent of muscle size.

INTRODUCTION

Reduced muscle strength and endurance are major clinical manifestations of juvenile dermatomyositis (DM), the most common idiopathic inflammatory myopathy (IIM) of childhood (1). Muscle involvement often comprises the proximal muscles of the extremities as well as truncal muscles, including neck flexors (2).

During the early phase of juvenile DM, decreased muscle function can be severe and is related to active myositis (3). Autoimmune-like mechanisms are believed to contribute to

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perivascular inflammation and vasculopathy, resulting in ischemic muscle fiber damage, perifascicular atrophy, and reduced capillary density (4). However, nonimmune mechanisms related to reduced blood flow also seem to be involved in impaired muscle function (3,5). Both immune and nonimmune processes may induce the release of myokines, which are cytokines derived from muscle tissue (6). Myokines are associated with muscle inflammation, but also are believed to mediate antiinflammatory effects related to exercise (6).

With treatment, muscle strength and endurance gradually improve. Yet, long-term outcome studies have shown persistent, mild muscle weakness and decreased muscle endurance, tested clinically using the unilateral Manual Muscle Testing in 8 groups (MMT-8) and the Childhood Myositis Assessment Scale (CMAS) (7–9), both of which are features that are more pronounced in patients with active juvenile DM than in those with inactive disease (10). Severe impairment is rare (7). However, a challenge related to the MMT-8 and CMAS is their frequently observed ceiling effects (11). Mild, but functionally important, muscle weakness may therefore be difficult to detect, especially in patients with inactive disease (10).

Testing of isometric strength and dynamic muscular endurance could provide a more objective and sensitive method for evaluating muscle function in juvenile DM patients who experience mild muscle impairment (12). Thigh muscles, including the knee extensors, are among the most commonly involved muscles in juvenile DM (13), comprising the muscle group most frequently examined by biopsy (14) and magnetic resonance imaging (MRI) (15). Therefore, knee extensors could serve as a representative test localization for proximal muscle function in juvenile DM.

After long-term disease in patients with juvenile DM, scores on the MMT-8 or CMAS have been found to be associated with levels of disease activity (9,16) and damage (16) and elevated serum myokine levels (17). Despite the association with active inflammation, myokines may also be involved in persistent muscle weakness in noninflamed muscle in which inflammation has been suppressed by targeted treatment (6). However, the associations between objective muscle test findings and these parameters in long-term juvenile DM are not known.

To our knowledge, no studies on muscle fiber composition exist in patients after long-term juvenile DM. A study of adult patients with DM found altered muscle fiber composition in those with chronic disease (18). Muscle fiber composition is dynamic, with the size and proportion of slow-twitch oxidative type I and fast-twitch fiber type II muscle fibers changing according to numerous factors, including age, sex, and exercise levels (19,20). Exercise was found to increase the proportion of type I muscle fibers in adult DM (21).

In this study, we aimed to compare isometric muscle strength and dynamic muscle endurance of the knee extensors, measured by sensitive, objective methods, between patients with long-term juvenile DM and controls, and between patients with active juvenile DM and those with inactive disease. Furthermore, we aimed to explore whether changes in thigh muscle strength and endurance in patients are associated with 1) disease parameters, including results of commonly used clinical muscle tests, 2) physical activity, and 3) structural or humoral adaptation of the skeletal muscle.

PATIENTS AND METHODS

Design. We used a controlled cross-sectional study design. The study was part of a larger project on physical fitness in juvenile DM patients at Oslo University Hospital (OUS) and the Norwegian School of Sport Sciences between 2013 and 2015. Patients were recruited from an already established juvenile DM cohort (22). In addition, 8 patients from a prospective juvenile DM cohort at OUS and 3 additional patients were invited.

The inclusion criteria were as follows: 1) a diagnosis of juvenile DM after 1970, 2) a diagnosis of definite or probable dermatomyositis according to the Bohan and Peter criteria (23), 3) having been diagnosed with juvenile DM at age <18 years, and 4) being age ≥10 years at the time of examination. Patients were excluded from the data analyses if they had not completed tests of isometric muscle strength and muscle endurance or had not undergone a muscle biopsy. Patients were scored retrospectively according to the 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for adult and juvenile IIMs (24).

Controls were randomly drawn from the Norwegian National Registry, and were age- and sex-matched 1:1 to the patients. Exclusion criteria were as follows: 1) mobility problems, 2) presence of inflammatory rheumatic disease, 3) presence of other active autoimmune disease, 4) presence of other autoimmune disease being treated with immunosuppressive agents, 5) presence of serious lung or heart disease, and 6) exclusion of the matched patient.

All participants (or if age <16 years, their guardians) provided signed informed consent, in accordance with the Declaration of Helsinki (25). The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (approval no. 2013/1039).

Clinical examination. In patients with juvenile DM, we used the Disease Activity Score (DAS) (scale 0–20) and the physician global assessment of disease activity visual analog scale (VAS) score (scale 0–10) to assess global disease activity, and used the Myositis Damage Index (MDI) (scale 0–40) and the physician global damage VAS score (scale 0–10) to assess global disease damage (11). We used the MMT-8 (scale 0–80) (including the separate MMT knee extensor component [scale 0–10]) and the CMAS (scale 0–52) to clinically assess muscle strength and endurance (11). We defined an MMT-8 score of <64 or CMAS score of <35 as severe impairment (7). We used the DAS muscle component score (scale 0–11) to assess disease activity in the muscle (26), and the MDI muscle damage extent score (scale 0–3) and MDI muscle VAS severity score (scale 0–10) to assess disease damage in the muscle (27). We divided patients into those with active disease and those with inactive disease based on the

original Paediatric Rheumatology International Trials Organisation criteria for inactive disease (28).

Self-reported health. To evaluate physical function, we used the Norwegian version of the 36-item Short-Form health survey physical component score (scale 0–100) in patients and controls who were age 14 years or older, and used the Childhood Health Assessment Questionnaire (C-HAQ) and adult HAQ (each on a scale of 0–3) in patients ages <18 years and ages ≥18 years, respectively (11).

Physical activity. As previously described, we measured physical activity levels in patients and controls using waist-borne accelerometers for 7 consecutive days (29). Physical activity was evaluated according to the number of minutes spent in sedentary, light, or moderate-to-vigorous physical activity (MVPA) for the total wear period, divided by the number of valid days. Each registered minute was labeled as sedentary, light, or MVPA based on the count value for the given minute (<100 counts, 100–1,999 counts, and >2,000 counts, respectively) (30). MVPA bouts were defined as the average daily time of MVPA in bouts of of at least 10 minutes' duration.

Objective muscle testing of patients and controls. We used the maximal voluntary isometric contraction (MVC) force of knee extension, expressed as the peak torque (in Nm), to measure muscle strength, and dynamic knee extensions, expressed as the total work (in Joules), to measure muscle endurance (collectively referred to as objective muscle tests). A custom-made knee extension device (GYM 2000AS; Vikersund) was set up as previously described (31). Following a warm-up protocol, participants performed 3 consecutive unilateral maximal isometric contractions of the knee extensors that, under strong verbal encouragement, lasted 5 seconds, with each separated by rest periods of 60 seconds. We processed the data using LabVIEW software (National Instruments), and used the average of the maximum force for each leg for statistical analyses. We calculated the peak torque (in Nm) as follows: peak torque = force (in Newtons) × lever arm length (in meters).

To measure muscle endurance, a resistance mass of 30% of the MVC force was attached to the knee extension device. Guided by a metronome paced at 1 Hz, participants performed rounds of full knee extension and 90° flection until exhaustion was reached (defined as the point at which the participant was incapable of full knee extension). The average maximal number of extensions between the right and left leg was used for statistical analyses. We calculated dynamic muscle endurance as the total work (in Joules), as follows: total work = 30% of peak torque (in Nm) × sin (90º) × number of repetitions.

MRI. Patients underwent MRI of the thigh muscles using a 1.5T scanner (Siemens) with phased-array body coils, including transversal T1 turbo-spin echo and short tau inversion recovery sequences. Three of the MRIs performed at local hospitals were summoned and scored collectively with the remaining cohort. Two experienced musculoskeletal radiologists (EK and EM) assessed the presence or absence of edema in the muscle and calcinosis in the soft tissue layers, and scored pathologic fatty infiltration in the muscle on a scale of 0–4 (32), in which a score of 0 = normal, 1 = fatty streaks (interpreted as not pathologic), 2 = muscle greater than fat, 3 = muscle equal to fat, and 4 = muscle less than fat. They also measured the maximal cross-sectional area (CSA; in cm^2) of the anterior thigh compartment (quadriceps femoris) separately for each leg (31). We took the maximal CSA of either leg and found the average between these maximal values by adding them and dividing by 2.

Measurement of muscle enzymes and myokines in the blood. We obtained serum samples from all subjects through venous blood sampling, and performed all procedures mentioned below according to the manufacturers' protocols.

In patients and controls, we analyzed serum levels of creatine kinase, lactate dehydrogenase, and aspartate amino transferase in the hospital's routine laboratory. We analyzed circulating levels of interleukin-6 (IL-6), IL-8, IL-15, interferon-γ (IFNγ), IFNγ-inducible protein 10 (IP-10), CCL5, and tumor necrosis factor using Luminex Xmap technology with the Bio-Plex Pro Human Cytokine 27-plex assay (M500KCAF0Y; Bio-Rad). The assay included a highly sensitive standard curve in order to detect very low concentrations of the cytokines. We used enzyme-linked immunosorbent assay kits to measure the levels of decorin (EHDCN; Thermo Scientific) as well as myostatin and monocyte chemotactic protein 1 (DGDF80 and DCP00, respectively; R&D Systems).

Muscle biopsy. We invited patients ages ≥18 years to undergo a percutaneous needle muscle biopsy (a more gentle procedure compared to open biopsy, as it was not intended for clinical purposes [33]) of the left vastus lateralis muscle. With the patient placed in a supine position and given local anesthesia (xylocaine 10 mg/ml + adrenaline 5 μg/ml), we used a 6-mm Pelomi needle with manual suction to obtain the muscle biopsy sample in a sterile procedure. We obtained 30–40 mg muscle tissue for histochemical analysis. Following excision, the muscle biopsy samples were frozen in OCT medium (CellPath) and dispersed in isopentane at freezing point, before storage at –80°C.

Histochemical analysis. In an atmosphere of –20°C, we cut serial 8-μm thick sections of the muscle biopsy tissue using a microtome (CM 1860 UV; Leica), before mounting the sample on microscopic slides (Superfrost Plus; Thermo Scientific). We performed hematoxylin and eosin staining in accordance with a standard protocol, followed by immunohistochemical analysis according to the method of Paulsen et al, using primary antibodies against myosin heavy chain (MHC) type 1, dystrophin, and CD31 to evaluate muscle fibers and capillaries (34), and CD68, tenascin

C, and embryonic MHC to evaluate active inflammation and regeneration (35) (for details, see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41174/abstract). We determined the distribution of muscle fiber types, fiber CSA, and capillary data using TEMA software (CheckVision). We expressed capillarization as the total number of capillaries per total number of fibers (CF), total number of capillaries around each muscle fiber type (type I and type II) (CAFI and CAFII, respectively), and total number of capillaries around each muscle fiber type related to muscle fiber area (CAFAI and CAFAII, respectively).

Statistical analysis. For statistical analyses, we used IBM SPSS statistical software, version 25. To compare patients and controls, we used a paired-sample *t*-test, Wilcoxon's signed rank test, or McNemar's test, as appropriate. To compare patients with active disease and those with inactive disease, we used an independent-sample *t*-test, Mann-Whitney U test, or chi-square test, as appropriate. Values are presented as the mean ± SD or median with interquartile range (IQR). We performed correlation analyses using Pearson's R or Spearman's rho correlation coefficients, as appropriate, with weak correlation defined as r < 0.3, moderate as r = 0.3–0.69, and strong as r ≥ 0.7. *P* values less than 0.05 were considered statistically significant. We did not correct for multiple comparisons because of the hypothesis-generating nature of our study, nor did we perform statistical analyses of the muscle biopsy results, due to the small number of patients with available muscle biopsy tissue samples.

RESULTS

Patient participation. Of the 72 invited patients, 45 (85%) of the 53 accepting the study invitation fulfilled the inclusion criteria. One patient was later excluded due to a change of diagnosis. We obtained muscle biopsy samples from 17 (46%) of 37 patients ages ≥18 years. All patients but 1 fulfilled the EULAR/ACR classification criteria for juvenile DM, while the remaining patient fulfilled the criteria for IIMs but lacked the classic juvenile DM presentation of rashes.

General characteristics. Among the patients with juvenile DM, 17 (39%) of 44 had active disease (14 [82%] of 17 were age >18 years) and 27 (61%) of 44 had inactive disease (23 [85%] of 27 were age >18 years) (Table 1). Regarding physical activity, patients had less time spent in MVPA than controls (mean 13.2

Table 1. General characteristics, physical activity measures, and disease variables in patients with juvenile dermatomyositis (DM) compared to controls*

	Patients with juvenile DM			
	Active disease (n = 17)	Inactive disease (n = 27)	Total (n = 44)	Controls (n = 44)
General characteristic				
Age, mean ± SD years	32.2 ± 14.6	28.7 ± 10.3	30.1 ± 12.1	30.49 ± 12.1
Female, no. (%)	11 (65)	16 (59)	27 (61)	27 (61)
Height, mean ± SD cm	165.7 ± 13.1	170.2 ± 9.3	168.5 ± 11.0	171.5 ± 10.1
Weight, mean ± SD kg	65.8 ± 19.1	69.2 ± 16.1	67.9 ± 17.0	67.8 ± 14.7
Physical activity				
Level, mean ± SD minutes/day				
Sedentary	551.6 ± 75.9	579.7 ± 67.0	569.2 ± 70.8	571.0 ± 625
LPA	168.2 ± 60.8	171.4 ± 57.7	170.2 ± 58.1	169.2 ± 60.3
MVPA	48.3 ± 28.0†	42.0 ± 22.1	44.4 ± 24.3‡	57.6 ± 21.1
Counts per minute, mean ± SD	389.4 ± 177.2†	335.2 ± 132.6	352.6 ± 149.6‡	438.7 ± 196.4
Disease variable				
Disease duration, mean ± SD years	23.2 ± 13.4	21.0 ± 10.8	21.8 ± 11.8	NA
Taking medication for juvenile DM, no. (%)	4 (24)	6 (22)	10 (23)	NA
DAS muscle (scale 0–20), mean ± SD§	5.2 ± 3.1	3.8 ± 2.0	4.3 ± 2.5	NA
MDI (scale 0–40), median (IQR)§	5.0 (2.0–5.5)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	NA
PhGA score (scale 0–10), median (IQR)§	0.4 (0.0–0.8)¶	0.0 (0.0–0.3)	0.2 (0.0–0.6)	NA
PhGD score (scale 0–10), median (IQR)§	1.0 (0.5–2.2)	0.8 (0.2–2.1)	1.0 (0.2–2.1)	NA
Self-reported physical health				
SF-36 PCS (scale 0–100)#	49.4 (33.2–53.2)†	56.3 (48.9–60.3)	52.4 (46.6–59.0)‡	58.1 (54.3–60.1)
CHAQ/HAQ score >0, no. (%)	9 (53)	9 (33)	18 (41)	NA

* Categorization into active versus inactive disease was based on the Paediatric Rheumatology International Trials Organisation criteria for inactive disease. LPA = light physical activity; MVPA = moderate-to-vigorous physical activity; NA = not applicable; DAS = Disease Activity Score; MDI = Myositis Damage Index; IQR = interquartile range; PhGA = physician global assessment of disease activity; PhGD = physician global assessment of damage; SF-36 PCS = Short-Form 36 physical component summary score; CHAQ/HAQ = childhood/adult Health Assessment Questionnaire.
† $P < 0.01$ versus patients with inactive disease.
‡ $P < 0.01$ versus age- and sex-matched controls.
§ Higher scores indicate more impairment/worse function.
¶ $P < 0.05$ versus patients with inactive disease.
# Lower scores indicate more impairment/worse function.

fewer minutes/day, 95% confidence interval [95% CI] 4.6–21.8; $P = 0.003$). While there was no significant difference in the MVPA between patients with active disease and respective controls, nor between the control groups of active/inactive disease (data not shown), patients with inactive disease had less time spent in MVPA than respective controls (mean 16.4 fewer minutes/day, 95% CI 6.5–26.2; $P = 0.002$). In patients ages <18 years (n = 6), the MVPA was a mean ± SD 58.5 ± 34.3 minutes/day, while in adults ages ≥18 years (n = 37), it was 341.8 ± 131.6 minutes/day.

A DAS score >0 was found in 42 (95%) of 44 patients with juvenile DM. The MDI score of muscle damage in patients was a mean ± SD 3.3 ± 2.4, and 27 (61%) of 44 patients had an MDI global VAS muscle score of >0.2 cm. In the whole patient group, there were no correlations between age and any physical activity variables determined by accelerometer.

Muscle characteristics. Patients with juvenile DM had a lower peak torque compared to controls (mean difference 29 Nm, 95% CI 13–46; $P = 0.001$) (Table 2). The total work of the knee extensors was a median 738J (IQR 565–1,155) in patients compared to a median 1,249J (IQR 815–1,665) in controls ($P < 0.001$). Peak torque and total work were also lower in patients

Table 2. Muscle characteristics in patients with juvenile dermatomyositis (DM) compared to controls*

	Patients with juvenile DM			
	Active disease (n = 16)	Inactive disease (n = 27)	Total (n = 43)	Controls (n = 44)
Objective muscle test variable				
Peak torque, mean ± SD Nm	98.0 ± 37.8†	127.0 ± 35.8	116.2 ± 38.8‡	145.5 ± 46.6
Repetitions, mean ± SD	22.2 ± 8.7	26.2 ± 7.9	24.7 ± 8.3‡	29.5 ± 8.2
Total work, median (IQR) Joules	565 (350–1,032)†	994 (651–1,175)	738 (565–1,155)§	1,249 (815–1,665)
Peak torque/CSA, median (IQR) Nm/cm^2	2.0 (1.6–2.2)	2.1 (2.0–2.2)	2.0 (1.8–2.2)	NA
Total work/CSA, median (IQR) Joules/cm^2	10.0 (8.3–14.3)†	16.5 (12.4–18.9)	14.1 (9.3–18.5)	NA
Clinical variable				
MMT-8 score (scale 0–80), median (IQR)¶	75.0 (73.0–77.0)#	78.0 (77.0–79.0)	77.5 (74.3–79.0)	NA
CMAS score (scale 0–52), median (IQR)¶	48.0 (45.0–51.5)†	50.5 (49.0–52.0)	50.0 (48.0–52.0)	NA
DAS muscle (scale 0–11), median (IQR)**	2.0 (1.0–4.5)	1.0 (1.0–2.0)	1.8 (1.0–2.5)	NA
MDI muscle (scale 0–3), mean ± SD**	1.5 ± 0.7‡	0.7 ± 0.6	1.0 ± 0.7	NA
MDI muscle VAS score (scale 0–10)				
Median (IQR)**	0.6 (0.3–1.6)#	0.2 (0.0–0.4)	0.3 (0.0–1.0)	NA
Score >0.2, no. (%)	13 (77)†	11 (41)	24 (55)	NA
Laboratory parameter				
CK, median (IQR) units/liter	179 (84–266)	108 (67–131)	118 (79–180)	116 (86–182)
LD, mean ± SD units/liter	181 ± 40	160 ± 19	168 ± 30	170 ± 37
ASAT, median (IQR) units/liter	29 (24–31)	24 (22–33)	26 (22–31)	23 (20–29)
Decorin, median (IQR) pg/ml	177 (156–195)	191 (156–252)	182 (156–238)††	157 (135–184)
IP-10, median (IQR) pg/ml	765 (517–1,477)	863 (547–1,175)	799 (531–1,175)††	579 (461–863)
MCP-1, mean ± SD pg/ml	375 ± 213	290 ± 125	327 ± 168	309 ± 110
Myostatin, mean ± SD pg/ml	1,873 ± 720 (n = 12)	1,983 ± 855 (n = 16)	1,844 ± 629 (n = 26)	2,446 ± 908
CCL5, mean ± SD pg/ml	6,224 ± 2,072	6,046 ± 2,058 (n = 26)	6,122 ± 1,822	6,530 ± 1,610
IL-6, median (IQR) pg/ml	0.6 (0.4–1.1) (n = 16)	1.0 (0.5–1.4) (n = 26)	0.9 (0.4–1.4)	1.0 (0.6–1.5)
IL-8, median (IQR) pg/ml	8.8 (4.6–9.7) (n = 16)	6.5 (5.1–9.8) (n = 26)	6.7 (5.0–9.6)	8.3 (5.1–12.1)
TNF, mean ± SD pg/ml	19.9 ± 11.3	20.9 ± 12.3	20.0 ± 10.6	18.9 ± 7.8
MRI muscle				
Edema, no. (%)‡‡	1 (6)	2 (7)	3 (7)	NA
Fatty infiltration, no. (%)	10 (63)	11 (41)	21 (49)	NA
Grade 2	8 (50)	9 (33)	17 (40)	NA
Grade 3	2 (13)	2 (7)	4 (9)	NA
Calcinosis, no. (%)‡‡	1 (6)	3 (11)	4 (9)	NA
Quadriceps CSA, median (IQR) cm^2	48.5 (39.8–58.7)†	56.7 (50.6–62.5)	53.2 (45.0–62.3)	NA

* Peak torque/cross-sectional area (CSA) and total work/CSA represent the peak torque and total work per maximal quadriceps CSA. Fatty infiltration is defined as the presence of pathologic fatty infiltration. IQR = interquartile range; NA = not applicable; MMT-8 = unilateral Manual Muscle Testing in 8 muscle groups; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; MDI = Myositis Damage Index (score for muscle damage extent); MDI VAS = MDI visual analog scale (score for muscle damage severity); CK = creatine kinase; LD = lactate dehydrogenase; ASAT = aspartate amino transferase; IP-10 = interferon-γ–inducible protein 10; MCP-1 = monocyte chemotactic protein 1; IL-6 = interleukin-6; TNF = tumor necrosis factor; MRI = magnetic resonance imaging.
† $P < 0.05$ versus patients with inactive disease.
‡ $P < 0.01$ versus age- and sex-matched controls.
§ $P < 0.001$ versus age- and sex-matched controls.
¶ Lower scores indicate more impairment/worse function.
# $P < 0.01$ versus patients with inactive disease.
** Higher scores indicate more impairment/worse function.
†† $P < 0.05$ versus age- and sex-matched controls.
‡‡ Due to the small numbers of patients, data on edema and calcinosis were not statistically analyzed.

with active disease and patients with inactive disease compared to their respective controls (each $P < 0.034$ versus controls), and in patients with active disease compared to those with inactive disease ($P = 0.016$ for peak torque and $P = 0.019$ for total work) (Table 2). When these muscle strength and endurance values were normalized to the quadriceps femoris CSA, only total work/CSA remained significantly lower in patients with active disease compared to those with inactive disease ($P = 0.027$).

In the total patient group, 38 patients (86%) had an MMT-8 score <80, and 27 (61%) had a CMAS score <52; only 1 (2.3%) had an MMT-8 score <64 and a CMAS score <35 (indicating severe muscle impairment). Muscle dysfunction, as measured by the MDI, was found in 9 patients (21%), muscle weakness was found in 31 patients (71%), and muscle atrophy was found in 5 patients (11%). The MMT-8 and CMAS scores (included in the definition of active/inactive disease) were lower and the extent of muscle damage (MDI muscle scores) and severity of muscle damage (MDI VAS muscle scores) were higher in patients with active disease compared to patients with inactive disease (all $P < 0.005$) (Table 2).

The total patient group had higher serum levels of decorin and IP-10 (myokines related to inflammation) compared to controls. However, there were no significant differences in any of the serum myokine levels between patients with active disease and those with inactive disease (Table 2). Myokine levels were not found to be correlated with the total DAS scores or MDI muscle scores.

Of the MRI-assessed variables in the thigh muscle, none showed a significant difference between patients with active disease and those with inactive disease. Nevertheless, a numerically larger proportion of patients with active disease had pathologic muscle fatty infiltration as compared to patients with inactive disease (Table 2). No patients had fatty infiltration of the muscle of more than 50% (grade 4). The quadriceps CSA was smaller in patients with active disease compared to patients with inactive disease ($P = 0.017$) (Table 2).

Associations between objective muscle test findings and disease variables/physical activity measures. In patients with active disease, peak torque and total work of the knee extensors showed moderate-to-strong correlations with the MMT-8 score, MMT knee extensor component score, and CMAS score (Table 3 and Figure 1). There were no significant correlations between the findings on clinical tests and findings on objective tests

Table 3. Correlations between peak torque or total work of the knee extensors and general, disease-related, and muscle characteristics in patients with DM*

	Peak torque			Total work		
	Active juvenile DM	Inactive juvenile DM	Total	Active juvenile DM	Inactive juvenile DM	Total
General characteristic						
Height†	0.662‡	0.602‡	0.650§	0.735‡	0.518‡	0.678§
Weight†	0.360	0.532‡	0.464‡	0.206	0.394¶	0.412‡
Physical activity						
MVPA†	0.092	0.395¶	0.227	0.066	0.228	0.139
MVPA bouts	0.260	0.203	0.133	0.254	−0.005	0.066
Disease or muscle variable						
Disease duration†	0.272	0.150	0.165	0.387	0.107	0.220
MMT-8	0.770§	0.270	0.521§	0.838§	0.194	0.533§
CMAS	0.574¶	0.140	0.456‡	0.574¶	0.309	0.519§
DAS muscle	−0.667‡	−0.436¶	−0.605§	−0.706‡	−0.385¶	−0.576§
MDI muscle†	−0.144	−0.292	−0.359¶	−0.091	−0.182	−0.228
MRI fatty infiltration	0.315	−0.223	−0.153	0.347	−0.184	−0.090
CSA†	0.560¶	0.469¶	0.450‡	0.609¶	0.770§	0.756§
MCP-1†	0.515	−0.395¶	−0.076	0.309	−0.048	0.063
Myostatin†	0.247	0.428	0.345	0.259	0.341	0.294
Decorin	0.182	−0.416¶	0.019	0.338	−0.138	0.138
IP-10	−0.025	0.020	0.056	−0.071	−0.234	−0.093
CCL5†	0.324	−0.197	−0.021	0.214	−0.141	0.034
IL-6	0.536¶	−0.053	0.203	0.105	0.054	0.184
IL-8	0.096	−0.277	−0.098	0.063	−0.079	−0.007
TNF†	0.466	0.113	0.236	0.014	−0.002	0.043

* Correlations were determined using Pearson's R and Spearman's rho correlation tests. Moderate-to-vigorous physical activity (MVPA) bouts refer to the average time (in minutes) of MVPA spent in bouts lasting 10 minutes each. The myokines presented were selected on the basis of associations seen in the present and previous studies of myokines in patients with juvenile dermatomyositis (DM). MMT-8 = unilateral Manual Muscle Testing in 8 muscle groups; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; MDI = Myositis Damage Index; MRI = magnetic resonance imaging; CSA = (quadriceps) cross-sectional area; MCP-1 = monocyte chemotactic protein 1; IP-10 = interferon-γ–inducible protein 10; IL-6 = interleukin-6; TNF = tumor necrosis factor.
† Normally distributed variable.
‡ $P < 0.01$.
§ $P < 0.001$.
¶ $P < 0.05$.

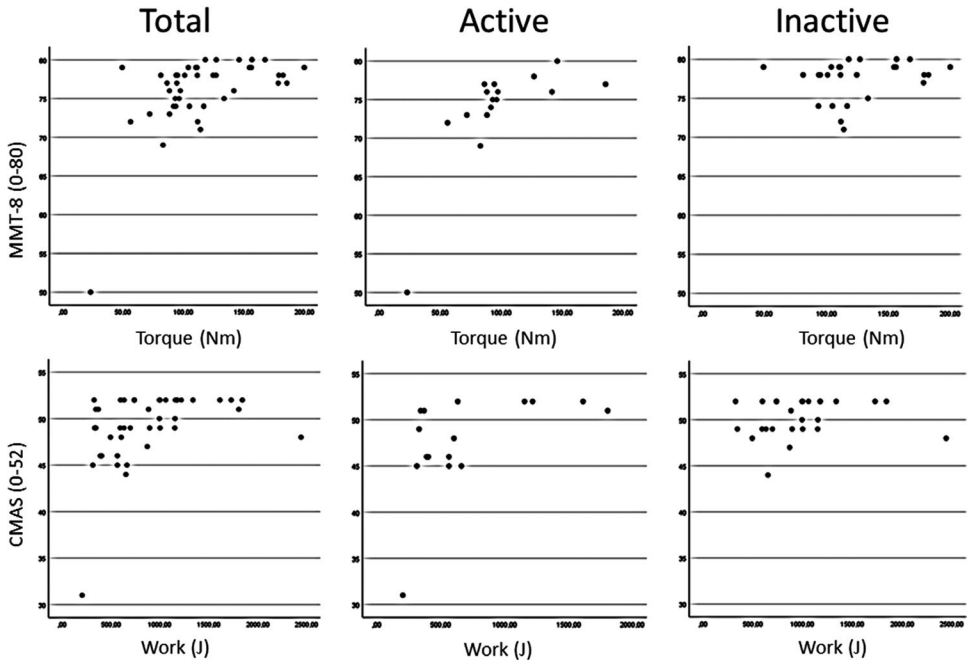

Figure 1. Correlations between objective muscle measures (peak torque of muscle strength and total work of dynamic muscle endurance) and clinical muscle test findings (both general and knee extensor) in patients with juvenile dermatomyositis in total, and in patients with active disease and those with inactive disease. Correlation analyses were performed using Pearson's R or Spearman's rho. MMT-8 = Manual Muscle Testing of 8 muscle groups (unilateral); CMAS = Childhood Myositis Assessment Scale.

of muscle strength or endurance in patients with inactive disease (Table 3 and Figure 1). Peak torque correlated weakly with the MVPA in patients with inactive disease. Both peak torque and total work correlated with DAS muscle scores both in patients with active disease and in patients with inactive disease. In the whole patient group, peak torque correlated negatively with the MDI muscle score. No significant correlations were found between peak torque or total work and MDI muscle scores or MRI findings in the patient subgroups. In patients with active disease, peak torque showed a moderate, positive correlation with serum IL-6 levels (Table 3).

Characteristics of the muscle biopsy tissue. Twelve (71%) of 17 muscle biopsy samples from patients with juvenile DM were of adequate quality for muscle fiber assessment, and 11 (65%) of 17 samples were adequate for capillary assessment. The muscle biopsy samples that were deemed to be of inadequate quality had tissue resembling muscle tissue, but had a texture unsuitable for slicing. Among the patients with adequate-quality muscle biopsy samples, the median time from clinical examination to the needle muscle biopsy was 11.0 months (IQR 9.0–16.3), and none reported major changes in lifestyle or disease activity during this time.

General characteristics of the 12 patients with adequate-quality muscle biopsy samples were not significantly different from the remaining cohort of patients ages ≥18 years (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41174/abstract). Seven (58%) of the 12 patients had active disease, and 5 (42%) had inactive disease, with comparable age and sex distribution between the groups. None of the 12 patients were taking antiinflammatory medications at the time of biopsy. Eight (67%) of the 12 patients had fatty infiltration evident on MRI of the thigh muscle.

Muscle biopsy tissue samples were stained with hematoxylin and eosin, with results showing that 1 patient had increased variability of muscle fiber size and 2 patients had muscle fibers with centralized nuclei (signs of muscle degeneration/regeneration). None of the 12 muscle biopsy samples had pathologic fatty infiltration or definite cell infiltration.

Results of immunohistochemical analyses of the muscle tissue demonstrated that 1 patient with active disease had abnormally large muscle fibers and showed signs of perifascicular atrophy. None of the patients had inflammatory infiltrates (accumulation of CD68+ cells) or the inflammation markers tenascin C or embryonic MHC. There was a numeric trend toward patients with active disease having a larger area of type I muscle fibers compared to type II muscle fibers (Table 4). In addition, patients with active disease tended to have a larger area of type I muscle fibers compared to patients with inactive disease. This trend was reversed in patients with inactive disease, as they had a larger area of type II fibers compared to type I fibers, and had larger type II fibers compared to patients with active disease. There was also a numerically smaller proportion of type I fibers in patients with active compared to inactive disease (Figure 2). There were no significant differences in capillary features between the active disease and inactive disease groups.

Table 4. Muscle biopsy results in patients with juvenile DM*

	Active juvenile DM (n = 7)	Inactive juvenile DM (n = 5)	Total (n = 12)
Type I fiber area, μm^2			
Total	4,497 (2,701–8,560)	4,045 (2,643–4,576)	4,212 (3,233–4,600)
Men	4,608 (3,143–8,560) (n = 3)	4,311 (4,045–4,576) (n = 2)	4,576 (3,143–8,560)
Women	4,098 (2,701–5,387) (n = 4)	3,503 (2,643–4,379) (n = 3)	3,699 (2,643–5,387)
Type II fiber area, μm^2			
Total	4,030 (1,951–12,275)	5,081 (2,319–5,873)	4,255 (2,939–5,434)
Men	4,720 (2,922–12,275) (n = 3)	5,713 (5,552–5,873) (n = 2)	5,552 (2,922–12,275)
Women	3,611 (1,951–4,479) (n = 4)	2,990 (2,319–5,081) (n = 3)	3,191 (1,951–5,081)
Type I fibers/total number of fibers, %	39 (33–64)	47 (33–52)	43 (33–53)
Capillarization†			
CF	1.7 (1.1–1.9)	1.8 (1.5–2.0)	1.7 (1.4–2.0)
CAFI	4.3 (3.3–4.7)	4.0 (3.7–4.4)	4.2 (3.7–4.5)
CAFII	3.6 (3.4–3.9)	3.7 (3.0–4.5)	3.6 (3.3–4.1)
CAFAI	0.9 (0.8–1.2)	0.9 (0.8–1.2)	0.9 (0.8–1.2)
CAFAII	1.0 (0.7–1.3)	0.9 (0.6–1.1)	1.0 (0.7–1.3)

* No statistical analyses of the muscle biopsy data were performed due to the small number of needle biopsy samples available. Type I and type II fibers refer to muscle fiber types. Values are the median (interquartile range).
† Data on capillarization are expressed as the total number of capillaries per total number of fibers (CF), total number of capillaries around type I and type II muscle fibers (CAFI and CAFII, respectively), and total number of capillaries around type I and type II muscle fibers per fiber area (CAFAI and CAFAII, respectively). The number of samples for capillary data were as follows: active juvenile dermatomyositis (DM) n = 7, inactive juvenile DM n = 4, total patient group n = 11.

DISCUSSION

In our study focusing on long-term skeletal muscle outcomes in patients with juvenile DM, we found lower muscle strength and lower muscle endurance in the knee extensors of patients compared to age- and sex-matched controls. Moreover, patients with active disease had lower muscle strength and endurance compared to patients with inactive disease. Corrected for muscle size (the quadriceps CSA), only muscle endurance remained

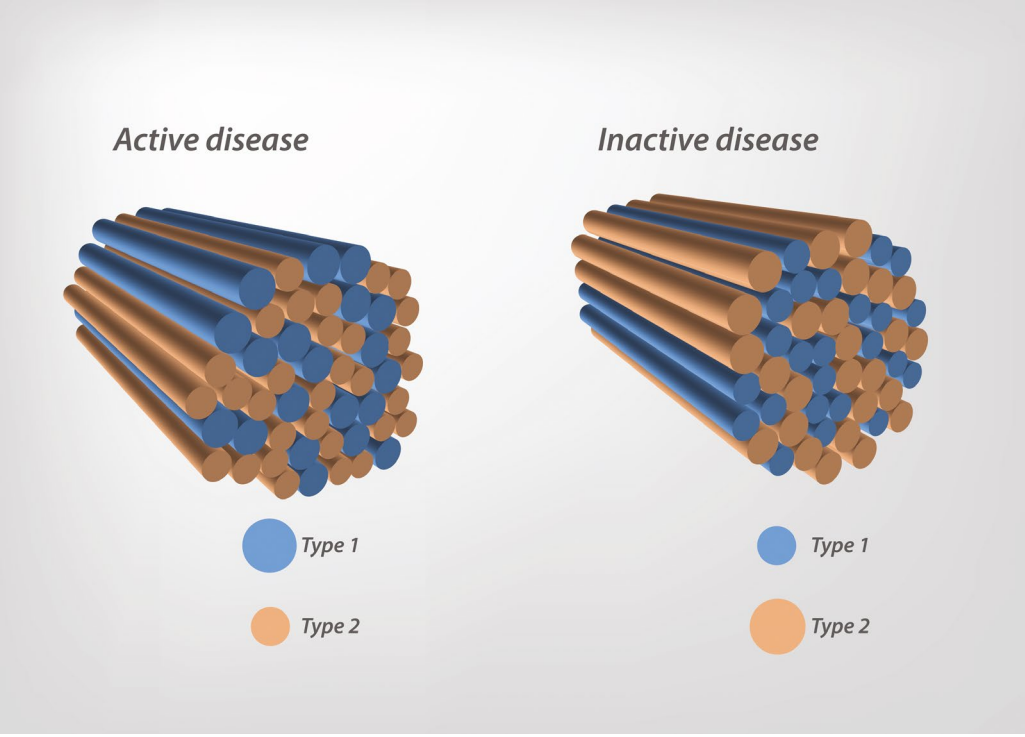

Figure 2. Visual images of the muscle fiber composition (types I and II muscle fibers) and relative size of the muscle fibers in patients with active juvenile dermatomyositis (DM) and those with inactive juvenile DM.

significantly lower in patients with active disease compared to patients with inactive disease. Clinically assessed muscle damage was higher in patients with active disease compared to those with inactive disease. The results of objective muscle tests of the knee extensors correlated with the findings from clinical tests of muscle strength and endurance only in patients with active disease. Muscle biopsy results indicated that capillary density was similar but muscle fiber composition was different between the active and inactive disease groups. To our knowledge, this is the first long-term study to assess functional, laboratory, serologic, radiographic, and histologic muscle outcomes simultaneously in patients with juvenile DM.

Our patients were older, had a longer disease duration, and were comparable in sex distribution when compared to patients in other studies of juvenile DM outcomes (7,8). Compared to those other studies (7,8), more patients in our study had a DAS >0, and our study had a comparable proportion of patients with an MDI global VAS muscle score >0.2; however, the MDI scores were higher in our patients. The physical activity levels of our patients were similar to those in a Danish juvenile DM cohort and higher than those in a Brazilian juvenile DM cohort (36,37). Based on our findings, the patients in our study presented with fairly high levels of physical activity despite frequently having relatively high levels of disease activity and damage.

The control subjects were randomly selected from the Norwegian National Registry, which is a strength of our study. They were age- and sex-matched to our patients in order to account for the large age dispersion and to exclude the potential for age-related confounders in our main results. The physical activity levels of our adult control subjects resembled those of the general Norwegian adult population (38), supporting the representativeness of our control group.

Isometric muscle strength and muscle endurance of the knee extensors as well as MMT-8 scores and CMAS scores were lower in patients with active disease compared to patients with inactive disease, but the findings of these clinical and objective muscle tests correlated only in patients with active disease. Although objective muscle tests were only assessed in the knee extensors, peak torque also correlated with the MMT knee component scores only in patients with active disease. Taken together, these results support the ceiling effects of the MMT-8 and CMAS scoring systems. A precise scoring of mild muscle weakness and dysfunction, especially in patients with inactive disease, may therefore require more objective and sensitive muscle testing.

The MMT-8 and CMAS scores were mildly reduced (median MMT-8 score 77.5 and median CMAS 50.0), similar to that in a Danish study of juvenile DM patients assessed after a disease duration of 13.9 years, in which the mean values were 78.0 and 48.8, respectively (8). An MMT-8 score <80 and CMAS score <52 were, however, more frequent in our study (86% and 61%, respectively) than in a multinational outcome study of 490 juvenile DM patients whose mean disease duration was 7.7 years (41% and 53%, respectively) (7). Nevertheless, severe muscle weakness/dysfunction was rare; only 1 patient (2.3%) had serious muscle weakness and dysfunction based on having an MMT-8 score <64 and CMAS score <35, as compared to 7% having an MMT-8 score <64 and 8% having a CMAS score <35 in the multinational study. A longer disease duration in our study could be the reason for this difference. Even though the CMAS has been used in mixed pediatric/adult juvenile DM populations (7–9), it has not been validated for adults with juvenile DM. However, our group has shown moderate correlations between the CMAS score and disease measures (MMT-8, DAS muscle scores, and the MDI) in patients ages >18 years (9), supporting the use of the tool in this adult age group.

Objective muscle strength and muscular endurance were lower in patients (both in those with active disease and in those with inactive disease) compared to controls. Multiple factors may have contributed to these results, including exercise habits and disease-related features (39) (age/sex effects were controlled for by matching). We did not systematically collect data on strength-training habits, a limitation to our study. However, only patients with inactive disease had a lower MVPA compared to controls, and there was a correlation between the MVPA and mean peak torque in patients with inactive disease. This suggests that deconditioning may play a larger role in explaining the lower muscle strength in these patients compared to patients with active disease, although muscle disease activity and damage were also present in this patient group.

Patients with active disease had higher muscle damage (based on MDI muscle and MDI VAS muscle scores, as well as numeric values of MRI-detected damage, including fatty infiltration), but not muscle activity (based on DAS muscle scores, muscle enzyme levels, or MRI-detected edema), compared to patients with inactive disease. However, muscle damage scores did not correlate with isometric muscle strength or muscle endurance in either patient group. This suggests that the difference in peak torque and total work between active and inactive juvenile DM may be attributed to disease-related factors other than the classic juvenile DM measures of disease damage.

Muscle CSA was lower in patients with active disease compared to patients with inactive disease; this might represent a larger reduction in volume due to muscle atrophy in patients with active disease. The CSA correlated with findings on objective muscle tests in both patient groups. However, when correcting the measurements of muscle strength and muscle endurance for the quadriceps CSA, only total work remained lower in patients with active disease compared to those with inactive disease. This could indicate that muscle endurance associated with active disease is influenced by structural or functional differences within the muscle tissue independent of muscle size. This hypothesis was supported by the muscle biopsy results. We found no signs of muscle inflammation in the biopsy samples. However, although not statistically tested, there were numeric trends of different muscle fiber composition between patients with active disease and

those with inactive disease. In patients with active disease, type I muscle fibers were relatively larger and type II muscle fibers were relatively smaller compared to patients with inactive disease, and patients with active disease had a lower proportion of type I fibers. Given the numerically higher MVPA in patients with active disease, this difference in fiber composition was unexpected, as exercise is found to increase the size of type II fibers and the proportion of type I fibers in adult patients with DM (21). However, there is evidence that long-term physical inactivity or chronic disease can cause a greater percentage of type II fibers (40).

Hypoxia has been suggested as a possible mechanism for the reduction in muscle endurance in patients with juvenile DM, attributable to the fact that blood flow increases more poorly in response to exercise (41). In patients with severe chronic obstructive pulmonary disease, which leads to chronic hypoxia, the proportion of type I muscle fibers has been found to be decreased, together with an increase in the type II muscle fiber area (42), similar to the findings in our patients with active disease. With regard to capillarization, we found that the histologic capillary density was similar to that in studies of healthy populations (43), and there was no difference in capillary features between patients with active disease and those with inactive disease. However, the presented biopsy results do not tell us anything about the potential for functional impairment of the capillaries in juvenile DM (41).

Myokines are known to be secreted from muscle tissue in response to exercise or inflammatory stimuli (6). We found higher levels of IP-10 in patients compared to controls, similar to previous data from our own cohort (17), supporting the notion that this myokine is up-regulated even after long-term disease. IP-10 was recently validated as a strong, reliable, and sensitive biomarker for active juvenile DM (44). We did not, however, find significant differences in IP-10 levels between the active and inactive disease groups, suggesting that our study may be underpowered, or that the myokine may be a less stable marker of disease activity over a longer disease duration. In addition, our patients had higher circulating levels of decorin compared to controls. Decorin is known to be both antifibrotic and proinflammatory (45,46). Higher levels of decorin may be attributable to increased levels of visceral fat (VAT) depots, as has been previously described (47) (VAT is a greater source of decorin than subcutaneous fat [46]), and may reflect the inflammatory state of juvenile DM. Surprisingly, we found a positive association between the serum IL-6 levels and the peak torque in patients with active disease. IL-6 is known as a biomarker for active inflammation in juvenile DM (48). Interestingly, it was also recently found to be both expressed and secreted from type I muscle fibers in mice (49), while torque was associated with type I fibers in female athletes (50). Thus, we could speculate that the association between IL-6 levels and torque is related to an increase in the area of type I muscle fibers in patients with active disease.

In addition to the limitations to our study already mentioned, the time delay between muscle biopsies and other examinations may have affected the interpretation of the biopsy results, although none of the patients who underwent a muscle biopsy reported experiencing lifestyle changes, including physical activity habits. The small number of patients in each group (active and inactive disease) may have created Type II errors in the statistical analyses. For the lowest numbers, therefore, we chose not to perform statistical analyses, but rather we described numeric differences. We also isolated the muscle subscores of the validated tools DAS and MDI, and the knee extensor component of MMT-8, although these subscores have not been validated separately.

In conclusion, after an average disease duration of almost 22 years, objectively measured muscle strength and muscle endurance of the knee extensors were lower in patients with juvenile DM compared to controls, and in patients with active disease compared to those with inactive disease. The results of objective muscle tests and clinical muscle tests correlated only in patients with active disease, suggesting the need for more objective and sensitive muscle tests in this clinical setting. Based on the results of the present study, we can hypothesize that impaired muscle endurance of the knee extensors in patients with active disease may be influenced by structural and functional adaptions of muscle tissue independent of muscle size. Further study of these concepts should be carried out in patients with juvenile DM.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Berntsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bernsten, Raastad, Sjaastad, Sanner.

Acquisition of data. Bernsten, Raastad, Marstein, Kirkhus, Merckoll, Sanner.

Analysis and interpretation of data. Bernsten, Raastad, Marstein, Kirkhus, Merckoll, Cumming, Flatø, Sjaastad, Sanner.

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