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Damage Extent and Predictors in Adult and Juvenile Dermatomyositis and Polymyositis as Determined With the Myositis Damage Index

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Objective. **We undertook this study to validate the Myositis Damage Index (MDI) in juvenile and adult myositis, to describe the degree and types of damage and to develop predictors of damage.**

Methods. **Retrospective MDI evaluations and prospective assessment of disease activity and illness features were conducted. Patients with juvenile-onset disease (n = 143) were evaluated a median of 18 months after diagnosis; 135 patients were assessed 7–9 months later, and 121 were last assessed a median of 82 months after diagnosis. Ninety-six patients with adult-onset dermatomyositis or polymyositis had a baseline assessment a median of 30 months after diagnosis; 77 patients had a 6-month followup evaluation, and 55 had a final assessment a median of 60 months after diagnosis.**

Results. **Damage was present in 79% of juvenile patients and in 97% of adult patients. In juveniles, scarring, contractures, persistent weakness, muscle dysfunction, and calcinosis were most frequent (23–30%) at the last evaluation. In adults, muscle atrophy, muscle dysfunction, and muscle weakness were most frequent (74–84%). MDI severity correlated with physician-assessed global damage, serum creatinine, and muscle atrophy on magnetic resonance imaging, and in juveniles also with functional disability and weakness. MDI damage scores and frequency were highest in patients with a chronic illness course and in adult patients who died. Predictors of damage included functional disability, duration of active disease, disease severity at diagnosis, physician-assessed global disease activity, and illness features, including ulcerations in children and pericarditis in adults.**

Conclusion. **Damage is common in myositis after a median duration of 5 years in patients with adult-onset disease and 6.8 years in patients with juvenile-onset disease. The MDI has good content, construct, and predictive validity in juvenile and adult myositis.**

The idiopathic inflammatory myopathies (IIMs) constitute a common cause of acquired myopathy in adults and children. These systemic autoimmune diseases, although treatable with immunosuppressive medications, often result in a chronic illness course, func-

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tional disability, and increased mortality (1). Although the mortality rate is relatively low in patients with juvenile dermatomyositis (DM), up to 40% of these patients have long-term dystrophic calcification and functional disability (2,3). The 5-year mortality rate in adult IIM patients ranges from 5% to 37%, and their most common causes of death are malignancy, cardiovascular disease, and respiratory failure (for review, see ref. 4).

The International Myositis Assessment and Clinical Studies (IMACS) Group, a multidisciplinary consortium of adult and pediatric specialists with interest and expertise in myositis, has defined disease damage as persistent or permanent change in anatomy, physiology, and function, which develops from previously active disease, complications of therapy, or other events (5). The IMACS Group recommended a core set of measures for inclusion in therapeutic trials and clinical studies to assess disease activity and damage, to provide consistency in myositis outcomes (5). The IMACS Group developed the Myositis Damage Index (MDI), which is patterned after the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (6). A list of IMACS Group participants and other contributors, in addition to the authors of this article, is shown in Appendix A.

The MDI documents persistent changes in 11 items (9 organ systems and infection and malignancy; collectively termed "organ systems") thought to be related to damage. Because severity of damage can differ from extent of damage, the IMACS Group includes a series of visual analog scales (VAS) to quantify damage severity in a given organ system (7). The MDI was also structured for both pediatric and adult patients, and certain items are scored solely in each population. The MDI has undergone interrater reliability testing in adult polymyositis (PM)/DM patients (7). The purposes of this study were to describe the degree and types of damage in study populations with longer term followup, to further validate the MDI in patients with adult or juvenile IIM, and to find risk factors for damage.

PATIENTS AND METHODS

Patients and assessment methods. This study included 134 patients with juvenile DM and 9 patients with juvenile PM age <18 years at diagnosis, as well as 38 patients with DM and 58 patients with PM age ≥18 years at diagnosis. To qualify for inclusion, patients had at least 2 assessments 6–9 months apart. Patients met probable or definite Bohan and Peter criteria for myositis (8) and were enrolled in National Institutes of Health (NIH) Institutional Review Board–approved protocols in compliance with the Declaration of Helsinki. Juvenile and adult IIM patients differed in several demographic and clinical assessment characteristics (Table 1).

We enrolled 143 consecutive patients with juvenile IIM from 12 participating centers in the US, Canada, and Europe into a natural history study. All patients were assessed a median of 18 months (interquartile range [IQR] 7–37 months) after diagnosis; 135 patients (94%) were assessed 7–9 months later, and 121 (85%) had a last available assessment a median of 82 months (IQR 52–108 months) after diagnosis. Patients were evaluated between April 1993 and November 2002. Illness features and laboratory and disease activity assessment measures were determined/obtained prospectively (9).

Ninety-six patients with adult DM and PM were enrolled in protocols at the NIH. Patients had a baseline assessment a median of 30 months after diagnosis (IQR 12–57 months); 77 (80%) had a 6-month followup evaluation, and 55 (57%) had a final assessment a median of 60 months after diagnosis (IQR 40–104 months). Patients were assessed between May 1985 and December 2001. Thirty were enrolled in a natural history study, and 66 were enrolled in treatment protocols (cyclophosphamide [n = 8] [10], methotrexate/azathioprine [n = 27] [11], fludarabine [n = 15] [12], and methimazole [n = 16] [13]).

The MDI was completed retrospectively by participating physicians who were trained in the use of the instrument and its definitions at a workshop and provided with online resources demonstrating the features of cutaneous damage. The MDI consists of 11 scales (including muscular, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, and ocular organ systems, and infection and malignancy), each with 2–8 items scored as present or absent, as well as a 10-cm VAS score for each organ system, anchored at the ends and midpoint, to capture severity of damage in each organ system. An item must be observed for ≥6 months to be scored as present and consistent with damage, and each damage item has been defined.

The presence or absence of each item was summed to provide a total MDI extent of damage score (potential range 0–35 in children age <12 years, 0–37 in adolescents, and 0–38 in adults). Seven items in the cardiovascular, peripheral vascular, and endocrine systems are assessed only in pediatric or adult patients, related to the age appropriateness of the items. Two items, irregular menses and primary or secondary amenorrhea, are scored only for female patients. The VAS scores of the 11 scales were summed to provide a total MDI severity of damage score (potential range 0–110). The 10-cm VAS and a 0–4 Likert scale physician-assessed global damage score were recorded separately as previously described (14). In juvenile IIM patients, these scores were assessed during the study visits and, in adult patients, during the record review. The optional items were not included in the current study. The MDI is available online at http://www.niehs.nih.gov/research/resources/collab/imacs/diseasedamage.cfm.

We used other assessments of disease severity and damage to assess construct validity of the MDI, including measures of strength, functional disability, serum creatinine, and muscle atrophy assessed by magnetic resonance imaging (MRI), based on studies suggesting that changes in these measures accumulate over time and could reflect disease damage (5). Manual muscle strength testing (MMT) on a

Table 1. Demographic features at baseline evaluation and disease characteristics and assessment measures at final evaluation in the juvenile and adult patients with IIM*

Characteristic	Juvenile IIM patients (n = 143)	No. of patients in sample	Adult IIM patients (n = 96)	No. of patients in sample	*P*
Diagnosis, %		143		96	<0.001
DM	94		39.8		
PM	6		60.2		
Age, years	12.5 (10.0–16.0)	143	41.6 (32.2–48.9)	96	<0.001
Race, %		143		96	<0.001
Caucasian	80.6		63.2		
African American	7.4		29.5		
Hispanic	6		5.3		
Other	6		2.1		
Female sex, %	66.4	143	76.6	96	0.15
Age at diagnosis, years	6 (4–9.25)	138	38 (29–46)	95	<0.001
Severity at onset, 0–4	2 (1–3)	143	2 (2–3)	96	0.46
Autoantibody status (n)	Anti-SRP positive (1), MSA negative (61)	62	Anti–Jo-1 positive (20), other antisynthetase positive (6), anti-SRP positive (10), anti–Mi-2 positive (3), MSA negative (43)	82	<0.001
Disease duration at final evaluation, months	82 (52–108)	121	60 (40–104)	55	0.018
Delay to diagnosis, months	3 (1–6.1)	143	3.1 (0–11.2)	96	0.53
Calcinosis, %	25.9	143	15.8	96	0.23
Ulceration, skin/GI, %	24.2/2.8	143	4.2/1	96	<0.001
Disease course, %		143		89	<0.001
Monocyclic	25		2.1		
Polycyclic	30.4		31.1		
Chronic continuous	34.4		51.1		
Undefined	10.2		7.8		
Physician-assessed global disease activity, 0–10-cm VAS	0.3 (0–1.2)	143	4.1 (1.8–6)	96	<0.001
MMT score, 0–120	112 (105–117)	58	92 (76–103)	80	<0.001
CMAS score, 0–52	47 (41–51)	129	NA	–	–
C-HAQ score, 0–3†	0 (0–0.7)	143	NA	–	–
Modified Convery ADL assessment scale score, 0–91†	NA	–	58 (42–67)	67	–
Steinbrocker functional class	I (I–I)	142	II (II–III)	96	<0.001
CK, 0–252 units/liter	84 (44–147)	117	448 (106–1,334)	96	<0.001
LDH, 0–226 units/liter	200 (169–249)	83	306 (231–437)	78	<0.001
Aldolase, 0–7 units/liter	6 (4.4–8)	90	14 (5.9–26.2)	85	<0.001
Creatinine, mg/dl‡	0.6 (0.5–0.7)	85	0.7 (0.6–0.9)	85	0.0003
Extramuscular global disease activity, 0–4 Likert scale	0.5 (0–1)	136	1 (1–2)	55	<0.001
T1-weighted MRI score, 0–4	0.25 (0–1.4)	34	2 (1–3)	74	<0.001

* Except where indicated otherwise, values are the median (interquartile range). DM = dermatomyositis; PM = polymyositis; anti-SRP = anti–signal recognition particle; MSA = myositis-specific autoantibody; GI = gastrointestinal; VAS = visual analog scale; MMT = manual muscle strength testing; CMAS = Childhood Myositis Assessment Scale; NA = not assessed; CK = creatine kinase; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging.

† The Childhood Health Assessment Questionnaire (C-HAQ) score was assessed in juvenile patients with idiopathic inflammatory myopathies (IIMs), and the modified Convery Activities of Daily Living (ADL) assessment scale score was assessed in adult IIM patients.

‡ The lower limit of normal was 0.5 mg/dl for juvenile IIM and 0.7 mg/dl for adult IIM.

0–10-point scale was performed in 58 patients with juvenile-onset disease and 80 patients with adult-onset disease (15), and the total score was adjusted to a scale of 0–120; physical therapists were blinded to other clinical assessments. The Childhood Health Assessment Questionnaire (C-HAQ) (16) and the modified Convery Activities of Daily Living (ADL) assessment scale (17) were used to assess functional disability in juvenile and adult IIM patients, respectively. Serum creatinine, a measure of muscle atrophy (18), was adjusted to a common scale, accounting for sex and age differences, using a lower limit of normal of 0.5 mg/dl for children and 0.7 mg/dl for adults. T1-weighted MR images of the thighs were available for 34 patients with juvenile-onset disease and 74 patients with adult-onset disease, and these were read by 1 musculo-

skeletal radiologist who was blinded to the clinical assessment; muscle atrophy and fatty infiltration were graded on a 0–4 Likert scale and averaged to provide an overall T1-weighted MRI score (19).

Disease course was defined as monocyclic, polycyclic, or chronic continuous if at least 2 years of followup after diagnosis was available (20). Duration of active disease was defined as the duration from diagnosis to the date of the last assessment at which the myositis remained active, whereas disease duration was defined as the time from diagnosis to last assessment. Mortality status in the adult patients as of February 2008 was obtained using the Social Security Death Index (http://www.deathindexes.com/ssdi.html). Age and sex were not significant predictors of mortality, so mortality was not adjusted based on these variables.

Statistical analysis. Analyses were performed using Stata version 10 (Stata Corporation, College Station, TX). Analyses describing the frequency of damage and damage scores used data from the last available assessment, whereas construct validation was performed using the first assessment. Continuous and ordinal data were expressed as the median and IQR. Analyses included chi-square tests to compare percentages, rank sum or Kruskal-Wallis tests to compare scores, and Spearman's rank correlation coefficients (r_s) for construct validity with a priori assumptions that correlations >0.7 were considered high, correlations 0.4–0.7 were considered moderate, and correlations <0.4 were considered low.

For change in damage over time, a daily rate of change using the first and last assessments was converted to an annual rate of change in damage scores. Generalized estimating equations (GEEs) (21) were used to predict the total MDI extent and severity of damage to allow for multiple observations of a patient over time; data from all available assessments were used in these analyses. Demographic features, illness characteristics, and disease activity measures were used to develop predictors of total MDI extent and severity of damage using GEE modeling, and significant variables from univariable analysis were used to develop multivariable models. Backward stepping procedures removed variables with $P > 0.15$ (22), and/or for variables in which >10% of data were missing, only patients with complete data were used for GEE modeling. We have not adjusted the probabilities for multiple testing.

RESULTS

Severity of damage by organ system. Fewer juvenile IIM patients (79.1%) than adult IIM patients (96.9%) had damage based on the total MDI severity of damage score at the last available assessment ($P < 0.0001$) (Table 2). In juvenile IIM patients, the cutaneous system was damaged most frequently, followed by the muscular, skeletal, endocrine, and gastrointestinal systems (Table 2). In adult IIM patients, the muscular system was damaged most frequently, followed by the pulmonary, gastrointestinal, and cardiovascular systems (Table 2). These organ systems also contributed most to the total MDI severity of damage score in adults.

Damage in 4 systems (muscular, gastrointestinal, pulmonary, and cardiovascular) and damage arising from infection severity, as assessed by the organ system severity of damage scores, were more frequent in adult IIM patients than in juvenile IIM patients. In addition, cutaneous severity of damage (70.3% versus 43.9%; $P = 0.005$) and peripheral vascular severity of damage (10.8% versus 2.3%; $P = 0.021$) were more frequent in adult than juvenile DM patients. Adult PM and DM patients had similar overall frequencies of damage, except that cardiovascular damage was more frequent in PM patients than in DM patients (62.5% versus 21.6%; $P < 0.0001$), and, as expected, cutaneous damage was more frequent in DM patients than in PM patients (70.3% versus 17.9%; $P < 0.0001$).

Frequency of damage. Fourteen damage items were more frequent in adult IIM patients, and 2 items were more frequent in juvenile IIM patients (Table 2). In juvenile IIM, the most frequent damage items at the last available evaluation included cutaneous scarring, joint contracture, persistent weakness, muscle dysfunction, and calcinosis; frequencies ranged from 23% to 30% (Table 2). In adult IIM patients, muscle atrophy, persistent muscle dysfunction, and muscle weakness were the most frequent damage items at the last evaluation (74–84%), followed by dysphagia and impaired lung function (53% and 49%, respectively) (Table 2). In adults, all damage items were seen in ≥1 patients, whereas in juvenile IIM patients all items but digit loss, amenorrhea, and malignancy were observed.

The same frequencies of damage were generally observed in adult and juvenile DM. However, adult DM patients had cutaneous scarring (61.1% versus 27.3%; $P < 0.001$), poikiloderma (13.9% versus 3.6%; $P = 0.018$), and thrombosis (8.1% versus 0.7%; $P = 0.007$) more frequently than juvenile DM patients at the last available evaluation.

Adult DM and PM patients had a similar frequency of detectable damage for the total MDI extent of damage at the last available assessment. As expected, 4 damage items related to the cutaneous system were more frequent in adult DM patients than in adult PM patients, including calcinosis (34.2% versus 3.5%; $P < 0.0001$), alopecia (27% versus 5.3%; $P = 0.003$), cutaneous scarring (63.2% versus 1.8%; $P < 0.0001$), and poikiloderma (10.5% versus 0.0%; $P = 0.023$). In contrast, 3 items related to muscle and cardiovascular damage were more frequent in adult PM patients than in adult DM patients, including persistent muscle weakness (82.1% versus 62.2%; $P = 0.031$), hypertension (36.8%

Table 2. Frequency of damage in the juvenile and adult IIM patients at the last available assessment using the Myositis Damage Index (MDI)*

Damage item	Juvenile IIM patients (n = 143)	Adult IIM patients (n = 96)	*P*
Muscle severity, VAS	37.8	94.8	<0.0001
Muscle atrophy	10.5	83.3	<0.0001
Weakness	26.6	74.0	<0.0001
Muscle dysfunction	23.1	84.4	<0.0001
Skeletal severity, VAS	33.6	30.3	0.69
Joint contracture	27.3	7.3	<0.0001
Osteoporosis with fracture	10.5	11.5	0.80
Avascular necrosis	3.5	6.2	0.50
Arthropathy	4.2	17.7	<0.0001
Cutaneous severity, VAS	49.0	35.5	0.053
Calcinosis	25.9	15.8	0.08
Alopecia	4.9	14.6	0.018
Cutaneous scarring	30.1	27.1	0.72
Poikiloderma	3.5	8.3	0.18
Lipodystrophy	11.2	2.1	0.018
Gastrointestinal severity, VAS	16.8	56.3	<0.0001
Dysphagia	13.3	53.1	<0.0001
Gastrointestinal dysmotility	7.7	36.5	<0.0001
Gastrointestinal infarction	1.4	1.0	0.73
Pulmonary severity, VAS	15.4	60.4	<0.0001
Dysphonia	15.4	20.8	0.36
Impaired lung function	3.5	49.0	<0.0001
Pulmonary fibrosis	0.7	28.1	<0.0001
Pulmonary hypertension	0.7	4.2	0.17
Cardiovascular severity, VAS	4.2	45.9	<0.0001
Hypertension	2.8	29.2	<0.0001
Ventricular dysfunction	0.7	20.8	<0.0001
Angina	NA	1.0	NA
Myocardial infarction	NA	2.1	NA
Peripheral vascular severity, VAS	2.8	6.3	0.32
Tissue pulp loss	1.4	1.0	0.73
Digit loss	0.0	1.0	0.84
Thrombosis	0.7	3.1	0.36
Claudication	NA	3.1	NA
Endocrine severity, VAS	27.3	34.5	0.30
Growth failure	14.0	NA	NA
Delay in secondary sexual characteristics	3.5	NA	NA
Hirsutism	7.7	2.1	0.11
Irregular menses	1.4	3.1	0.12
Amenorrhea	0.0	3.1	0.65
Diabetes	1.4	15.6	<0.0001
Infertility	NA	3.1	NA
Sexual dysfunction	NA	5.2	NA
Ocular severity, VAS	7.0	12.5	0.22
Cataract	2.1	10.4	0.013
Vision loss	1.4	2.1	0.91
Infection severity, VAS	6.3	16.8	0.019
Chronic infection	2.8	13.5	0.004
Multiple infections	2.8	2.1	0.94
Malignancy severity, VAS	0	3.2	0.12
Malignancy	0.0	3.2	0.12
Total damage			
Total MDI severity of damage >0†	79.1	96.9	<0.0001
Total MDI extent of damage >0‡	72.9	97.9	<0.0001

* Values are the percent of patients. NA = not applicable (see Table 1 for other definitions).
† Severity of damage was assessed in 9 organ systems and 2 categories of illness (infection and malignancy) and summed to provide a total MDI severity of damage score.
‡ Individual damage items were assessed in each organ system and category of illness and summed to provide a total MDI extent of damage score.

Table 3. Construct validity of the Myositis Damage Index (MDI) in juvenile and adult IIM patients*

Correlate	Juvenile IIM patients			Adult IIM patients		
	n	r_s	*P*	n	r_s	*P*
Physician-assessed global damage score (0–4 Likert scale)						
Total MDI extent of damage	143	0.79	<0.0001	96	0.42	<0.0001
Total MDI severity of damage	143	0.88	<0.0001	96	0.82	<0.0001
C-HAQ score (0–3) or modified Convery ADL assessment scale score (0–91)†						
Total MDI severity of damage	142	0.45	<0.0001	59	−0.16	0.22
Muscle severity of damage	142	0.48	<0.0001	60	−0.14	0.27
Skeletal severity of damage	142	0.43	<0.0001	60	−0.14	0.28
Pulmonary severity of damage	142	0.22	0.008	60	−0.05	0.68
Total MMT score (0–120)						
Total MDI severity of damage	53	−0.52	<0.0001	73	−0.07	0.56
Muscle severity of damage	55	−0.39	0.004	74	−0.15	0.20
Serum creatinine						
Total MDI severity of damage	78	−0.16	0.16	84	−0.24	0.027
Muscle severity of damage	82	−0.37	0.0006	85	−0.54	<0.0001
T1-weighted MRI score (0–4)‡						
Total MDI severity of damage	34	0.58	0.003	72	0.04	0.73
Muscle severity of damage	34	0.47	0.011	73	0.25	0.031

* See Table 1 for other definitions.
† The C-HAQ score was assessed in juvenile IIM patients, and the modified Convery ADL assessment scale score was assessed in adult IIM patients.
‡ Average of muscle atrophy and fatty infiltration.

versus 13.2%; $P = 0.018$), and ventricular dysfunction (27.3% versus 5.3%; $P = 0.007$).

Severity and extent of damage. The median total MDI severity of damage score was 10.8 (IQR 6.4–20.6) in adult IIM patients and 0.9 (IQR 0.2–4.6) in juvenile IIM patients at the last evaluation ($P < 0.0001$). The median total MDI extent of damage score was 1 (IQR 0–3) in juvenile IIM patients and 6 (IQR 4–9) in adult IIM patients at the last evaluation ($P < 0.0001$).

There was no difference in the total MDI extent or severity of damage scores between adult DM and PM patients. The median cutaneous extent and severity of damage scores were higher in adult DM than in adult PM, and the median cardiovascular extent and severity of damage scores were higher in adult PM than in adult DM ($P < 0.0001$ for each), but scores did not differ among the other organ systems.

The total MDI severity and extent of damage scores differed between juvenile and adult DM. For juvenile DM, the median total MDI severity of damage score at the last assessment was 0.9 (IQR 0.2–4.9), whereas in adult DM it was 10.6 (IQR 5.6–16.2) ($P < 0.0001$). The median total MDI extent of damage score was 1 (IQR 0–3) in juvenile DM and 6 (IQR 4–9) in adult DM. Both severity and extent of damage scores were higher in adult DM patients than in juvenile DM patients in the muscular, cutaneous, gastrointestinal, pulmonary, and cardiovascular organ systems, whereas in the peripheral vascular system only the severity of damage score was higher.

Construct validation of the MDI. Using data from the first evaluation, we found that the total MDI extent and severity of damage scores were highly correlated ($r_s = 0.87$ in juvenile IIM and $r_s = 0.75$ in adult IIM, $P < 0.0001$). In both juvenile and adult IIM patients, the total MDI extent and severity of damage scores correlated highly with the physician-assessed global damage score (Table 3). Correlations were generally higher with the total MDI severity of damage score than with the total MDI extent of damage score. The C-HAQ score correlated moderately with the total MDI severity of damage score as well as with muscular, skeletal, and pulmonary severity of damage subscores in juvenile IIM patients. In contrast, the Convery ADL assessment scale score did not correlate well with the total MDI severity or extent of damage scores or with these organ system subscores. The total MMT score also correlated moderately with the total MDI severity of damage and muscle severity of damage scores in juvenile IIM patients, but not in adult IIM patients. Serum creatinine, a measure of muscle atrophy (18), correlated inversely with muscle severity of damage in both juvenile

Table 4. Predictive validity of Myositis Damage Index (MDI) scores for disease course*

	Disease course			
	Monocyclic	Polycyclic	Chronic continuous	*P*†
Juvenile IIM‡				
Total MDI extent of damage				
First visit	1 (0–2)	2 (1–4.5)	3 (1–6)	0.0001
Last visit	0 (0–1)	1 (0–3)	3 (1–5)	0.0001
Total MDI severity of damage				
First visit	0.4 (0–1.9)	2.0 (0.55–6.8)	3.1 (1.2–10.4)	0.0001
Last visit	0.3 (0–0.5)	0.65 (0–4.4)	4.3 (0.9–10.4)	0.0001
Adult IIM‡				
Total MDI extent of damage				
First visit	5.0 (4.0–6.0)	4.5 (3.0–6.0)	7.0 (4.0–10.0)	0.27
Last visit	5.0 (4.0–6.0)	4.0 (3.0–7.5)	7.0 (4.0–10.0)	0.058
Total MDI severity of damage				
First visit	2.1 (1.8–2.4)	7.5 (5.2–11.0)	11.8 (5.8–17.2)	0.006
Last visit	5.1 (3.1–7.1)	8.2 (5.5–11.2)	14.6 (8.9–25.5)	0.003

* Values are the median (interquartile range). Disease course was determined at the last available assessment. The median disease duration was 19 months and 72 months, respectively, at the first and last visits in patients with juvenile idiopathic inflammatory myopathy (IIM) and 30 months and 53 months, respectively, at the first and last visits in patients with adult IIM. Note that undefined and missing disease courses are not included.

† By Kruskal-Wallis test.

‡ Of the patients with juvenile IIM, the disease course was monocyclic in 36, polycyclic in 43, and chronic continuous in 49. Of the patients with adult IIM, the disease course was monocyclic in 2, polycyclic in 30, and chronic continuous in 49.

and adult IIM patients and with total MDI severity of damage in adult IIM patients. Although only some patients had undergone MRI, a T1-weighted MRI score that averaged muscle atrophy and fatty infiltration correlated moderately with muscle severity of damage in juvenile and adult IIM patients and with total MDI severity of damage in juvenile IIM patients (Table 3).

Change in damage over time. Adult IIM patients had a measurable increase in the annual change in the total MDI severity of damage score, with a median increase of 2.4 points (IQR 0–6.3), whereas the annual rate of change in the total MDI extent of damage score was undetectable (median 0 [IQR 0–0.02]). For juvenile IIM patients, there was no measurable increase in either score.

Predictive validity of the MDI. The total MDI extent and severity of damage scores were lowest in patients with a monocyclic illness course, intermediate in patients with a polycyclic course, and highest in patients with a chronic continuous course, in juvenile IIM patients at the last visit and in adult IIM patients for severity of damage scores, as well as at the baseline evaluation in juvenile patients (Table 4). In juvenile IIM patients, the proportion of patients with detectable total MDI extent and severity of damage also increased commensurate with disease course (47.2% with a monocyclic illness course versus 66.7% with a polycyclic illness course versus 81.2% with a chronic course had a total MDI extent of damage score >0 at the last evaluation [$P = 0.001$]). Trends were similar for total MDI severity of damage ($P = 0.012$).

In adult IIM patients, the annual rate of change in total MDI severity of damage was greatest in those with a chronic illness course (median annual increase in damage of 3.9 points) compared with those with a monocyclic or polycyclic course (median annual increase of 0.5 and 0.0 points, respectively) ($P = 0.0002$). There was no difference in the annual rate of change in total MDI severity or extent of damage by disease course subtype in the juvenile IIM patients.

Adult IIM patients who died (n = 25) had higher total MDI severity and extent of damage scores at the last available assessment than did surviving patients (n = 69) ($P = 0.038$). For example, the median total MDI severity of damage score at the last followup visit was 14.2 (IQR 8.0–26.9) in those who died versus 9.4 (IQR 6.1–17.1) in patients who were alive as of February 2008. Patients who died had greater damage in the cardiovascular (median severity of damage 1 [IQR 0.0–3.2]) and pulmonary (median severity of damage 1.2 [IQR 0.0–4.3]) systems than those who were living as of February 2008 (median 0 [IQR 0.0–1.1] and median 0.1 [IQR

Table 5. Predictors of damage in juvenile and adult IIMs found in multivariable analysis using GEE modeling*

	Juvenile IIM†				Adult IIM†			
	Severity of damage		Extent of damage		Severity of damage		Extent of damage	
Predictor	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
C-HAQ score	2.1 (0.41, 3.7)	0.015	0.95 (0.42, 1.5)	0.003	NA	–	NA	–
Creatine kinase level	NA	–	NA	–	−0.0004 (−0.0007, −0.0001)	0.0001	NA	–
Duration of active disease	0.03 (0.01, 0.05)	0.004	NA	–	NA	–	NA	–
Extramuscular global disease activity	1.1 (0.14, 2.0)	0.023	0.36 (−0.04, 0.77)	0.079	NA	–	NA	–
Steinbrocker functional class	2.9 (0.74, 5.1)	0.009	0.83 (0.24, 1.4)	0.006	NA	–	NA	–
Physician-assessed global disease activity	NA	–	NA	–	−0.92 (−1.8, −0.08)	0.032	NA	–
Pericarditis	NA	–	NA	–	3.0 (1.4, 4.5)	0.0001	0.38 (0.18, 0.57)	0.0001
Severity of illness at diagnosis	NA	–	NA	–	3.4 (1.7, 5.0)	0.0001	0.55 (−0.14, 1.2)	0.12
Ulcerations, cutaneous or GI	1.9 (−0.37, 4.1)	0.102	1.3 (0.43, 2.1)	0.003	NA	–	NA	–
Delay to diagnosis	NA	–	NA	–	NA	–	0.002 (0.001, 0.002)	0.0001

* Total Myositis Damage Index (MDI) severity of damage and extent of damage were modeled after identifying significant predictors from univariable analyses and performing backward stepping procedures. The juvenile IIM generalized estimating equation (GEE) model of severity of damage is based on 283 observations in 121 patients (Wald $\chi^2 = 31.6$, $P < 0.0001$), and the juvenile IIM GEE model of extent of damage is based on 285 observations in 121 patients (Wald $\chi^2 = 50.2$, $P < 0.0001$). The adult IIM GEE model of severity of damage is based on 215 observations in 92 patients (Wald $\chi^2 = 59.3$, $P < 0.0001$), and the adult IIM GEE model of extent of damage is based on 223 observations in 93 patients (Wald $\chi^2 = 76.5$, $P < 0.0001$). 95% CI = 95% confidence interval; NA = not applicable (see Table 1 for other definitions).

† Predictors of the total MDI severity of damage and extent of damage in juvenile IIM patients that were significant in univariable GEE models using data from all available assessments included delay to diagnosis, duration of remission, illness severity at diagnosis, enrollment center, presence of cutaneous or GI ulcerations, C-HAQ and CMAS scores, and Steinbrocker functional class, as well as physician-assessed global disease activity and extramuscular global disease activity scores. Duration of active disease was also a predictor of the total MDI severity of damage score in univariable models, and the presence of cardiopulmonary changes was also a predictor of the total MDI extent of damage score in univariable models. Predictors of total MDI severity of damage and extent of damage in adult IIM that were significant in univariable models included serum levels of muscle enzymes, the presence of pericarditis, illness severity at diagnosis, delay to diagnosis, the presence of arrhythmia or a myositis-specific autoantibody, and extramuscular global disease activity. In addition, disease duration, age, race, and physician-assessed global disease activity were predictors of the total MDI severity of damage but not of the total MDI extent of damage. Other variables that were not significant predictors of total MDI severity of damage or extent of damage in univariable models for either juvenile or adult IIM included sex, disease course, initial creatine kinase level, activity in thigh muscles on STIR MRI, and the presence of erythroderma or overlapping autoimmune diseases. All variables were examined in both juvenile and adult IIM, except for the CMAS, which was examined only in juvenile IIM.

0.0–4.0], respectively) ($P = 0.007$ and $P = 0.004$, respectively). The cardiovascular severity of damage score was also higher at first assessment in those who died than in those who lived (median 0.6 [IQR 0.2–2.6] versus median 0 [IQR 0.0–0.75]; $P = 0.0012$), and the median pulmonary extent of damage score was higher at first assessment in those who died than in those who lived (median 1.5 [IQR 0.0–2.0] versus median 0.5 [IQR 0.0–2.0]; $P = 0.049$).

The annual rate of change of total MDI severity of damage was greater in those who died than in those who lived (median annual increase 5.1 [IQR 2.7–9.7] versus 0.9 [IQR 0.0–4.3]; $P = 0.0006$). However, there was no difference in the rate of change in the total MDI extent of damage. The annual rate of increase in cardiovascular and pulmonary organ system severity of damage scores was higher in those who died (median annual increase 1.0 and 4.3, respectively) than in those who lived (median annual increase 0.0 and 0.1, respectively) ($P = 0.007$ and $P = 0.004$, respectively).

Predictors of myositis damage. In juvenile IIM patients, predictors of the total MDI severity of damage in a multivariable model included Steinbrocker functional class (23), the C-HAQ score, the presence of gastrointestinal or cutaneous ulcerations, extramuscular global disease activity, and duration of active disease (Table 5). Except for duration of active disease, each of these was also a significant predictor of the total MDI extent of damage in a multivariable GEE model.

In adult IIM patients, significant predictors of the total MDI severity of damage in a multivariable model included severity of illness at diagnosis and the presence of pericarditis, whereas physician-assessed global disease activity and serum creatine kinase level were weak negative predictors of damage severity (Table 5). Severity of illness at diagnosis, the presence of pericarditis,

and delay to diagnosis were multivariable predictors of the total MDI extent of damage (Table 5).

DISCUSSION

We found that damage, as measured by the MDI, was detectable in most patients with juvenile IIM and in almost all patients with adult IIM, with a median followup of 6.8 years in patients with juvenile-onset disease and of 5 years in patients with adult-onset myositis. The MDI appears to perform well and is a valid tool to assess damage in both juvenile and adult IIM. It has good content validity, with almost every item endorsed. There is good construct validity; damage severity correlates well with physician-assessed global damage, muscle atrophy detected by MRI, and functional disability and strength in juvenile IIM patients. The MDI has good predictive validity, with higher damage scores and greater frequencies of damage in patients with a chronic illness course and in adult patients who died. Although the total MDI extent and severity of damage scores correlate highly and may be redundant measures, the total MDI severity of damage score appears more sensitive in detecting damage, in its correlations with other illness features, and in detecting change in damage over time. Because the items constituting the total MDI extent of damage score provide a detailed assessment of the underlying factors contributing to damage, we currently recommend that both scores be used together.

Although possible referral biases and variations in the demographic, illness severity features, and composition of the juvenile and adult IIM study populations preclude definitive conclusions about the differences in the frequency or severity of damage in these 2 populations, they differ in notable ways. In juvenile IIM patients, primary features of damage are cutaneous scarring, calcinosis, joint contractures, persistent weakness, and muscle dysfunction, with frequencies ranging from 23% to 30% at the last available assessment. Conversely, adult IIM patients have more muscle atrophy, persistent muscle dysfunction, and muscle weakness as well as more persistent dysphagia and impaired lung function than do juvenile IIM patients. Damage scores and the rate of accrual of damage are also higher in adult than in juvenile IIM patients, although juvenile IIM patients had longer median disease duration (6.8 years) than adult IIM patients (5 years). This finding differs from that for systemic lupus erythematosus (SLE), in which greater damage and rate of damage accrual were found in an inception cohort of patients with childhood-onset SLE compared with patients with adult-onset SLE (24).

We found separate predictors of damage in juvenile and adult IIM. Predictors of total MDI severity of damage for juvenile patients included disease duration, functional disability, extramuscular global disease activity, and the presence of ulcerations, while predictors for adult patients included illness severity at diagnosis and pericarditis. Factors such as age, race, illness characteristics, and autoantibody status were predictors of damage in univariable but not multivariable analyses. In studies of damage in SLE, similar factors predict damage in adult and juvenile SLE (25–29). We did not examine the effects of treatment on damage, but in patients with SLE, corticosteroid usage and use of additional immunosuppressive agents, such as cyclophosphamide, did affect damage (30). We plan further analyses using propensity scores to examine the effects of therapies on damage in myositis (31).

In our study, damage scores were higher at 2 time points in adult IIM patients who died compared with those who survived. Although the cause of death in these patients is unknown, cardiovascular and pulmonary damage scores were also higher at 2 different time points in patients who died than in patients who survived, suggesting good predictive validity of the MDI for overall survival. Cardiovascular disease and respiratory failure, including pneumonia, are common causes of death in adult IIM patients (4). In children, the mortality rate is relatively low, but the correlation of damage scores with disease course subtype, a marker of long-term morbidity (2), also suggests good predictive validity. In patients with SLE, high damage scores and early accumulation of damage, using the SDI, predict later mortality (32).

The MDI provides a single instrument for evaluating both juvenile and adult patients and can be used throughout a patient's lifetime (32,33). The instrument was developed by adult and pediatric specialists who recognized that certain items of damage are applicable only to pediatric or adult patients, particularly in the cardiovascular, peripheral vascular, and endocrine systems, and should be scored only in the appropriate age group. For example, growth failure and pubertal delay were present in 14% and 3.5% of juvenile IIM patients, respectively, which is comparable with frequencies observed in pediatric SLE patients using a modification of the SDI (34). A strength of the MDI is that, since damage might be reversible, particularly in children, it defines damage not as irreversible change but as persis-

tent change due to a noninflammatory or scarring process (32).

Our study is the first to describe the spectrum of damage in both juvenile and adult IIM and to identify risk factors for damage in myositis. However, our study does have limitations. The MDI was completed retrospectively through medical record review, which could underestimate the extent of damage or inaccurately reflect the severity of damage. Of note, however, Bernatsky et al demonstrated good agreement between retrospectively and prospectively completed SDIs in patients with SLE (35). Although the pediatric portion of the study was conducted at multiple centers, the participating investigators received training in the use of the instrument; hence, interrater reliability for the MDI has been reasonably good (7). The juvenile and adult IIM populations were not inception cohorts and differed in their demographic features, illness severity and characteristics, and enrollment centers. We used consecutive patients to attempt to decrease selection bias; however, there may have been a greater extent or severity of damage in using a referral population from these centers. A prospective inception cohort would provide better ability to directly compare damage in juvenile and adult IIM patients, as has been done in SLE (24). Finally, the rate of change of damage was estimated based on conversion to an annual rate of change. This could result in an over- or underestimation of the actual rate of damage accrual, since the rate of change might not be constant but could increase with longer disease duration, as in patients with SLE (36).

In summary, the present study on the frequency and spectrum of damage in patients with juvenile and adult IIM shows that damage is common in patients who have had juvenile-onset myositis for a median of 6.8 years and in patients who have had adult-onset myositis for a median of 5 years. We have shown that the MDI has good content, construct, and predictive validity and that the scores change as expected over time in both juvenile and adult IIM patients. Risk factors for myositis damage include functional disability, duration of active disease, illness severity at diagnosis, global or extramuscular global disease activity, and important features of the illness, such as the presence of ulcerations in children or pericarditis in adults. The study of damage in myositis using the MDI should help us better understand the long-term outcomes of patients with myositis and potentially lead to new therapeutic approaches to treat and prevent these complications.

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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. Rider 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.

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