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Clinical values of FDG PET in polymyositis and dermatomyositis syndromes: imaging of skeletal muscle inflammation

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ABSTRACT

Objectives: [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET), a standard tool for evaluating malignancies, can also detect inflammatory lesions. However, its use in evaluating muscle lesions in polymyositis and dermatomyositis syndromes (PM/DM) has not been established.

Methods: Thirty-three patients with PM/DM who had undergone FDG PET were retrospectively analyzed. FDG uptake was visually evaluated (visually identified FDG uptake: vFDG) in 16 regions of the body. We also calculated the maximum standardized uptake value (SUVmax) in four limbs of patients with PM/DM as well as in 22 patients with amyotrophic lateral sclerosis (ALS), whose disabilities were similar. In 24 patients with PM/DM, the findings of MRI and FDG PET were compared.

Results: vFDG was observed in over the two-thirds of the PM/DM patients in multiple muscle lesions with varying distributions, most of them were symmetrical. Numbers of vFDG-positive regions were correlated with mean SUVmax in four limbs ($p < 0.0001$). Histological grades of biopsied muscles and serum creatine kinase levels were higher in the patients with more than two vFDG-positive regions than in those with two or less vFDG-positive regions ($p < 0.05$). While the inflamed muscles showed diffuse signal abnormality using MRI, FDG uptake was more localized and often inside the muscles. Compared with ALS, SUVmax was significantly higher in PM/DM ($p < 0.0001$) and showed a striking correlation in the bilateral muscle reflecting symmetrical muscle involvement in PM/DM.

Conclusions: FDG PET enables us to evaluate skeletal muscle comprehensively, which can improve clinical practice as well as provide insight into pathomechanism of PM/DM.

Strength and limitation of this study

This is the first study investigating FDG PET in muscles of polymyositis dermatomyositis syndromes comprehensively by two methods; visual evaluation and SUV measurement. The study demonstrated usefulness of visual assessment which can be used in clinical practice.

The limitation of the study is that this is a retrospective study. The patients underwent FDG PET for detection of occult cancer and the imaging range was therefore from the head to the middle of the thighs. Information on difference in FDG PET findings between polymyositis dermatomyositis syndromes and non-inflammatory myopathies was not obtained.

INTRODUCTION

Idiopathic inflammatory myopathies are a heterogeneous group of disorders characterized clinically by progressive proximal muscle weakness and pathologically by mononuclear cell infiltration and fiber necrosis in muscles. Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis are the representative phenotypes.[1] Both PM and DM are thought to be immune-mediated disorders, which can be successfully treated if they are properly managed. In contrast, in inclusion body myositis, degenerative processes also play an equal or greater role and effective treatments remain to be elucidated.[2] Patients with PM and DM syndromes (PM/DM) may present with other organ involvement such as interstitial lung disease.[3,4] They may also evolve with other collagen diseases and malignancies.[4 5] In addition, the extent and pattern of muscle involvement are variable. PM/DM can present prominent truncal muscle weakness or preferential involvement of respiratory muscles.[6 7] Thus, it is essential to systemically diagnose and evaluate patients with PM/DM.

[^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET) is a standard tool for detecting malignancies. FDG also accumulate in inflammatory lesions where glucose-consuming inflammatory cells infiltrate. [8] FDG PET is useful for diagnosing systemic inflammatory diseases including collagen vascular disorders such as rheumatoid arthritis, vasculitis, and polymyalgia rheumatica.[9-11] In PM/DM, only a limited number of studies have demonstrated that FDG PET detects inflammatory muscle lesions. Owada et al. visually assessed FDG uptake (FDG uptake that was equal to or more than that of the liver) in proximal muscles using FDG PET in 24 patients with PM/DM. They found that increased FDG uptake was more frequent in patients with PM/DM than in controls (33% versus 2%).[12] Pipitone et al. measured the maximum standardized uptake value (SUVmax) in proximal muscles of four limbs and calculated the muscle/liver SUVmax ratio in 12 patients with PM/DM using FDG PET/computed tomography (CT). They showed that the proximal

muscle SUV ratio was higher in patients with PM/DM than in controls.[13] In these two studies, increased FDG uptake in proximal muscles was not correlated with clinical parameters or MRI findings. In contrast, Tanaka et al. measured the mean standardized uptake value (SUV) using FDG PET/CT in 14 proximal muscle groups in 20 patients with PM/DM and demonstrated that increased SUV in proximal muscles of the myositis group as well as the mean proximal muscle SUV was correlated with serum creatine kinase (CK) and muscle strength.[14] They also found that local SUV was correlated with degrees of inflammation in the muscle biopsies and weakness of the corresponding muscles. However, their method using global SUV calculations may not be feasible in daily clinical practice. For successful clinical application of FDG PET, a simple and reliable way to assess inflammation in muscles is preferable.

In this study, we evaluated visually FDG PET findings in patients with PM/DM in detail and determined the extent and pattern of inflammation in individual patients. We compared visually evaluated FDG PET findings with SUVmax in proximal muscles as well as with clinical and pathological findings. Furthermore we compared MRI findings with FDG uptake in same muscle regions. We also compared SUVmax in proximal muscles between patients with PM/DM and those with ALS.

MATERIALS AND METHODS

Patients

Thirty-three patients with recent-onset PM/DM were enrolled in this study. They had undergone FDG PET or FDG PET/CT for investigating malignancies before or shortly after receiving an initial corticosteroid treatment from January 2009 to July 2013. They were identified by retrospectively reviewing medical records in our department. Clinically they showed symmetrical proximal muscle weakness, elevated serum muscle enzymes, and myositis-compatible

electrophysiological findings.[15] Muscle biopsies were conducted in all patients in whom inflammatory infiltrates and muscle fiber necrosis and/or expression of HLA class 1 on muscle fibers were observed. A few patients showed either inflammatory infiltrates or muscle fiber necrosis. Subsequent therapies with corticosteroid alone or additional immunomodulatory therapies were effective in all but one patient who died before beginning the treatment. Clinical records, laboratory data and muscle MRIs from each patient were collected. Patients with inclusion body myositis were not included. We identified 22 patients with amyotrophic lateral sclerosis (ALS), who were admitted our hospital for diagnosis and had undergone FDG PET/CT for the detection of occult cancer. These patients were included in this study as disease controls. Eighteen patients fulfilled the diagnostic criteria for clinically definite, clinically probable or clinically probable-laboratory supported ALS according to the revised El Escorial criteria of the World Federation of Neurology. [16] Four patients showed only lower motor neuron symptoms, with exclusion of other diseases. Degrees of disability in patients with PM/DM and those with ALS were similar; all these patients were able to walk and performed activities of daily life independently, but with some difficulties. The study was approved by the Tohoku University School of Medicine ethics committee.

FDG PET imaging

The patients fasted for a minimum of 4 h before the ^{18}F-FDG injection. Blood glucose levels were measured and the patients whose blood glucose level was greater than 150 mg/dl were not included in the study. After the injection of approximately 185 MBq (3.1 MBq/kg) of ^{18}F-FDG, the patients rested on the bed for 1 hour. PET scan was then performed from the head to the mid-thigh using a PET scanner (ECAT EXACT HR+, Siemens, Erlangen, Germany) or PET/CT scanner (Biograph Duo or 40, Siemens, Erlangen, Germany). PET/CT scanners have been used since April 2009 and have replaced a dedicated PET scanner in our institute. FDG uptake was visually

evaluated (visually identified FDG uptake, vFDG) in skeletal muscles using dedicated workstations by two radiologists (AA, TK). FDG uptake was independently assessed in a blinded manner. vFDG was evaluated in 16 regions that included the upper arms: shoulders: sternocleidomastoid muscles: paraspinal muscles of cervical, thoracic, and lumbar levels: buttocks: and upper part of the thighs in both sides (Figure 1). The regions that had an FDG uptake equal to or more than that of the blood vessels in the mediastinum were considered positive (1+) [17] and those that had an FDG uptake equal to or more than that of the liver were considered strongly positive (2+).[12] Scores given by the two radiologists were added and the regions where total scores were two or more were judged as vFDG positive. In addition, SUV was calculated in patients with PM/DM and in 22 patients with ALS in biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh (hamstrings, abductor magnus, gracilis) on both sides. In one patient with PM, SUV was not able to calculate in biceps brachii, because sectional area of the muscle was insufficient to place ROI. The region of interest (ROI: 20mm) was placed in the highest FDG uptake area in each muscle region. SUV was calculated as both the maximum value (SUVmax) and mean value (SUVmean) of ROI. The mean proximal muscles SUVmax (mean SUVmax) and mean proximal muscles SUVmean (mean SUVmean) were calculated by averaging the values found in these six muscle regions.

Muscle MRI

Muscle MRI images were acquired during a routine examination using a 1.5T Intera scanner (Philips, Best, the Netherlands) before treatment. Results were assessed by experienced radiologists. Abnormal signals in skeletal muscles were identified on T2-weighted images with fat suppression (T2W/FS) or short tau inversion recovery (STIR) sequence with long TE. In the patients who were also had undertaken gadolinium contrast-enhancement, the abnormal enhancement in the muscle and/or muscle fascia was evaluated.

Muscle biopsy

Muscle biopsies were performed before treatment in all patients with PM/DM. The muscle was taken from the biceps brachii (26 patients), deltoid (three patients), quadriceps femoris (three patients), or gastrocnemius (one patient). Biopsied muscles were snap frozen and a routine histochemical study was conducted. The most affected lesions in the specimens were photographed with objective lens of 10-fold magnifications. Histological findings were assessed in a blinded manner by an experienced neurologist who was well versed in neuropathology (TM). The extent of mononuclear cell infiltration was graded as follows: 0, none or slight; 1, one focus of mononuclear cell infiltration; 2, more than one focus of mononuclear cell infiltration; and 3, diffuse mononuclear cell infiltration. Muscle fiber necrosis and regeneration were graded as follows: 0, none; 1, 1% or less of muscle fibers showed necrosis or regeneration; 2, more than 1% and no more than 10% of muscle fibers showed necrosis or regeneration; and 3, more than 10% of muscle fibers showed necrosis or regeneration. The total grading scores were calculated for each patient by adding the grade of mononuclear infiltration and the muscle fiber necrosis and regeneration grade.

Statistical analysis

Statistical analysis was performed using JNP8 (SAS Institute Inc., Cary, NC, USA). Statistical significance was analyzed by Wilcoxon rank sum test (nonparametric test), Simple regression analysis, and Spearman rank correlation. Comparisons were considered to be statistically significant if $p < 0.05$.

RESULTS

Patient Characteristics

A summary of the 33 patients with PM/DM (males 10, females 23; mean age 56 ± 17.9 years) who underwent FDG PET (eight patients) or FDG PET/CT (25 patients) is shown in Table1. FDG PET was performed before any treatment in 25 patients. In eight patients, FDG PET was performed soon after beginning corticosteroid treatment (2 to 9 days, mean 6.1 days). We provisionally divided the patients into PM/DM with and without other collagen diseases. The latter included DM and PM without other collagen diseases. Numbers of patients of each clinical group and those of relevant clinicopathological classifications[18] in each clinical group (parenthesis) were as follows: 11 patients with DM (four patients with definite DM, seven with probable DM), 11 patients with PM without other collagen diseases (nine patients with nonspecific myositis, one with definite PM, and one with probable PM), and 11 patients with PM/DM with other collagen diseases (eight patients with nonspecific myositis, two with probable PM, and one with definite PM). Two patients with DM and one patient with PM without other collagen diseases were proven to have malignancies. Abnormal FDG uptake was noted in the lung in several patients, and most of these patients were diagnosed as having interstitial lung diseases. FDG uptake in the lymph nodes was observed in 50% of patients with DM, 18.2% of patients with PM without other collagen diseases, and 75% of patients with PM/DM with other collagen diseases.

Visual assessment of FDG uptake in skeletal muscles in patients with PM/DM

vFDG in skeletal muscles was observed in 21 out of 33 patients with PM/DM (63.6%). vFDG was detected in multiple regions in 14 patients (42.4%) with various patterns (Table1) and almost symmetrical distribution. Shoulders and buttocks were the most frequent positive regions. A fraction of patients with DM showed vFDG-positivity in most of the regions. A representative case is shown in Figure 1. Numbers of vFDG-positive regions were correlated with the mean SUVmax of four extremities ($r = 0.86$, $p < 0.0001$; Fig. 2A), implying that SUVmax in extremities could be

inferred by the extent of vFDG-positive regions. In addition, serum CK levels were higher in patients with more than two vFDG-positive regions than in those with two or less vFDG-positive regions ($p = 0.0179$; Fig. 2B). The total histological scores were also higher in the patients with more than two vFDG-positive regions than in those with two or less vFDG-positive regions ($p = 0.0127$; Fig. 2C). These findings suggest that the distribution of vFDG-positive regions could reflect clinical and pathological severities of PM/DM.

Relationships between SUV and clinicopathological findings in patients with PM/DM

The mean SUVmax was not significantly correlated with serum CK levels or the duration of the illness. The mean SUVmean was higher in male patients than female patients, but not significant ($p = 0.0715$). There were no significant differences between each DM, PM without other collagen diseases, and PM/DM with other collagen diseases. The degree of pathological findings was correlated with mean SUVmax ($r = 0.60$, $p = 0.0002$; Fig. 2D). The degree of pathological findings was also correlated with SUVmax in the biopsied muscles in the patients with PM/DM in whom biopsies were done in biceps brahii or quadriceps femoris ($r = 0.52$, $p = 0.005$).

Comparison of FDG PET and MR findings in PM/DM

25 patients with PM/DM were undergone both FDG PET and muscle MRI. Muscle MRI was performed in the thighs (18 patients), upper arms (six patients) or shoulders (one patient). Among them, 20 patients had been judged as MRI positive. In the MRI-positive regions of each patient, vFDG was positive in four patients. There was no difference in SUVmax of the muscles between MRI-positive and MRI-negative muscles ($p = 0.1537$; Fig. 2E). In contrast, SUVmax of relevant muscles was significantly higher in vFDG-positive patients than in vFDG-negative patients ($p = 0.0076$; Fig. 2F). These findings suggested that MRI is a sensitive tool for detecting inflammatory

edema. However, high signals in MRI might not simply reflect the degree of inflammation.

The pattern of abnormal signals was different between FDG PET and MRI (Figs. 1 & 3). In MRI, affected muscles showed a diffuse high signal, which may reflect inflammatory edema (Figs 1 & 3). In contrast, FDG uptake was more localized in each muscle in most patients. The highest uptake was predominantly inside of the muscles, a few centimeters from the muscle surface.

SUVmax in skeletal muscles of patients with PM/DM and ALS

The mean SUVmax was higher in the patients with PM/DM than in those with ALS (1.463 ± 0.483 versus 1.004 ± 0.136, $p < 0.0001$; Fig. 4A). The mean SUVmean was also higher in the patients with PM/DM (1.106 ± 0.370 versus 0.733 ± 0.139, $p < 0.0001$).

The SUVmax in the biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh in both sides was compared. In patients with PM/DM, SUVmax of one muscle region and that of another muscle region was correlated (biceps brachii versus medial and posterior compartments of the thigh, quadriceps versus biceps brachii, quadriceps versus medial and posterior compartments of the thigh). There was a striking correlation between the same muscles on both sides (biceps brachii, quadriceps femoris, medial and posterior compartments of the thigh). The scatter plots suggested symmetrical muscle involvement in PM/DM (Fig. 4B). Only moderate symmetry of SUVmax was found in patients with ALS (Fig. 4C).

DISCUSSION

In the present study, we assessed skeletal muscles of patients with PM/DM using FDG PET in two ways, visual assessment and SUV measurement. We found that the mean value of SUVmax in four extremities of PM/DM patients was approximately 1.5 and the mean value of SUVmean in four extremities was approximately 1.1. These results are consistent with those of previous

studies.[13 14] A major mechanism underlying the accumulation of FDG in the inflamed tissue is uptake by metabolically active cells such as macrophages, young granulation tissue, and fibroblasts.[8 9] Because FDG uptake in inflamed muscles is fairly moderate compared with that in the neoplasm, setting an appropriate criterion for visual assessment is challenging. In a previous study using liver, in which SUV was around 3, as a positivity criterion demonstrated that 33% of patients with PM/DM patients had positive muscle regions.[12] In the present study, we chose the mediastinum blood vessels, where SUV is approximately 2, as a positivity criterion for vFDG.[17] We found that 63.6% of patients with PM/DM had positive muscle regions. In addition, we divided the proximal body muscle in 16 regions, which enabled us to evaluate the extent and patterns of vFDG-positive regions. We report that vFDG-positive muscle regions correlated with the serum CK levels, histological grades, as well as meanSUVmax in four limbs. These findings suggest that vFDG, using mediastinum blood vessels as the positivity criterion, is useful in the assessment of systemic muscle lesions. In addition, the extent of vFDG-positive regions could be an indicator of the disease activity in PM/DM.

MRI is now widely used to diagnose and to determine biopsy sites in PM/DM.[19 20] Because MRI detects inflammatory edema and FDG PET detects FDG uptake by metabolically active cells, the images of the two modalities are different. MRI positivity was not correlated with SUVmax in the same muscles in the present study. MRI can sensitively detect muscle edema, however, it is not specific to inflammatory myopathies.[21] In MRI images, affected muscles often showed diffuse abnormal signals. On the other hand, in FDG PET, although the sensitivity may be inferior to that in MRI, FDG uptake was more localized and was frequently found deep inside each muscle. Because FDG uptake is theoretically confined to metabolically active sites, the findings imply that the pathology of the biopsied muscles may not present the most affected lesions. This may be a possible reason why we only found a moderate correlation between grades of pathological findings

and SUVmax of the corresponding muscles. Further investigation including the pathological findings may be required to clarify the precise nature of abnormal signals in these two measures.

Previous reports have shown that SUV in skeletal muscles is higher in patients with PM/DM than in control patients without a disability.[13 14] Comparisons of SUV between patients with PM/DM and disabled control patients have never been reported. ALS is characterized by progressive muscle weakness caused by degeneration of upper and lower motor neurons. We found that the mean SUVmax was significantly higher in patients with PM/DM patients than in those with ALS. The findings suggest that FDG PET can distinguish between muscle weakness resulting from muscle fiber destruction with inflammation and that resulting from neurogenic atrophy.

PM/DM is clinically characterized by symmetrical proximal muscle weakness.[4] In the present study, we found a strong correlation between SUVmax of the same muscles on both sides including bilateral quadriceps femoris, bilateral medial and posterior components of thighs, and bilateral biceps brachii. The correlation coefficient was higher in quadriceps femoris on both sides and medial and posterior components of thigh in both sides than in quadriceps femoris and medial and posterior components of the same side of the legs. The findings verified statistically that the inflammatory muscle damage progressed symmetrically in PM/DM, although muscle lesions are often multifocal in each muscle. The current pathological mechanism of PM/DM based on immunopathology cannot explain the symmetrical muscle damage in PM/DM.[4 22] Several possible mechanisms may explain the symmetry, such as an involvement of anatomical factors, including vasculatures and peripheral nerves, or some immune or physiological factors of the individual muscles that could influence the extent of inflammation.

The present study had several limitations. The study was retrospective and FDG PET was performed to detect malignancies. The extent of the imaging range was therefore from the head to the middle of the thighs. Thus evaluation of the thighs was limited; however, a negligible number

of false negatives in vFDG were most likely produced. In this study, we could not study whether FDG uptake in skeletal muscles changed after immunomodulatory treatment, because only a few patients underwent FDG PET twice or more. We could not compare FDG PET findings between PM/DM patients and noninflammatory myopathies, such as muscular dystrophy.

In conclusion, our findings indicated the utility and convenience of FDG PET in clinical characterization of PM/DM. The visual assessment of FDG uptake could be adopted in clinical practice. The greatest advantage of FDG PET is screening the whole body in a single scan. We can visually evaluate the extent and pattern of muscle inflammation systemically and include structures that are not routinely screened by MRI. Apart from malignancies,[23] this methods can also evaluate lung inflammation [24] and swelling of lymph nodes. In addition, semiquantitative evaluation using SUV is useful for statistical analysis of muscle inflammation. On the other hand, the disadvantages of FDG PET are considerable costs and exposure to ionizing radiation. It is important to keep in mind that FDG uptake in muscles is influenced by hyperglycemia, uptake by other organs, and voluntary or involuntary muscle movement during the uptake phase; thus, careful examination is a prerequisite.[25] Although further prospective investigations in a larger sample may be needed to examine cost effectiveness, addition of FDG PET to conventional examinations may be useful for comprehensive diagnosis and management as well as investigation of the pathological mechanism underlying PM/DM.

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Contributions MT, KF and TK were involved in setup the study and writing the draft. TM was involved in the analysis of the muscle biopsies. TK and AA contributed to the visual evaluation of FDG PET. All the authors contributed to discussion of the data and reviewing and revising the manuscript.

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Competing Interests

None.

Ethic approval

Tohoku University School of Medicine ethical approval.

Provenance and peer review

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Data sharing statement

No additional data are available.

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Figure legend

Figure 1. FDG PET and MRI findings in a patient with dermatomyositis (Patient 11). Serial sections of FDG PET/CT (A). Using FDG uptake in mediastinum vessels as a positivity standard, positive regions were found in the body, including paraspinal muscles, shoulders, upper arms, and lumbar girdles, in a predominantly symmetric distribution. An FDG PET image of the upper arm level (B). Frontal view of an FDG PET image indicating FDG uptake in shoulders, upper arms, and iliopsoas (C). MRI of the thighs (D) showing high signal areas in bilateral quadriceps femoris (T2-weighted images with fat suppression).

Figure 2. Numbers of vFDG-positive muscle regions are correlated with the mean value of SUVmax in four extremities (A). Serum values of creatinine kinase (CK) are higher in patients with more than two vFDG-positive muscle regions than in those with two or less vFDG positive muscle regions (B). Total histological scores are higher in patients with more than two vFDG-positive muscle regions than in those with two or less vFDG-positive muscle regions (C). Mean values of SUVmax in four extremities are correlated with total histological scores (D). There are no difference in SUVmax in corresponding muscles between the muscles with abnormal MRI signals and those without abnormal MRI signals (E). In the muscle regions examined by MRI, SUVmax in the corresponding muscles are higher in vFDG-positive muscles than in vFDG-negative muscles (F).

Figure 3. FDG PET (A) and MRI findings (B) of thighs in a patient with PM (Patient 14). In MRI, muscles show a diffuse high signal. In contrast, FDG uptake is more localized and predominantly inside of the muscles.

Figure 4. The mean values of SUVmax in four extremities are higher in the patients with PM/DM than in those with ALS (A). In the patients with PM/DM, SUVmax in bilateral same muscles is highly correlated, suggesting symmetrical muscle inflammation (B). Correlation coefficient is as follows: bilateral quadriceps femoris, $\rho = 0.91$, $p < 0.0001$; bilateral medial and posterior components of thigh, $\rho = 0.88$, $p < 0.0001$; right quadriceps femoris and right medial and posterior components of thigh, $\rho = 0.58$, $p = 0.0004$; left quadriceps and left medial and posterior components of thigh, $\rho = 0.69$, $p < 0.0001$. In patients with ALS, only a moderate correlation is found between bilateral same muscles (Spearman rank correlation) (C).

Table 1 Summary of patients with PM/DM

Clinical findings							Visually identified FDG uptakes in muscles§								FDG uptakes in other organs				Muscle biopsy findings¶			MRI findings**		
	Age	Sex	Clinical diagnosis	Dur*	CK†	Therapy at PET‡	SCM	PC	S	U	PT	PL	B	T	Lung	Lymph nodes.	Malig-nancy.	others	Sites	Cell inf	Nec/reg	Sites	High signals	Consistency with PET
PM/DM without other collagen diseases																								
1	24	M	DM	1	3000	5d P80	■	■	■	■	■	■	■	■		↑			BB	2	3	thigh	(+)	P (+)
2	82	M	DM	1	4307	5d P50	■	■	■	■	■			■				porta hepatis	BB	0	1	thigh	(+)	(-)
3	52	F	DM	4	436	(-)		■	■	■			■	■					BB	3	3	thigh	(+)	P (+)
4	20	F	DM	3	312	(-)										↑			BB	0	1	thigh	(+)	(-)
5	37	F	DM ILD	1	783	7d P20			■						↑				BB	1	1	thigh	(+)	(-)
6	33	F	DM	3	51	(-)			■							↑		stomach,.uterus	BB	1	1	Not done		
7	33	F	DM	2	274	(-)							■			↑		marrow,spleen	BB	0	0	Not done		
8	73	F	DM	1	182	(-)	■	■	■	■	■	■				↑		stomach	BB	3	3	Not done		
9	66	M	DM	4	239	(-)													BB	0	2	should.br	(+)	P (+)
10	65	M	DM	2	377	(-)										↑		lung	Deltoid	1	2	brachium	(+)	(-)
11	53	M	DM	4	2488	(-)	■	■	■	■	■	■	■						BB	2	2	thigh	(+)	P (+)
12	25	F	PM	4	926	(-)													BB	2	0	thigh	(+)	P (+)
13	76	F	PM ILD	2	1343	(-)					■	■	■		↑				BB	1	3	thigh	(+)	P (+)
14	54	M	PM ILD	14	6347	2d P60			■	■			■	■	↑				Gastro	1	1	thigh	(+)	P (+)
15	56	F	PM ILD	8	362	(-)									↑	↑		joints	QF	2	1	thigh	(+)	(-)
16	55	F	PM	12	1019	(-)		■	■	■					↑	↑		spleen	BB	1	1	Not done		
17	69	F	PM	60	758	(-)	■											myocardium	Deltoid	1	2	Not done		
18	79	F	PM	7	9627	(-)			■	■			■					lung	BB	0	2	thigh	(+)	(-)
19	52	M	PM	60	3372	9d P60													Deltoid	2	1	thigh	(+)	(-)
20	40	F	PM	2	1842	7d P60													BB	1	2	Not done		

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21	50	F	PM	36	7182	(-)												BB	0	2	brachium	(-)	(-)
22	73	M	PM ILD	1	1377	13d P55	■		■			■					diaphragm	BB	2	1	Not done		
PM/DM with other collagen diseases																							
23	27	F	MCTD	7	200	8d P50									↑		salivary gland	BB	2	1	thigh	(-)	(-)
24	72	F	PM, SSC	18	1442	(-)									↑	↑	pudenda	BB	2	1	brachium	(+)	P (+)
25	73	F	PM, SSC	14	126	(-)										↑	thyroid gland.	BB	0	0	thigh	(-)	N (+)
26	70	F	PM RA Sjs	24	761	(-)									↑	↑		BB	2	2	thigh	(+)	(-)
27	72	F	PM CREST	36	386	(-)		■				■				↑	joints	QF	2	1	thigh	(+)	P (+)
28	42	M	MCTD	3	5585	(-)				■			■			↑		BB	3	3	thigh	(+)	P (+)
29	65	F	PM Sjs	2	1764	(-)			■		■	■	■		↑	↑	joints	BB	2	2	thigh	(-)	(-)
30	70	F	PM RA	3	1050	(-)							■		↑	↑		QF	2	1	Not done		
31	63	M	PM SSC	7	1396	(-)		■										BB	1	2	brachium	(-)	N (+)
32	52	F	PM SSC	1	1142	(-)		■							↑	↑		BB	0	1	brachium	(+)	(-)
33	75	F	MCTD	7	2123	(-)		■	■		■		■	■			peritoneum	BB	2	2	brachium	(+)	P (+)

*Duration of the illness (months).

†Serum creatine kinase level (IU/L).

‡Duration (days, d) and daily dose (mg) of prednisolone (P) at the time of PET study.

§The regions of positive vFDG at least in either side of the region are filled. We describe the positivity criterion of vFDG in Material and Methods.

¶We describe our criteria for grading of pathological findings in Material and Methods.

**P (+), both PET and MRI showed positive findings; N (+), both PET and MRI were negative; (-), either PET or MRI showed positive findings and the other was negative.

B, buttock; BB, biceps brachii; cell inf, mononuclear cell infiltration; CREST, CREST syndrome; DM, dermatomyosiits; Gastro, gastrocnemius; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; nec/reg, muscle fiber necrosis and regeneration; PC, paraspinal muscles at cervical levels; PL, paraspinal muscles at lumbar levels; PM, polymyositis; PT, paraspinal muscles at thoracic levels; QF, quadriceps femoris; RA, rheumatoid arthritis; S, shoulders; SCM, sternoclidomastoid muscles; Sjs, Sjögren syndrome; SSC, systemic sclerosis; T, thighs.

Figure 1

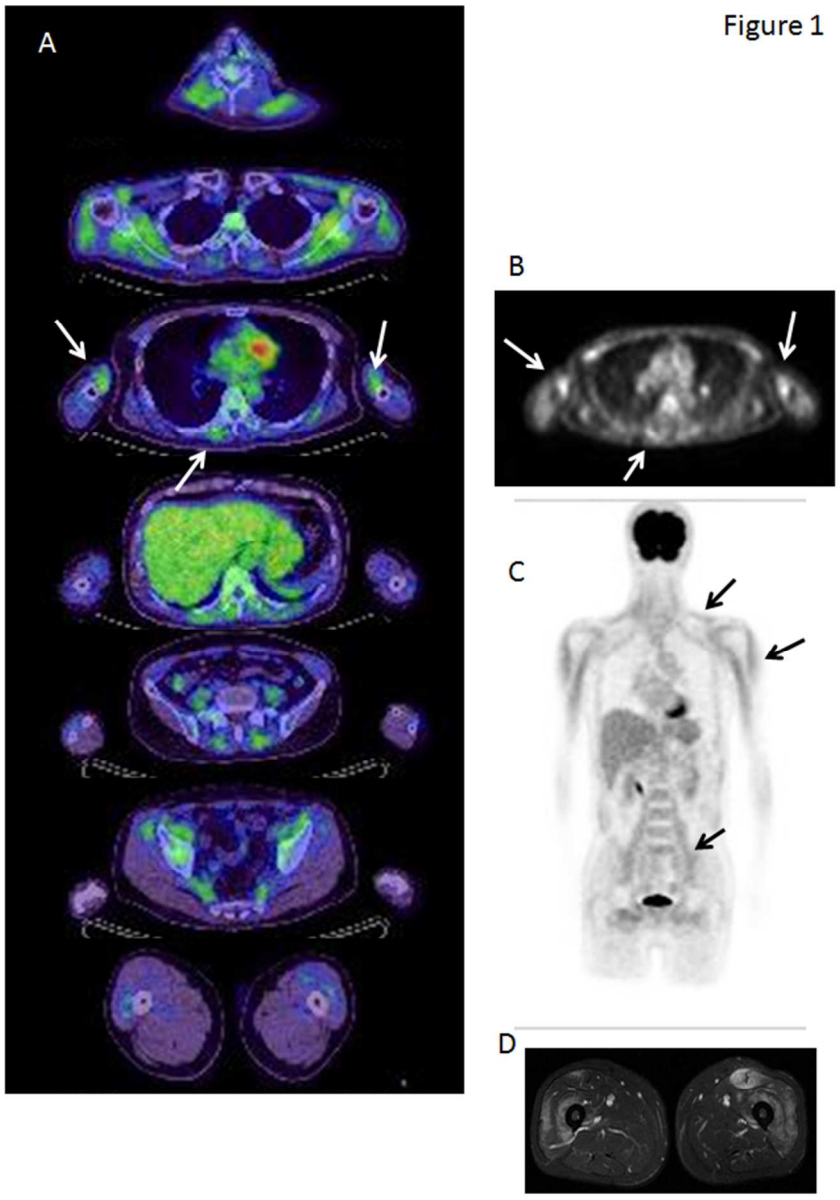

Figure 1. FDG PET and MRI findings in a patient with dermatomyositis (Patient 11). Serial sections of FDG PET/CT (A). Using FDG uptake in mediastinum vessels as a positivity standard, positive regions were found in the body, including paraspinal muscles, shoulders, upper arms, and lumbar girdles, in a predominantly symmetric distribution. An FDG PET image of the upper arm level (B). Frontal view of an FDG PET image indicating FDG uptake in shoulders, upper arms, and iliopsoas (C). MRI of the thighs (D) showing high signal areas in bilateral quadriceps femoris (T2-weighted images with fat suppression).
57x76mm (300 x 300 DPI)

Figure 2

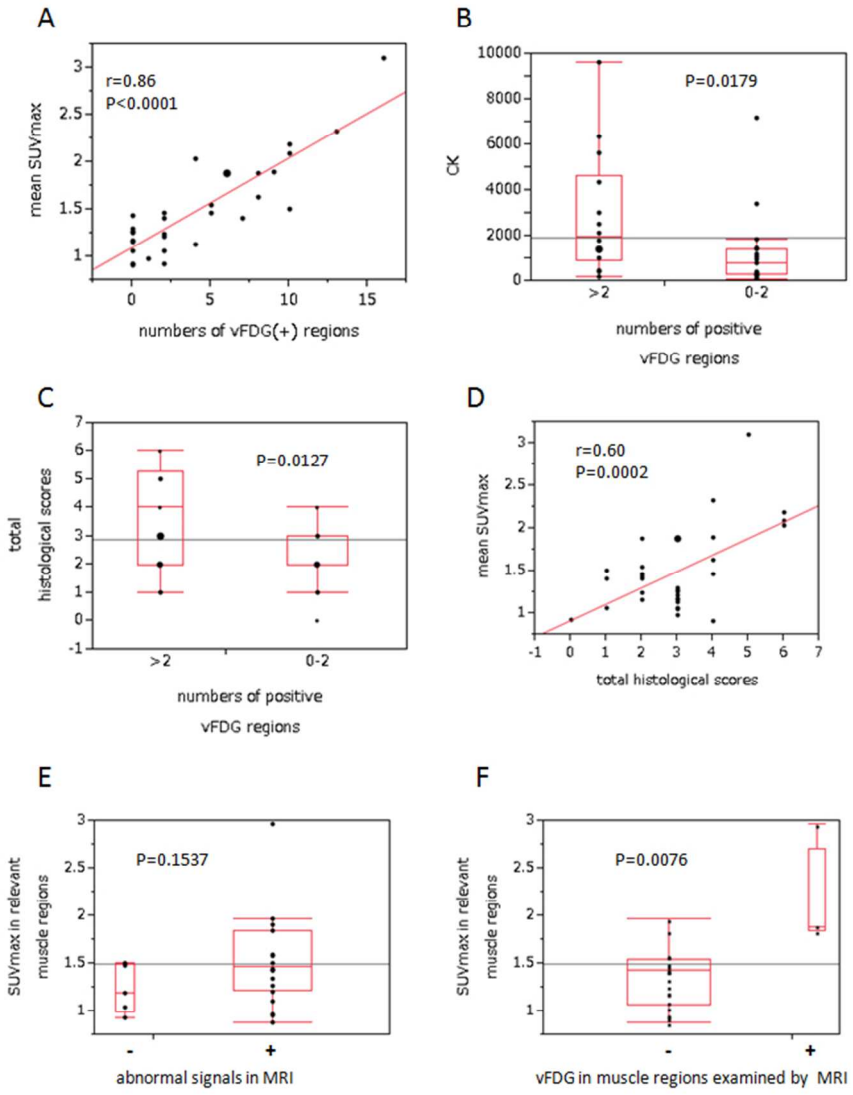

Figure 2. Numbers of vFDG-positive muscle regions are correlated with the mean value of SUVmax in four extremities (A). Serum values of creatinine kinase (CK) are higher in patients with more than two vFDG-positive muscle regions than in those with two or less vFDG positive muscle regions (B). Total histological scores are higher in patients with more than two vFDG-positive muscle regions than in those with two or less vFDG-positive muscle regions (C). Mean values of SUVmax in four extremities are correlated with total histological scores (D). There are no difference in SUVmax in corresponding muscles between the muscles with abnormal MRI signals and those without abnormal MRI signals (E). In the muscle regions examined by MRI, SUVmax in the corresponding muscles are higher in vFDG-positive muscles than in vFDG-negative muscles (F).
57x76mm (300 x 300 DPI)

Figure 3

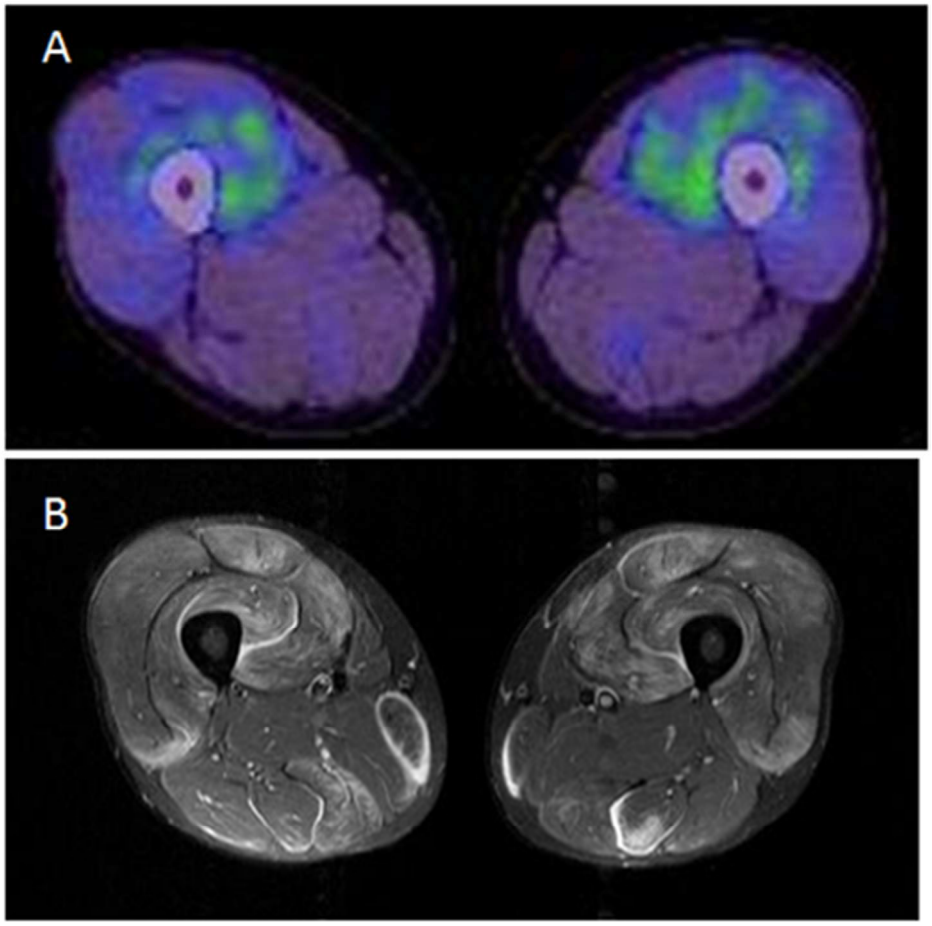

Figure 3. FDG PET (A) and MRI findings (B) of thighs in a patient with PM (Patient 14). In MRI, muscles show a diffuse high signal. In contrast, FDG uptake is more localized and predominantly inside of the muscles.
42x46mm (300 x 300 DPI)

Figure 4

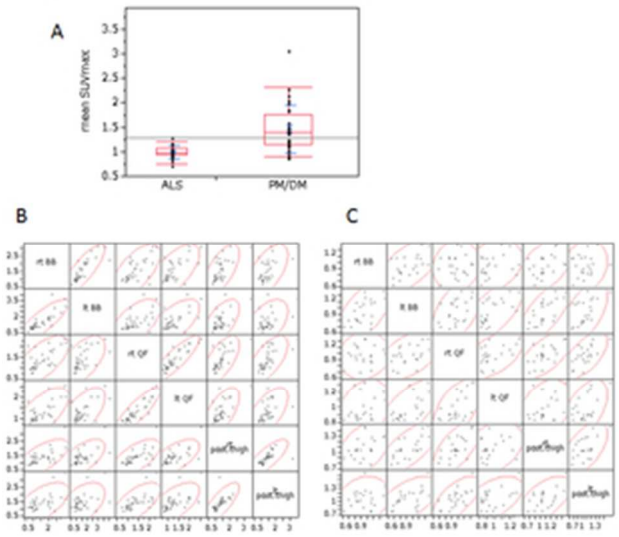

Figure 4. The mean values of SUVmax in four extremities are higher in the patients with PM/DM than in those with ALS (A). In the patients with PM/DM, SUVmax in bilateral same muscles is highly correlated, suggesting symmetrical muscle inflammation (B). Correlation coefficient is as follows: bilateral quadriceps femoris, $\rho = 0.91$, $p < 0.0001$; bilateral medial and posterior components of thigh, $\rho = 0.88$, $p < 0.0001$; right quadriceps femoris and right medial and posterior components of thigh, $\rho = 0.58$, $p = 0.0004$; left quadriceps and left medial and posterior components of thigh, $\rho = 0.69$, $p < 0.0001$. In patients with ALS, only a moderate correlation is found between bilateral same muscles (Spearman rank correlation) (C).
13x12mm (600 x 600 DPI)

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Clinical values of FDG PET in polymyositis and dermatomyositis syndromes: imaging of skeletal muscle inflammation

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ABSTRACT

Objectives: [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET), a standard tool for evaluating malignancies, can also detect inflammatory lesions. However, its usefulness in evaluating muscle lesions in polymyositis and dermatomyositis syndromes (PM/DM) has not been established.

Methods: Thirty-three patients with PM/DM who had undergone FDG PET were retrospectively analyzed. FDG uptake was visually evaluated (visually identified FDG uptake, vFDG) in 16 regions of the body using mediastinum blood vessels as a positivity criterion. We also calculated the maximum standardized uptake value (SUVmax) in all four limbs of the patients with PM/DM as well as in 22 patients with amyotrophic lateral sclerosis (ALS) with similar disabilities. In 24 patients with PM/DM, MRI and FDG PET findings were compared.

Results: vFDG was observed in multiple muscle lesions with varying distributions in two-thirds of the PM/DM patients, with most lesions being symmetrical. The number of vFDG-positive regions strongly correlated with the mean SUVmax in all four limbs ($p < 0.0001$). Histological grades of biopsied muscles correlated with both the mean SUVmax and number of vFDG-positive regions. Serum creatine kinase levels were higher in patients with more than two vFDG-positive regions than in those with two or less regions ($p < 0.05$). While the inflamed muscles showed diffuse, patchy, or marginal signal abnormalities on MRI, FDG uptake was most prominent inside the muscles. Compared with ALS, the mean SUVmax was significantly higher in the PM/DM patients ($p < 0.0001$) and showed a striking correlation in the bilateral muscles reflecting symmetrical muscle involvement in PM/DM.

Conclusions: The visual assessment of FDG uptake as well as calculation of SUV enabled us to comprehensively evaluate skeletal muscle. This method can improve clinical practices and provide insights into pathomechanisms of PM/DM.

Strengths and limitations of this study

This is the first study that comprehensively investigated the usefulness of FDG PET in evaluating muscle lesions in patients with polymyositis dermatomyositis syndromes using visual evaluation and SUV measurement. The study demonstrated the usefulness of these two methods. Visual evaluation of FDG uptake can be used in clinical practice.

The limitation of the study is that it is retrospective. Patients underwent FDG PET for the detection of occult cancer, therefore, the imaging range was from the head to the middle of the thighs. Eight patients underwent FDG PET and 25 patients underwent FDG PET/CT. Data regarding manual muscle test was not obtained. Polymyositis dermatomyositis syndromes and non-inflammatory myopathies were not compared.

INTRODUCTION

Idiopathic inflammatory myopathies are a heterogeneous group of disorders clinically characterized by progressive proximal muscle weakness and pathologically by mononuclear cell infiltration and fiber necrosis in muscles. Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis are representative phenotypes.[1] Both PM and DM are thought to be immune-mediated disorders that can be successfully treated if properly managed. In contrast, in inclusion body myositis, degenerative processes also play an equal or greater role and effective treatments remain to be elucidated.[2] Patients with PM and DM syndromes (PM/DM) may present with other organ involvement, such as interstitial lung disease.[3 4] They may also evolve with other collagen diseases and malignancies.[4 5] In addition, the extent and pattern of muscle involvement are variable. PM/DM can present with prominent truncal muscle weakness or preferential involvement of respiratory muscles.[6 7] Thus, it is essential to systemically diagnose and evaluate patients with PM/DM.

[^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET) is a standard tool for detecting malignancies. FDG also accumulates in inflammatory lesions where glucose-consuming inflammatory cells infiltrate.[8] FDG PET is useful for diagnosing systemic inflammatory diseases, including collagen vascular disorders such as rheumatoid arthritis, vasculitis, and polymyalgia rheumatica.[9-11] In PM/DM, only a limited number of studies have demonstrated FDG PET detection of inflammatory muscle lesions. Owada et al. visually assessed FDG uptake (FDG uptake greater than or equal to that of the liver) in proximal muscles using FDG PET in 24 patients with PM/DM. They found that increased FDG uptake was more frequent in patients with PM/DM than in controls (33% versus 2%).[12] Pipitone et al. measured the maximum standardized uptake value (SUVmax) in the proximal muscles of all four limbs and calculated the muscle/liver SUVmax ratio in 12 patients with PM/DM using FDG PET/computed tomography (CT). They showed that the proximal muscle

SUV ratio was higher in patients with PM/DM than in controls.[13] In these two studies, increased FDG uptake in proximal muscles did not correlate with clinical parameters or MRI findings. In contrast, Tanaka et al. measured the mean SUV using FDG PET/CT in 14 proximal muscle groups of 20 patients with PM/DM and demonstrated that an increased SUV in proximal muscles of myositis patients as well as the mean proximal muscle SUV was correlated with serum creatine kinase (CK) and muscle strength.[14] They also found that local SUV correlated with the degree of inflammation in muscle biopsies and weakness of the corresponding muscles. However, their method using global SUV calculations may not be feasible in daily clinical practice. For successful clinical application of FDG PET, a simple and reliable way to assess PM/DM muscles is preferable.

In this study, we visually evaluated FDG PET findings in patients with PM/DM in detail and determined the extent and pattern of inflammation. We compared visually evaluated FDG PET findings with SUVmax in proximal muscles as well as with clinical and pathological findings. We also compared MRI findings with FDG uptake in the same muscle regions. Furthermore, we compared SUVmax in proximal muscles between patients with PM/DM and those with ALS.

MATERIALS AND METHODS

Patients

Thirty-three patients with recent-onset PM/DM were enrolled in this study. Patients underwent FDG PET or FDG PET/CT to investigate malignancies before or shortly after receiving an initial corticosteroid treatment from January 2009 to July 2013. They were identified by a retrospective review of medical records in our department. Clinically, patients showed symmetrical proximal muscle weakness, elevated serum muscle enzymes, and myositis-compatible electrophysiological findings proposed by Bohan and Peter.[15] Muscle biopsies were conducted in all patients and showed inflammatory infiltrates, muscle fiber necrosis, and/or expression of HLA class 1 on

muscle fibers. A few patients showed either inflammatory infiltrates or muscle fiber necrosis. In these patients, other muscle diseases were carefully excluded. Subsequent therapy with corticosteroids alone or additional immunomodulatory therapies were effective in all but one patient who died before treatment initiation. Clinical records, laboratory data, and muscle MRIs from each patient were collected. Patients with inclusion body myositis were not included. We identified 22 patients with amyotrophic lateral sclerosis (ALS) who were admitted to our hospital for diagnosis and had undergone FDG PET/CT for the detection of occult cancer. These patients were included in this study as disease controls. Eighteen patients fulfilled the diagnostic criteria for clinically definite, clinically probable, or clinically probable-laboratory supported ALS according to the revised El Escorial criteria of the World Federation of Neurology. [16] Four patients showed only lower motor neuron symptoms with exclusion of other diseases. Degrees of disability in patients with PM/DM and those with ALS were similar; all of these patients were able to walk and performed activities of daily life independently, but with some difficulties. The study was approved by the Tohoku University School of Medicine ethics committee.

FDG PET imaging

Patients fasted for a minimum of 4 h before the ^{18}F-FDG injection. Blood glucose levels were measured, and patients with blood levels > 150 mg/dl were not included. After injection of approximately 185 MBq (3.1 MBq/kg) of ^{18}F-FDG, the patients rested on the bed for 1 hour. PET scan was then performed from the head to the mid-thigh using a PET scanner (ECAT EXACT HR+, Siemens, Erlangen, Germany) or PET/CT scanner (Biograph Duo or 40, Siemens, Erlangen, Germany). PET/CT scanners have been used since April 2009 and have replaced a dedicated PET scanner in our institute. FDG uptake was visually evaluated (visually identified FDG uptake, vFDG) in skeletal muscles using dedicated workstations by two radiologists (AA, TK). FDG uptake

was independently assessed in a blinded manner. vFDG was evaluated in 16 regions, including the upper arms: shoulders: sternocleidomastoid muscles: paraspinal muscles of cervical, thoracic, and lumbar levels: buttocks: and upper part of the thighs in both sides (Figure 1). Regions with an FDG uptake greater than or equal to that of the mediastinum blood vessels were considered vFDG-positive.[17] Regions judged to be positive by both radiologists were defined as vFDG-positive and the number of vFDG- positive regions were counted (minimum = 0 and maximum = 16 in each patient). In addition, SUV was calculated in patients with PM/DM and in 22 patients with ALS in the biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh (hamstrings, abductor magnus, gracilis) on both sides. In one PM patient, we were not able to calculate SUV in the biceps brachii, because the sectional area of the muscle was of insufficient size to place the region of interest (ROI). The ROI (20mm) was placed in the highest FDG uptake area in each muscle region. SUV was calculated as both the maximum value (SUVmax) and mean value (SUVmean) in ROIs. The mean proximal muscles SUVmax (mean SUVmax) and SUVmean (mean SUVmean) were calculated by averaging the values obtained for the six muscle regions.

Muscle MRI

Muscle MRI was performed during a routine examination using the 1.5T Intera scanner (Philips, Best, the Netherlands) before treatment. Results were assessed by experienced radiologists. Abnormal signals in skeletal muscles were identified on T2-weighted images with fat suppression (T2W/FS) or short tau inversion recovery (STIR) sequence with long TE. In the patients who also underwent gadolinium contrast-enhancement, abnormal enhancement in the muscle and/or muscle fascia was evaluated.

Muscle biopsy

Muscle biopsies were obtained before treatment in all patients with PM/DM. The muscle was taken from the biceps brachii (26 patients), deltoid (three patients), quadriceps femoris (three patients), and gastrocnemius (one patient). Biopsied muscles were snap frozen and a routine histochemical study was conducted. The most affected lesions in each specimen were photographed with objective lens of 10-fold magnifications. Histological findings were assessed in a blinded manner by an experienced neurologist well versed in neuropathology (TM). The extent of mononuclear cell infiltration (mononuclear cell infiltration score) was graded as follows: 0, none or slight; 1, one focus of mononuclear cell infiltration; 2, more than one focus of mononuclear cell infiltration; and 3, diffuse mononuclear cell infiltration. Muscle fiber necrosis and regeneration (necrosis/regeneration score) were graded as follows: 0, none; 1, 1% or less of muscle fibers showing necrosis or regeneration; 2, more than 1% and no more than 10% of muscle fibers showing necrosis or regeneration; and 3, more than 10% of muscle fibers showing necrosis or regeneration. The total histological scores were calculated for each patient by adding the mononuclear cell infiltration and the necrosis/regeneration scores.

Statistical analysis

Statistical analysis was performed using JNP8 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was analyzed by the Wilcoxon rank sum test (nonparametric), simple regression analysis, and Spearman rank correlation. Comparisons were considered to be statistically significant if $p < 0.05$.

RESULTS

Patient characteristics

The characteristics of the 33 patients with PM/DM (10 males, 23 females; mean age 56 ± 17.9 years) who underwent FDG PET (eight patients) or FDG PET/CT (25 patients) are summarized in Table1. FDG PET was performed before any treatment in 25 patients. In eight patients, FDG PET was performed shortly after beginning corticosteroid treatment (2 - 9 days: mean 6.1 days). We provisionally divided PM/DM patients according to the presence or absence of other collagen diseases. The number of patients in each clinical group and those of relevant clinicopathological classifications proposed in the 119th European Neuromuscular Centre international workshop[18] in each clinical group (parenthesis) were as follows: 11 DM patients without other collagen diseases (four patients with definite DM, seven with probable DM), 11 PM patients without other collagen diseases (nine patients with nonspecific myositis, one with definite PM, and one with probable PM), and 11 PM/DM patients with other collagen diseases (eight patients with nonspecific myositis, two with probable PM, and one with definite PM). Two patients with DM and one with PM without other collagen diseases were shown to have malignancies. Abnormal FDG uptake was noted in the lung in several patients, and most were diagnosed as having interstitial lung diseases. FDG uptake in the lymph nodes was observed in 50% of patients with DM, 18.2% of patients with PM without other collagen diseases, and 75% of patients with PM/DM with other collagen diseases.

Visual assessment of FDG uptake in skeletal muscles of patients with PM/DM

vFDG in skeletal muscles was observed in 20/33 patients with PM/DM (60.6%). vFDG was detected in multiple regions in 14 patients (42.4%) with various patterns (Table1) and almost symmetrical distribution. The shoulders and buttocks were the most frequent vFDG-positive regions. A fraction of patients with DM showed vFDG-positivity in most of the regions: a representative case is shown in Figure 1. The number of vFDG-positive regions correlated with the

mean SUVmax of all four extremeties ($r = 0.87$, $p < 0.0001$; Fig. 2A), implying that SUVmax in extremities could be inferred by the extent of vFDG-positive regions. There was no correlation between serum CK levels and the number of vFDG-positive regions ($p = 0.20$). However, serum CK levels were higher in patients with more than two vFDG-positive regions than in those with two or less vFDG-positive regions ($p = 0.0179$; Fig. 2B). The number of vFDG-positive regions also correlated with the total histological score ($r = 0.49$, $p = 0.0038$; Fig. 2C). The number of vFDG-positive regions correlated with necrosis/regeneration scores ($r = 0.49$, $p = 0.0036$), but not with mononuclear cell infiltration scores ($p = 0.06$).

Relationship between SUV and clinicopathological findings in patients with PM/DM

The mean SUVmax did not correlate with the duration of the illness. The mean SUVmax was higher in males than females, although not significant ($p = 0.075$). There were no significant differences among patients with DM without other collagen diseases, PM without other collagen diseases, and PM/DM with other collagen diseases. The total histological score correlated with the mean SUVmax ($r = 0.60$, $p = 0.0002$; Fig. 2D). The mean SUVmax correlated more strongly with necrosis/regeneration scores ($r = 0.61$, $p = 0.0002$) than with mononuclear cell infiltration scores ($r = 0.40$, $p – 0.0198$). The total pathological score also correlated with SUVmax in the biopsied muscles in the patients with PM/DM in whom biopsies were done in biceps brahii or quadriceps femoris ($r = 0.58$, $p = 0.0017$). SUVmax in the biopsied muscles correlated more strongly with necrosis/regeneration scores ($r = 0.59$, $p = 0.0013$) than mononuclear cell infiltration scores ($r = 0.40$, $p = 0.0361$). On the other hand, the mean SUVmax did not correlate with serum CK levels. Serum CK levels did not correlated with total histological scores ($p = 0.08$), necrosis/regeneration scores ($p = 0.22$), and mononuclear cell infiltration scores ($p = 0.32$).

Comparison of FDG PET and MRI findings in PM/DM

Twenty-five patients with PM/DM underwent both FDG PET and muscle MRI. Muscle MRI was performed for the thighs (18 patients), upper arms (six patients), and shoulders (one patient). Twenty patients were judged to be MRI positive. In the MRI-positive regions of each patient, vFDG was positive in four patients. There were no patients that were MRI-negative and vFDG-positive. There was no difference in SUVmax of the muscles between MRI-positive and MRI-negative muscles ($p = 0.1537$; Fig. 2E). In contrast, SUVmax of relevant muscles was significantly higher in vFDG-positive patients than in vFDG-negative patients ($p = 0.0076$; Fig. 2F). These findings suggest that MRI is a sensitive tool for detecting inflammatory edema. However, high signals on MRI may not simply reflect the degree of inflammation.

Interestingly, the pattern of abnormal signals was different between FDG PET and MRI (Figs. 1 & 3). On MRI, affected muscles showed several patterns including diffuse or patchy high signals and high signals surrounding the muscles, which may reflect inflammatory edema (Figs 1 & 3). In contrast, FDG uptake was more localized in each muscle for most patients. The highest uptake was predominantly within muscles, a few centimeters from the muscle surface.

SUVmax in the skeletal muscles of patients with PM/DM and ALS

The mean SUVmax was higher in patients with PM/DM than in those with ALS (1.463 ± 0.483 versus 1.004 ± 0.136, $p < 0.0001$; Fig. 4A). The mean SUVmean was also higher in patients with PM/DM (1.106 ± 0.370 versus 0.733 ± 0.139, $p < 0.0001$).

The SUVmax in the biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh in both sides was compared. In patients with PM/DM, SUVmax of one muscle region and that of another muscle region was correlated (biceps brachii versus medial and posterior compartments of the thigh, quadriceps versus biceps brachii, quadriceps versus medial

and posterior compartments of the thigh). Moreover, there was a striking correlation between the same muscles on both sides (biceps brachii, quadriceps femoris, medial and posterior compartments of the thigh). The scatter plots suggested symmetrical muscle involvement in PM/DM (Fig. 4B). Only moderate symmetry in SUVmax was found in patients with ALS (Fig. 4C).

DISCUSSION

In the present study, we assessed the skeletal muscles of patients with PM/DM using FDG PET in two ways: visual assessment and SUV measurement. We found that the mean SUVmax in four extremities of PM/DM patients was approximately 1.5, and the mean SUVmean was approximately 1.1. These results are consistent with those of previous studies.[13 14] While a major mechanism underlying FDG accumulation in inflamed tissue caused by rheumatoid arthritis is uptake by metabolically active cells such as macrophages, young granulation tissue, and fibroblasts,[8 9] there has been no report on PM/DM. In the present study, we found that SUVmax of biopsied muscles correlated more strongly with necrosis/regeneration scores than with mononuclear cell infiltration scores. These findings imply that macrophages assembled in necrotic muscle fiber lesions and muscle fibers in regeneration stage may be a major background of FDG uptake in PM/DM.

Because FDG uptake in inflamed muscles is fairly moderate compared with that in the neoplasm, setting an appropriate criterion for visual assessment is challenging. In a previous study using liver in which an SUV of approximately 3 was the positivity criterion, 33% patients with PM/DM had FDG-positive muscle regions.[12] In the present study, we chose the mediastinum blood vessels, wherein SUV is approximately 2, as a positivity criterion for vFDG. [17] We found that 60.6% patients with PM/DM had vFDG-positive muscle regions. In addition, we divided the proximal body muscle into 16 regions, which enabled us to evaluate the extent and patterns of

vFDG-positive regions. Most notably, the extent of vFDG-positive regions correlated with the mean SUVmax and histological findings. There was only a mild correlation between the extent of vFDG-positive regions and serum CK levels. Serum CK levels are a major clinical parameter in PM/DM: however, it did not correlate with pathological severitiy in our patients. These findings suggest that vFDG, using mediastinum blood vessels as the positivity criterion, is useful for the assessment of systemic muscle lesions and that the extent of vFDG-positive regions can be an indicator of the disease activity in PM/DM.

We also evaluated vFDG using another scoring system, in which 1 point was assigned when the FDG uptake was greater than or equal to that of mediatinum blood vessels and 2 points assigned when FDG uptake was greater than or equal to that of the liver. The points given by two examiners were added in all the muscle regions in each patient (scores ranged from 0 to 64). These scores also strongly correlated with the mean SUVmax ($r = 0.90$, $p < 0.0001$) and total histological scores ($p = 0.0014$).

MRI is now widely used to diagnose and determine biopsy sites in PM/DM.[19 20] It can sensitively detect muscle edema in diseased muscle, including inflammatory myopathies.[21] Because MRI detects inflammatory edema and FDG PET detects FDG uptake by metabolically active cells, the images produced by the two modalities are different. In fact, MRI positivity did not correlate with SUVmax in the same muscles in the present study. On MRI images, abnormal signals were appeared as diffuse or patchy patterns in the muscles and sometimes surrounding the muscles. On the other hand, FDG uptake tended to localize and was frequently found deep within each muscle. Because FDG uptake theoretically reflects metabolically active sites, the pathology of the biopsied muscles may not represent the most affected lesions. This may be the reason why we only found a moderate correlation between the grade of pathological findings and SUVmax of corresponding muscles. In the present study, abnormal MRI signals were positive in 20/25 patients, while vFDG

was positive in four: therefore, the sensitivity of MRI seems to be superior. However, MRI was not evaluated in a blinded manner in this study, and comparison was only performed for MRI examination sites; other sites such as the paraspinal muscles and buttocks were not compared. Further investigation is required to clarify the precise nature of abnormal signals using these two measures.

Previous reports have shown that SUV in skeletal muscles is higher in patients with PM/DM than in control patients without disability.[13 14] Comparisons of SUV between patients with PM/DM and disabled control patients have never been reported. ALS is characterized by progressive muscle weakness caused by degeneration of the upper and lower motor neurons. We found that the mean SUVmax was significantly higher in patients with PM/DM patients than in those with ALS. These findings suggest that FDG PET can distinguish between muscle weakness resulting from muscle fiber destruction with inflammation and that resulting from neurogenic atrophy.

PM/DM is clinically characterized by symmetrical proximal muscle weakness.[4] In the present study, we found a strong correlation between SUVmax of the same muscles on both sides including bilateral quadriceps femoris, bilateral medial and posterior compartments of the thighs, and bilateral biceps brachii. The correlation coefficient was higher for quadriceps femoris in both sides and medial and posterior compartments of the thigh in both sides than in quadriceps femoris and medial and posterior compartments of the same side of the legs. These findings statistically verified that the inflammatory muscle damage progresses symmetrically in PM/DM, although muscle lesions are often multifocal in each muscle. The current pathological mechanism of PM/DM based on immunopathology cannot explain the symmetrical muscle damage in PM/DM.[4 22] Several possible mechanisms may explain the symmetry, such as an involvement of anatomical factors, including vasculatures and peripheral nerves, or some immune or physiological factors of individual muscles that can influence the extent of inflammation.

The present study has several limitations. The study was retrospective and FDG PET was performed to detect malignancies. The extent of the imaging range was therefore restricted from the head to the middle of the thighs, limiting evaluation of the thighs; however, a negligible number of false negatives in vFDG were most likely produced. Nevertheless, we propose that when FDG PET is conducted in PM/DM patients, scans should include, at least, the entire length of the thighs to produce more informative data. In this study, we could not study whether FDG uptake in skeletal muscles changed after immunomodulatory treatment, because only a few patients underwent FDG PET two times or more. A part of patients underwent FDG PET shortly after biginning corticosteroid. Manual muscle test (MMT) data were not obtained from all patients; therefore, we could not compare MMT and FDG PET findings. We were unable to compare FDG PET findings between PM/DM patients and noninflammatory myopathies, such as muscular dystrophy.

In conclusion, our findings indicated the utility and convenience of FDG PET in the clinical characterization of PM/DM. The greatest advantage of FDG PET is that it can screen the whole body in a single scan. Apart from malignancies,[23] this methods can also evaluate lung inflammation [24] and swelling of lymph nodes. We can visually evaluate the extent and pattern of muscle lesions systemically and include structures that are not routinely screened by MRI. In addition, the degree of pathology in muscle can be inferred from the extent of vFDG-psotivity. In addition, semiquantitative evaluation using SUV is useful for the statistical analysis of muscle inflammation. On the other hand, the disadvantages of FDG PET include the considerable costs incurred and exposure to ionizing radiation. It is important to keep in mind that FDG uptake in muscles is influenced by hyperglycemia, uptake by other organs, and voluntary or involuntary muscle movement during the uptake phase; therefore, careful examination is a prerequisite.[25] Although further prospective investigations in a larger sample size are necessary, addition of FDG

PET to conventional clinical examinations may be useful for comprehensive diagnosis and management as well as investigation of the pathological mechanisms underlying PM/DM.

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Contributions

MT, KF and TK were involved in study setup and draft writing. TM was involved in the analysis of the muscle biopsies. TK and AA contributed to the visual evaluation of FDG PET. All of the authors contributed to discussion of the data and review and revision of the manuscript.

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Competing Interests

None.

Ethic approval

Tohoku University School of Medicine ethics committee.

Provenance and peer review

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Data sharing statement

No additional data are available.

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Figure legends

Figure 1. FDG PET and MRI findings in a patient with dermatomyositis (Patient 11). Serial sections of FDG PET/CT (A). Using FDG uptake in mediastinum blood vessels as a positivity criterion, positive regions were found in the paraspinal muscles, shoulders, upper arms, and lumbar girdles in a predominantly symmetrical distribution. An FDG PET image of the upper arm level (B). Frontal view of an FDG PET image indicating FDG uptake in the shoulders, upper arms, and iliopsoas (C). MRI of the thighs (D) showing high signal areas in the bilateral quadriceps femoris (T2-weighted images with fat suppression).

Figure 2. The numbers of vFDG-positive muscle regions are correlated with the mean SUVmax in four extremities (A). Serum values of creatinine kinase (CK) were higher in patients with more than two vFDG-positive muscle regions than in those with two or less regions (B). The number of vFDG-positive muscle regions correlated with the total histological scores (C). The mean SUVmax in four extremities correlated with the total histological scores (D). There were no differences in SUVmax in corresponding muscles between muscles with abnormal MRI signals and those without (E). In muscle regions examined by MRI, SUVmax in the corresponding muscles was higher in vFDG-positive muscles than in vFDG-negative ones (F).

Figure 3. FDG PET (A) and MRI findings (B) for both thighs in a patient with PM (Patient 14). Distribution patterns of high signal on MRI and FDG PET are different. The FDG uptake is localized and predominantly within the muscles.

Figure 4. The mean SUVmax in four extremities was higher in patients with PM/DM than in those with ALS (A). In patients with PM/DM, SUVmax of bilateral muscles was highly correlated,

suggesting symmetrical muscle lesions (B). Correlation coefficients: bilateral quadriceps femoris, $\rho = 0.91$, $p < 0.0001$; bilateral medial and posterior compartments of the thighs, $\rho = 0.88$, $p < 0.0001$; right quadriceps femoris and right medial and posterior compartments of the thighs, $\rho = 0.58$, $p = 0.0004$; left quadriceps and left medial and posterior compartments of the thighs, $\rho = 0.69$, $p < 0.0001$. In patients with ALS, only a moderate correlation was found between bilateral muscles (Spearman rank correlation) (C).

Table 1 Summary of patients with PM/DM

Clinical findings							Visually identified FDG uptakes in muscles§								FDG uptakes in other organs				Muscle biopsy findings¶			MRI findings**		
	Age	Sex	Clinical diagnosis	Dur*	CK†	Therapy at PET‡	SCM	PC	S	U	PT	PL	B	T	Lung	Lymph nodes.	Malig-nancy.	others	Sites	Cell inf	Nec/reg	Sites	High signals	Consistency with vFDG
PM/DM without other collagen diseases																								
1	24	M	DM	1	3000	5d P80	■	■	■	■	■	■	■	■	↑				BB	2	3	thigh	(+)	P (+)
2	82	M	DM	1	4307	5d P50	■	■	■	■	■							porta hepatis	BB	0	1	thigh	(+)	(-)
3	52	F	DM	4	436	(-)		■	■	■			■	■					BB	3	3	thigh	(+)	P (+)
4	20	F	DM	3	312	(-)									↑				BB	0	1	thigh	(+)	(-)
5	37	F	DM ILD	1	783	7d P20			■						↑				BB	1	1	thigh	(+)	(-)
6	33	F	DM	3	51	(-)			■							↑		stomach,.uterus	BB	1	1	Not done		
7	33	F	DM	2	274	(-)							■			↑		marrow,spleen	BB	0	0	Not done		
8	73	F	DM	1	182	(-)	■	■	■	■	■	■				↑		stomach	BB	3	3	Not done		
9	66	M	DM	4	239	(-)													BB	0	2	should.br	(+)	(-)
10	65	M	DM	2	377	(-)										↑		lung	Deltoid	1	2	brachium	(+)	(-)
11	53	M	DM	4	2488	(-)	■	■	■	■	■	■	■						BB	2	2	thigh	(+)	(-)
12	25	F	PM	4	926	(-)													BB	2	0	thigh	(+)	(-)
13	76	F	PM ILD	2	1343	(-)					■	■	■		↑				BB	1	3	thigh	(+)	(-)
14	54	M	PM ILD	14	6347	2d P60			■	■			■	■	↑				Gastro	1	1	thigh	(+)	P (+)
15	56	F	PM ILD	8	362	(-)									↑	↑		joints	QF	2	1	thigh	(+)	(-)
16	55	F	PM	12	1019	(-)		■	■	■					↑	↑		spleen	BB	1	1	Not done		
17	69	F	PM	60	758	(-)	■											myocardium	Deltoid	1	2	Not done		
18	79	F	PM	7	9627	(-)			■	■			■					lung	BB	0	2	thigh	(+)	(-)
19	52	M	PM	60	3372	9d P60													Deltoid	2	1	thigh	(+)	(-)
20	40	F	PM	2	1842	7d P60													BB	1	2	Not done		

21	50	F	PM	36	7182	(-)												BB	0	2	brachium	(-)	N(+)
22	73	M	PM ILD	1	1377	13d P55			■			■					diaphragm	BB	2	1	Not done		
PM/DM with other collagen diseases																							
23	27	F	MCTD	7	200	8d P50									↑		salivary gland	BB	2	1	thigh	(-)	N(+)
24	72	F	PM, SSC	18	1442	(-)									↑	↑	pudenda	BB	2	1	brachium	(+)	(-)
25	73	F	PM, SSC	14	126	(-)										↑	thyroid gland.	BB	0	0	thigh	(-)	N(+)
26	70	F	PM RA Sjs	24	761	(-)									↑	↑		BB	2	2	thigh	(+)	(-)
27	72	F	PM CREST	36	386	(-)		■				■				↑	joints	QF	2	1	thigh	(+)	(-)
28	42	M	MCTD	3	5585	(-)				■			■			↑		BB	3	3	thigh	(+)	(-)
29	65	F	PM Sjs	2	1764	(-)			■		■	■	■		↑	↑	joints	BB	2	2	thigh	(-)	N(+)
30	70	F	PM RA	3	1050	(-)									↑	↑		QF	2	1	Not done		
31	63	M	PM SSC	7	1396	(-)		■										BB	1	2	brachium	(-)	N (+)
32	52	F	PM SSC	1	1142	(-)		■							↑	↑		BB	0	1	brachium	(+)	(-)
33	75	F	MCTD	7	2123	(-)		■	■		■		■	■			peritoneum	BB	2	2	brachium	(+)	P (+)

*Duration of illness (months).

†Serum creatine kinase (CK) levels (IU/L).

‡Duration (days, d) and daily dose (mg) of prednisolone (P) at the time of the PET study.

§The regions of positive vFDG at least in either side of the region are filled. vFDG-positivity criterion is described in Material and Methods.

¶The criteria for grading of pathological findings is described in Material and Methods.

**P (+), both PET and MRI showed positive findings; N (+), both PET and MRI were negative; (-), either PET or MRI showed positive findings.

B, buttock; BB, biceps brachii; cell inf, mononuclear cell infiltration; CREST, CREST syndrome; DM, dermatomyosiits; Gastro, gastrocnemius; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; nec/reg, muscle fiber necrosis and regeneration; PC, paraspinal muscles at cervical levels; PL, paraspinal muscles at lumbar levels; PM, polymyositis; PT, paraspinal muscles at thoracic levels; QF, quadriceps femoris; RA, rheumatoid arthritis; S, shoulders; SCM, sternoclidomastoid muscles; Sjs, Sjögren syndrome; SSC, systemic sclerosis; T, thighs.

Figure 1

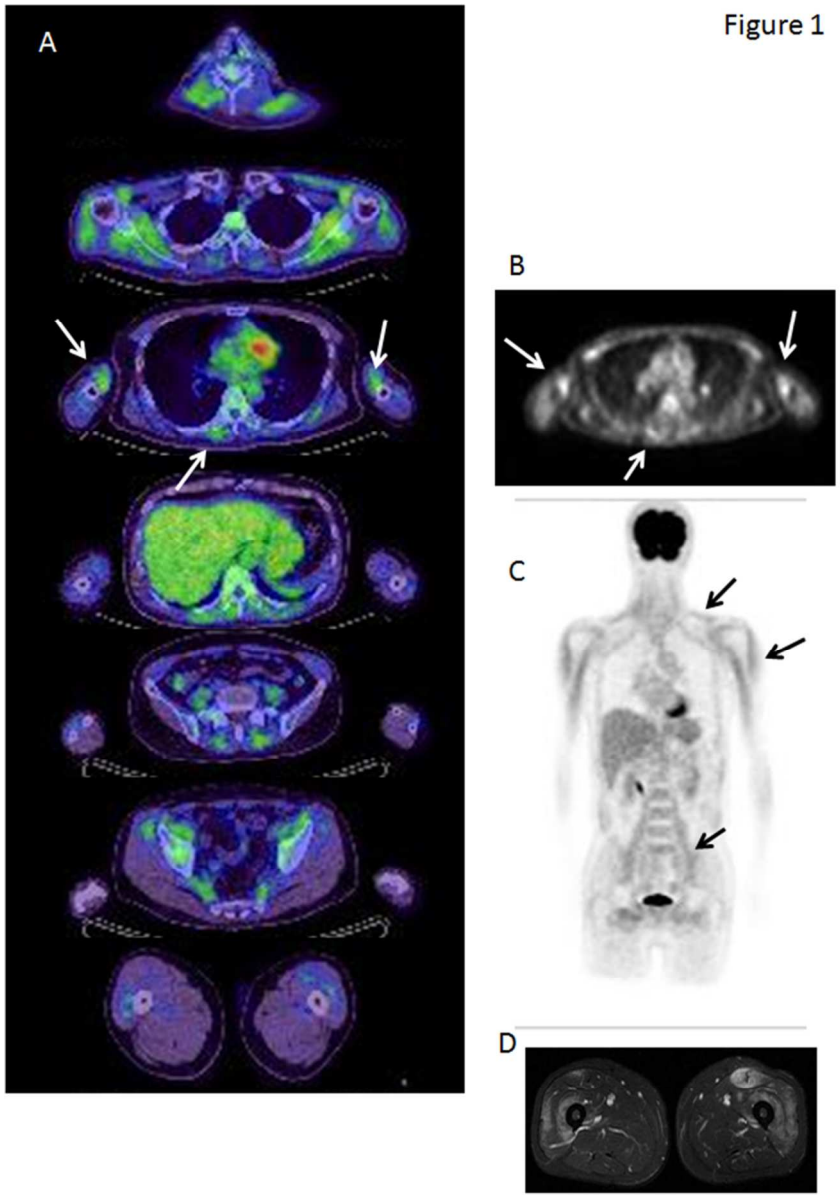

Figure 1. FDG PET and MRI findings in a patient with dermatomyositis (Patient 11). Serial sections of FDG PET/CT (A). Using FDG uptake in mediastinum blood vessels as a positivity criterion, positive regions were found in the paraspinal muscles, shoulders, upper arms, and lumbar girdles in a predominantly symmetrical distribution. An FDG PET image of the upper arm level (B). Frontal view of an FDG PET image indicating FDG uptake in the shoulders, upper arms, and iliopsoas (C). MRI of the thighs (D) showing high signal areas in the bilateral quadriceps femoris (T2-weighted images with fat suppression).
76x102mm (600 x 600 DPI)

Figure 2

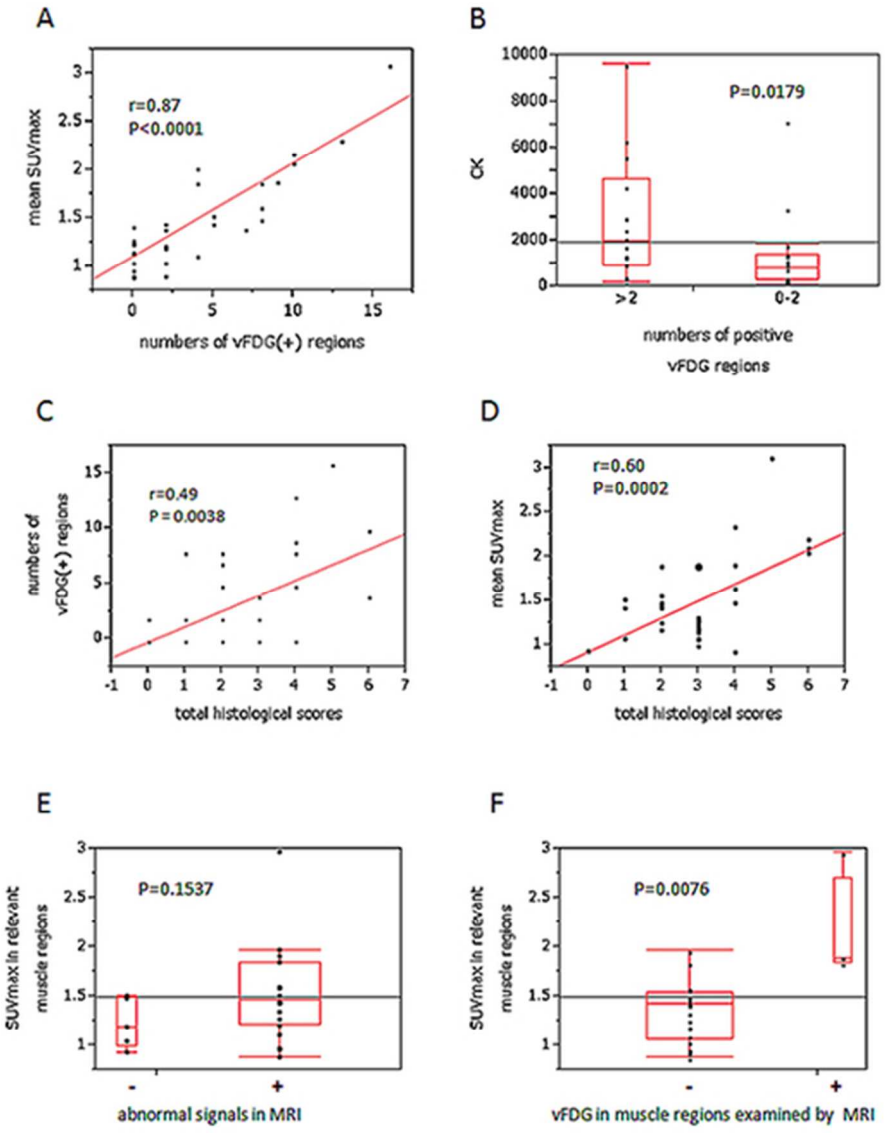

Figure 2. The numbers of vFDG-positive muscle regions are correlated with the mean SUVmax in four extremities (A). Serum values of creatinine kinase (CK) were higher in patients with more than two vFDG-positive muscle regions than in those with two or less regions (B). The number of vFDG-positive muscle regions correlated with the total histological scores (C). The mean SUVmax in four extremities correlated with the total histological scores (D). There were no differences in SUVmax in corresponding muscles between muscles with abnormal MRI signals and those without (E). In muscle regions examined by MRI, SUVmax in the corresponding muscles was higher in vFDG-positive muscles than in vFDG-negative ones (F).
22x29mm (600 x 600 DPI)

Figure 3

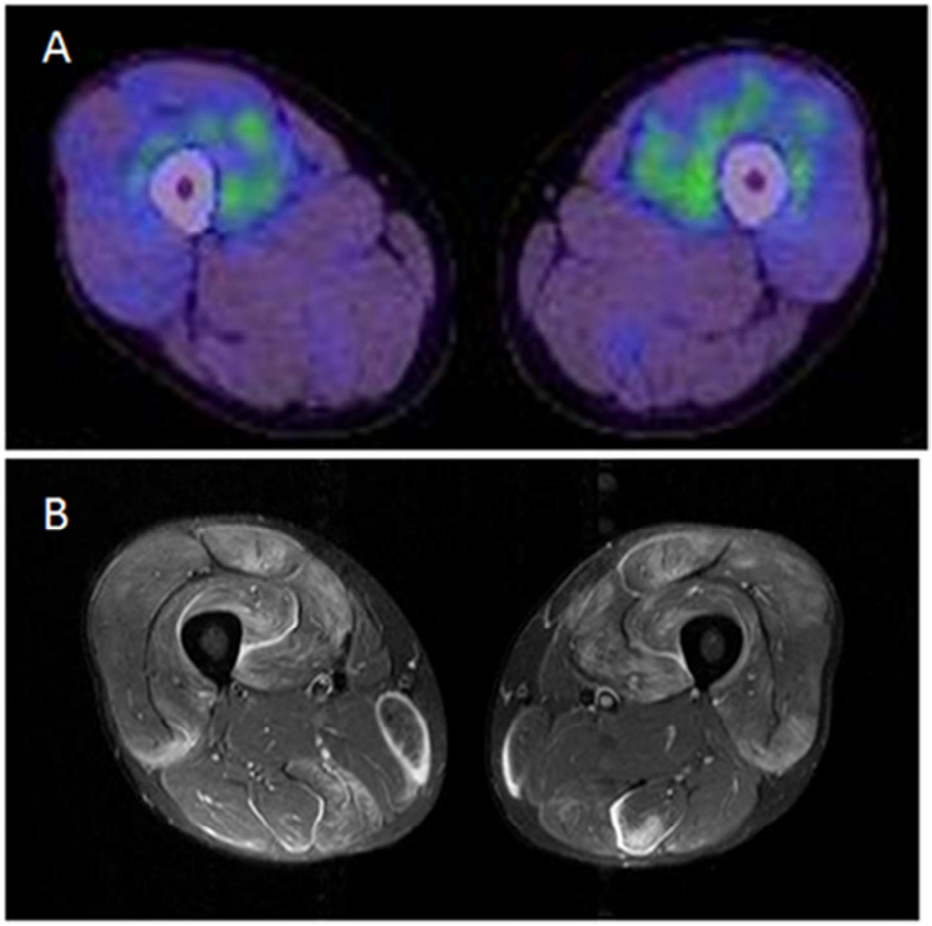

Figure 3. FDG PET (A) and MRI findings (B) for both thighs in a patient with PM (Patient 14). Distribution patterns of high signal on MRI and FDG PET are different. The FDG uptake is localized and predominantly within the muscles.

46x50mm (300 x 300 DPI)

Figure 4

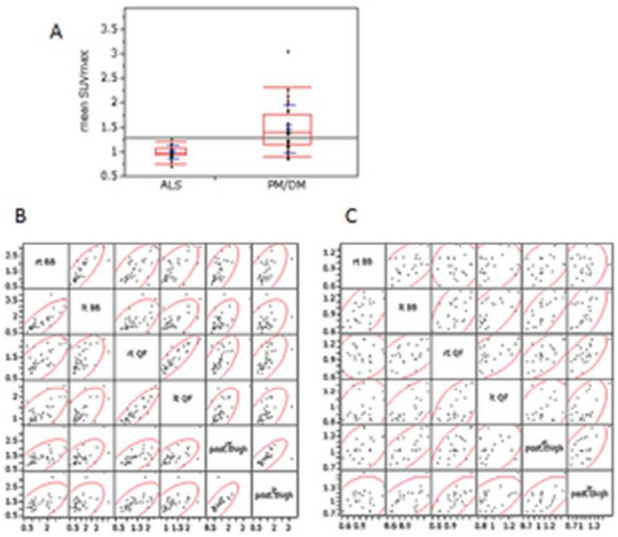

Figure 4. The mean SUVmax in four extremities was higher in patients with PM/DM than in those with ALS (A). In patients with PM/DM, SUVmax of bilateral muscles was highly correlated,
13x12mm (600 x 600 DPI)

Clinical values of FDG PET in polymyositis and dermatomyositis syndromes: imaging of skeletal muscle inflammation

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ABSTRACT

Objectives: [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET), a standard tool for evaluating malignancies, can also detect inflammatory lesions. However, its usefulness in evaluating muscle lesions in polymyositis and dermatomyositis syndromes (PM/DM) has not been established.

Methods: Thirty-three patients with PM/DM who had undergone FDG PET were retrospectively analyzed. FDG uptake was visually evaluated (visually identified FDG uptake, vFDG) in 16 regions of the body using mediastinum blood vessels as a positivity criterion. We also calculated the maximum standardized uptake value (SUVmax) in all four limbs of the patients with PM/DM as well as in 22 patients with amyotrophic lateral sclerosis (ALS) with similar disabilities. In 24 patients with PM/DM, MRI and FDG PET findings were compared.

Results: vFDG was observed in multiple muscle lesions with varying distributions in two-thirds of the PM/DM patients, with most lesions being symmetrical. The number of vFDG-positive regions strongly correlated with the mean SUVmax in all four limbs ($p < 0.0001$). Histological grades of biopsied muscles correlated with both the mean SUVmax and number of vFDG-positive regions. Serum creatine kinase levels were higher in patients with more than two vFDG-positive regions than in those with two or less regions ($p < 0.05$). While the inflamed muscles showed diffuse, patchy, or marginal signal abnormalities on MRI, FDG uptake was most prominent inside the muscles. Compared with ALS, the mean SUVmax was significantly higher in the PM/DM patients ($p < 0.0001$) and showed a striking correlation in the bilateral muscles reflecting symmetrical muscle involvement in PM/DM.

Conclusions: The visual assessment of FDG uptake as well as calculation of SUV enabled us to comprehensively evaluate skeletal muscle. This method can improve clinical practices and provide insights into pathomechanisms of PM/DM.

Strengths and limitations of this study

This is the first study that comprehensively investigated the usefulness of FDG PET in evaluating muscle lesions in patients with polymyositis dermatomyositis syndromes using visual evaluation and SUV measurement. The study demonstrated the usefulness of these two methods. Visual evaluation of FDG uptake can be used in clinical practice.

The limitation of the study is that it is retrospective. Patients underwent FDG PET for the detection of occult cancer, therefore, the imaging range was from the head to the middle of the thighs. Eight patients underwent FDG PET and 25 patients underwent FDG PET/CT. Data regarding manual muscle test was not obtained. Polymyositis dermatomyositis syndromes and non-inflammatory myopathies were not compared.

INTRODUCTION

Idiopathic inflammatory myopathies are a heterogeneous group of disorders clinically characterized by progressive proximal muscle weakness and pathologically by mononuclear cell infiltration and fiber necrosis in muscles. Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis are representative phenotypes.[1] Both PM and DM are thought to be immune-mediated disorders that can be successfully treated if properly managed. In contrast, in inclusion body myositis, degenerative processes also play an equal or greater role and effective treatments remain to be elucidated.[2] Patients with PM and DM syndromes (PM/DM) may present with other organ involvement, such as interstitial lung disease.[3 4] They may also evolve with other collagen diseases and malignancies.[4 5] In addition, the extent and pattern of muscle involvement are variable. PM/DM can present with prominent truncal muscle weakness or preferential involvement of respiratory muscles.[6 7] Thus, it is essential to systemically diagnose and evaluate patients with PM/DM.

[^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET) is a standard tool for detecting malignancies. FDG also accumulates in inflammatory lesions where glucose-consuming inflammatory cells infiltrate.[8] FDG PET is useful for diagnosing systemic inflammatory diseases, including collagen vascular disorders such as rheumatoid arthritis, vasculitis, and polymyalgia rheumatica.[9-11] In PM/DM, only a limited number of studies have demonstrated FDG PET detection of inflammatory muscle lesions. Owada et al. visually assessed FDG uptake (FDG uptake greater than or equal to that of the liver) in proximal muscles using FDG PET in 24 patients with PM/DM. They found that increased FDG uptake was more frequent in patients with PM/DM than in controls (33% versus 2%).[12] Pipitone et al. measured the maximum standardized uptake value (SUVmax) in the proximal muscles of all four limbs and calculated the muscle/liver SUVmax ratio in 12 patients with PM/DM using FDG PET/computed tomography (CT). They showed that the proximal muscle

SUV ratio was higher in patients with PM/DM than in controls.[13] In these two studies, increased FDG uptake in proximal muscles did not correlate with clinical parameters or MRI findings. In contrast, Tanaka et al. measured the mean SUV using FDG PET/CT in 14 proximal muscle groups of 20 patients with PM/DM and demonstrated that an increased SUV in proximal muscles of myositis patients as well as the mean proximal muscle SUV was correlated with serum creatine kinase (CK) and muscle strength.[14] They also found that local SUV correlated with the degree of inflammation in muscle biopsies and weakness of the corresponding muscles. However, their method using global SUV calculations may not be feasible in daily clinical practice. For successful clinical application of FDG PET, a simple and reliable way to assess PM/DM muscles is preferable.

In this study, we visually evaluated FDG PET findings in patients with PM/DM in detail and determined the extent and pattern of inflammation. We compared visually evaluated FDG PET findings with SUVmax in proximal muscles as well as with clinical and pathological findings. We also compared MRI findings with FDG uptake in the same muscle regions. Furthermore, we compared SUVmax in proximal muscles between patients with PM/DM and those with ALS.

MATERIALS AND METHODS

Patients

Thirty-three patients with recent-onset PM/DM were enrolled in this study. Patients underwent FDG PET or FDG PET/CT to investigate malignancies before or shortly after receiving an initial corticosteroid treatment from January 2009 to July 2013. They were identified by a retrospective review of medical records in our department. Clinically, patients showed symmetrical proximal muscle weakness, elevated serum muscle enzymes, and myositis-compatible electrophysiological findings proposed by Bohan and Peter.[15] Muscle biopsies were conducted in all patients and showed inflammatory infiltrates, muscle fiber necrosis, and/or expression of HLA class 1 on

muscle fibers. A few patients showed either inflammatory infiltrates or muscle fiber necrosis. In these patients, other muscle diseases were carefully excluded. Subsequent therapy with corticosteroids alone or additional immunomodulatory therapies were effective in all but one patient who died before treatment initiation. Clinical records, laboratory data, and muscle MRIs from each patient were collected. Patients with inclusion body myositis were not included. We identified 22 patients with amyotrophic lateral sclerosis (ALS) who were admitted to our hospital for diagnosis and had undergone FDG PET/CT for the detection of occult cancer. These patients were included in this study as disease controls. Eighteen patients fulfilled the diagnostic criteria for clinically definite, clinically probable, or clinically probable-laboratory supported ALS according to the revised El Escorial criteria of the World Federation of Neurology. [16] Four patients showed only lower motor neuron symptoms with exclusion of other diseases. Degrees of disability in patients with PM/DM and those with ALS were similar; all of these patients were able to walk and performed activities of daily life independently, but with some difficulties. The study was approved by the Tohoku University School of Medicine ethics committee.

FDG PET imaging

Patients fasted for a minimum of 4 h before the ^{18}F-FDG injection. Blood glucose levels were measured, and patients with blood levels > 150 mg/dl were not included. After injection of approximately 185 MBq (3.1 MBq/kg) of ^{18}F-FDG, the patients rested on the bed for 1 hour. PET scan was then performed from the head to the mid-thigh using a PET scanner (ECAT EXACT HR+, Siemens, Erlangen, Germany) or PET/CT scanner (Biograph Duo or 40, Siemens, Erlangen, Germany). PET/CT scanners have been used since April 2009 and have replaced a dedicated PET scanner in our institute. FDG uptake was visually evaluated (visually identified FDG uptake, vFDG) in skeletal muscles using dedicated workstations by two radiologists (AA, TK). FDG uptake

was independently assessed in a blinded manner. vFDG was evaluated in 16 regions, including the upper arms: shoulders: sternocleidomastoid muscles: paraspinal muscles of cervical, thoracic, and lumbar levels: buttocks: and upper part of the thighs in both sides (Figure 1). Regions with an FDG uptake greater than or equal to that of the mediastinum blood vessels were considered vFDG-positive.[17] Regions judged to be positive by both radiologists were defined as vFDG-positive and the number of vFDG- positive regions were counted (minimum = 0 and maximum = 16 in each patient). In addition, SUV was calculated in patients with PM/DM and in 22 patients with ALS in the biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh (hamstrings, abductor magnus, gracilis) on both sides. In one PM patient, we were not able to calculate SUV in the biceps brachii, because the sectional area of the muscle was of insufficient size to place the region of interest (ROI). The ROI (20mm) was placed in the highest FDG uptake area in each muscle region. SUV was calculated as both the maximum value (SUVmax) and mean value (SUVmean) in ROIs. The mean proximal muscles SUVmax (mean SUVmax) and SUVmean (mean SUVmean) were calculated by averaging the values obtained for the six muscle regions.

Muscle MRI

Muscle MRI was performed during a routine examination using the 1.5T Intera scanner (Philips, Best, the Netherlands) before treatment. Results were assessed by experienced radiologists. Abnormal signals in skeletal muscles were identified on T2-weighted images with fat suppression (T2W/FS) or short tau inversion recovery (STIR) sequence with long TE. In the patients who also underwent gadolinium contrast-enhancement, abnormal enhancement in the muscle and/or muscle fascia was evaluated.

Muscle biopsy

Muscle biopsies were obtained before treatment in all patients with PM/DM. The muscle was taken from the biceps brachii (26 patients), deltoid (three patients), quadriceps femoris (three patients), and gastrocnemius (one patient). Biopsied muscles were snap frozen and a routine histochemical study was conducted. The most affected lesions in each specimen were photographed with objective lens of 10-fold magnifications. Histological findings were assessed in a blinded manner by an experienced neurologist well versed in neuropathology (TM). The extent of mononuclear cell infiltration (mononuclear cell infiltration score) was graded as follows: 0, none or slight; 1, one focus of mononuclear cell infiltration; 2, more than one focus of mononuclear cell infiltration; and 3, diffuse mononuclear cell infiltration. Muscle fiber necrosis and regeneration (necrosis/regeneration score) were graded as follows: 0, none; 1, 1% or less of muscle fibers showing necrosis or regeneration; 2, more than 1% and no more than 10% of muscle fibers showing necrosis or regeneration; and 3, more than 10% of muscle fibers showing necrosis or regeneration. The total histological scores were calculated for each patient by adding the mononuclear cell infiltration and the necrosis/regeneration scores.

Statistical analysis

Statistical analysis was performed using JNP8 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was analyzed by the Wilcoxon rank sum test (nonparametric), simple regression analysis, and Spearman rank correlation. Comparisons were considered to be statistically significant if $p < 0.05$.

RESULTS

Patient characteristics

The characteristics of the 33 patients with PM/DM (10 males, 23 females; mean age 56 ± 17.9 years) who underwent FDG PET (eight patients) or FDG PET/CT (25 patients) are summarized in Table1. FDG PET was performed before any treatment in 25 patients. In eight patients, FDG PET was performed shortly after beginning corticosteroid treatment (2 - 9 days: mean 6.1 days). We provisionally divided PM/DM patients according to the presence or absence of other collagen diseases. The number of patients in each clinical group and those of relevant clinicopathological classifications proposed in the 119th European Neuromuscular Centre international workshop[18] in each clinical group (parenthesis) were as follows: 11 DM patients without other collagen diseases (four patients with definite DM, seven with probable DM), 11 PM patients without other collagen diseases (nine patients with nonspecific myositis, one with definite PM, and one with probable PM), and 11 PM/DM patients with other collagen diseases (eight patients with nonspecific myositis, two with probable PM, and one with definite PM). Two patients with DM and one with PM without other collagen diseases were shown to have malignancies. Abnormal FDG uptake was noted in the lung in several patients, and most were diagnosed as having interstitial lung diseases. FDG uptake in the lymph nodes was observed in 50% of patients with DM, 18.2% of patients with PM without other collagen diseases, and 75% of patients with PM/DM with other collagen diseases.

Visual assessment of FDG uptake in skeletal muscles of patients with PM/DM

vFDG in skeletal muscles was observed in 20/33 patients with PM/DM (60.6%). vFDG was detected in multiple regions in 14 patients (42.4%) with various patterns (Table1) and almost symmetrical distribution. The shoulders and buttocks were the most frequent vFDG-positive regions. A fraction of patients with DM showed vFDG-positivity in most of the regions: a representative case is shown in Figure 1. The number of vFDG-positive regions correlated with the

mean SUVmax of all four extremeties (r = 0.87, p < 0.0001; Fig. 2A), implying that SUVmax in extremities could be inferred by the extent of vFDG-positive regions. There was no correlation between serum CK levels and the number of vFDG-positive regions (p = 0.20). However, serum CK levels were higher in patients with more than two vFDG-positive regions than in those with two or less vFDG-positive regions (p = 0.0179; Fig. 2B). The number of vFDG-positive regions also correlated with the total histological score (r = 0.49, p = 0.0038; Fig. 2C). The number of vFDG-positive regions correlated with necrosis/regeneration scores (r = 0.49, p = 0.0036), but not with mononuclear cell infiltration scores (p = 0.06).

Relationship between SUV and clinicopathological findings in patients with PM/DM

The mean SUVmax did not correlate with the duration of the illness. The mean SUVmax was higher in males than females, although not significant (p = 0.075). There were no significant differences among patients with DM without other collagen diseases, PM without other collagen diseases, and PM/DM with other collagen diseases. The total histological score correlated with the mean SUVmax (r = 0.60, p = 0.0002; Fig. 2D). The mean SUVmax correlated more strongly with necrosis/regeneration scores (r = 0.61, p = 0.0002) than with mononuclear cell infiltration scores (r = 0.40, p – 0.0198). The total pathological score also correlated with SUVmax in the biopsied muscles in the patients with PM/DM in whom biopsies were done in biceps brahii or quadriceps femoris (r = 0.58, p = 0.0017). SUVmax in the biopsied muscles correlated more strongly with necrosis/regeneration scores (r = 0.59, p = 0.0013) than mononuclear cell infiltration scores (r = 0.40, p = 0.0361). On the other hand, the mean SUVmax did not correlate with serum CK levels. Serum CK levels did not correlated with total histological scores (p = 0.08), necrosis/regeneration scores (p = 0.22), and mononuclear cell infiltration scores (p = 0.32).

Comparison of FDG PET and MRI findings in PM/DM

Twenty-five patients with PM/DM underwent both FDG PET and muscle MRI. Muscle MRI was performed for the thighs (18 patients), upper arms (six patients), and shoulders (one patient). Twenty patients were judged to be MRI positive. In the MRI-positive regions of each patient, vFDG was positive in four patients. There were no patients that were MRI-negative and vFDG-positive. There was no difference in SUVmax of the muscles between MRI-positive and MRI-negative muscles ($p = 0.1537$; Fig. 2E). In contrast, SUVmax of relevant muscles was significantly higher in vFDG-positive patients than in vFDG-negative patients ($p = 0.0076$; Fig. 2F). These findings suggest that MRI is a sensitive tool for detecting inflammatory edema. However, high signals on MRI may not simply reflect the degree of inflammation.

Interestingly, the pattern of abnormal signals was different between FDG PET and MRI (Figs. 1 & 3). On MRI, affected muscles showed several patterns including diffuse or patchy high signals and high signals surrounding the muscles, which may reflect inflammatory edema (Figs 1 & 3). In contrast, FDG uptake was more localized in each muscle for most patients. The highest uptake was predominantly within muscles, a few centimeters from the muscle surface.

SUVmax in the skeletal muscles of patients with PM/DM and ALS

The mean SUVmax was higher in patients with PM/DM than in those with ALS (1.463 ± 0.483 versus 1.004 ± 0.136, $p < 0.0001$; Fig. 4A). The mean SUVmean was also higher in patients with PM/DM (1.106 ± 0.370 versus 0.733 ± 0.139, $p < 0.0001$).

The SUVmax in the biceps brachii, quadriceps femoris, and medial and posterior compartments of the thigh in both sides was compared. In patients with PM/DM, SUVmax of one muscle region and that of another muscle region was correlated (biceps brachii versus medial and posterior compartments of the thigh, quadriceps versus biceps brachii, quadriceps versus medial

and posterior compartments of the thigh). Moreover, there was a striking correlation between the same muscles on both sides (biceps brachii, quadriceps femoris, medial and posterior compartments of the thigh). The scatter plots suggested symmetrical muscle involvement in PM/DM (Fig. 4B). Only moderate symmetry in SUVmax was found in patients with ALS (Fig. 4C).

DISCUSSION

In the present study, we assessed the skeletal muscles of patients with PM/DM using FDG PET in two ways: visual assessment and SUV measurement. We found that the mean SUVmax in four extremities of PM/DM patients was approximately 1.5, and the mean SUVmean was approximately 1.1. These results are consistent with those of previous studies.[13 14] While a major mechanism underlying FDG accumulation in inflamed tissue caused by rheumatoid arthritis is uptake by metabolically active cells such as macrophages, young granulation tissue, and fibroblasts,[8 9] there has been no report on PM/DM. In the present study, we found that SUVmax of biopsied muscles correlated more strongly with necrosis/regeneration scores than with mononuclear cell infiltration scores. These findings imply that macrophages assembled in necrotic muscle fiber lesions and muscle fibers in regeneration stage may be a major background of FDG uptake in PM/DM.

Because FDG uptake in inflamed muscles is fairly moderate compared with that in the neoplasm, setting an appropriate criterion for visual assessment is challenging. In a previous study using liver in which an SUV of approximately 3 was the positivity criterion, 33% patients with PM/DM had FDG-positive muscle regions.[12] In the present study, we chose the mediastinum blood vessels, wherein SUV is approximately 2, as a positivity criterion for vFDG. [17] We found that 60.6% patients with PM/DM had vFDG-positive muscle regions. In addition, we divided the proximal body muscle into 16 regions, which enabled us to evaluate the extent and patterns of

vFDG-positive regions. Most notably, the extent of vFDG-positive regions correlated with the mean SUVmax and histological findings. There was only a mild correlation between the extent of vFDG-positive regions and serum CK levels. Serum CK levels are a major clinical parameter in PM/DM: however, it did not correlate with pathological severitiy in our patients. These findings suggest that vFDG, using mediastinum blood vessels as the positivity criterion, is useful for the assessment of systemic muscle lesions and that the extent of vFDG-positive regions can be an indicator of the disease activity in PM/DM.

We also evaluated vFDG using another scoring system, in which 1 point was assigned when the FDG uptake was greater than or equal to that of mediatinum blood vessels and 2 points assigned when FDG uptake was greater than or equal to that of the liver. The points given by two examiners were added in all the muscle regions in each patient (scores ranged from 0 to 64). These scores also strongly correlated with the mean SUVmax ($r = 0.90$, $p < 0.0001$) and total histological scores ($p = 0.0014$).

MRI is now widely used to diagnose and determine biopsy sites in PM/DM.[19 20] It can sensitively detect muscle edema in diseased muscle, including inflammatory myopathies.[21] Because MRI detects inflammatory edema and FDG PET detects FDG uptake by metabolically active cells, the images produced by the two modalities are different. In fact, MRI positivity did not correlate with SUVmax in the same muscles in the present study. On MRI images, abnormal signals were appeared as diffuse or patchy patterns in the muscles and sometimes surrounding the muscles. On the other hand, FDG uptake tended to localize and was frequently found deep within each muscle. Because FDG uptake theoretically reflects metabolically active sites, the pathology of the biopsied muscles may not represent the most affected lesions. This may be the reason why we only found a moderate correlation between the grade of pathological findings and SUVmax of corresponding muscles. In the present study, abnormal MRI signals were positive in 20/25 patients, while vFDG

was positive in four: therefore, the sensitivity of MRI seems to be superior. However, MRI was not evaluated in a blinded manner in this study, and comparison was only performed for MRI examination sites; other sites such as the paraspinal muscles and buttocks were not compared. Further investigation is required to clarify the precise nature of abnormal signals using these two measures.

Previous reports have shown that SUV in skeletal muscles is higher in patients with PM/DM than in control patients without disability.[13 14] Comparisons of SUV between patients with PM/DM and disabled control patients have never been reported. ALS is characterized by progressive muscle weakness caused by degeneration of the upper and lower motor neurons. We found that the mean SUVmax was significantly higher in patients with PM/DM patients than in those with ALS. These findings suggest that FDG PET can distinguish between muscle weakness resulting from muscle fiber destruction with inflammation and that resulting from neurogenic atrophy.

PM/DM is clinically characterized by symmetrical proximal muscle weakness.[4] In the present study, we found a strong correlation between SUVmax of the same muscles on both sides including bilateral quadriceps femoris, bilateral medial and posterior compartments of the thighs, and bilateral biceps brachii. The correlation coefficient was higher for quadriceps femoris in both sides and medial and posterior compartments of the thigh in both sides than in quadriceps femoris and medial and posterior compartments of the same side of the legs. These findings statistically verified that the inflammatory muscle damage progresses symmetrically in PM/DM, although muscle lesions are often multifocal in each muscle. The current pathological mechanism of PM/DM based on immunopathology cannot explain the symmetrical muscle damage in PM/DM.[4 22] Several possible mechanisms may explain the symmetry, such as an involvement of anatomical factors, including vasculatures and peripheral nerves, or some immune or physiological factors of individual muscles that can influence the extent of inflammation.

The present study has several limitations. The study was retrospective and FDG PET was performed to detect malignancies. The extent of the imaging range was therefore restricted from the head to the middle of the thighs, limiting evaluation of the thighs; however, a negligible number of false negatives in vFDG were most likely produced. Nevertheless, we propose that when FDG PET is conducted in PM/DM patients, scans should include, at least, the entire length of the thighs to produce more informative data. In this study, we could not study whether FDG uptake in skeletal muscles changed after immunomodulatory treatment, because only a few patients underwent FDG PET two times or more. A part of patients underwent FDG PET shortly after biginning corticosteroid. Manual muscle test (MMT) data were not obtained from all patients; therefore, we could not compare MMT and FDG PET findings. We were unable to compare FDG PET findings between PM/DM patients and noninflammatory myopathies, such as muscular dystrophy.

In conclusion, our findings indicated the utility and convenience of FDG PET in the clinical characterization of PM/DM. The greatest advantage of FDG PET is that it can screen the whole body in a single scan. Apart from malignancies,[23] this methods can also evaluate lung inflammation [24] and swelling of lymph nodes. We can visually evaluate the extent and pattern of muscle lesions systemically and include structures that are not routinely screened by MRI. In addition, the degree of pathology in muscle can be inferred from the extent of vFDG-psotivity. In addition, semiquantitative evaluation using SUV is useful for the statistical analysis of muscle inflammation. On the other hand, the disadvantages of FDG PET include the considerable costs incurred and exposure to ionizing radiation. It is important to keep in mind that FDG uptake in muscles is influenced by hyperglycemia, uptake by other organs, and voluntary or involuntary muscle movement during the uptake phase; therefore, careful examination is a prerequisite.[25] Although further prospective investigations in a larger sample size are necessary, addition of FDG

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PET to conventional clinical examinations may be useful for comprehensive diagnosis and management as well as investigation of the pathological mechanisms underlying PM/DM.

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Contributions

MT, KF and TK were involved in study setup and draft writing. TM was involved in the analysis of the muscle biopsies. TK and AA contributed to the visual evaluation of FDG PET. All of the authors contributed to discussion of the data and review and revision of the manuscript.

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Competing Interests

None.

Ethic approval

Tohoku University School of Medicine ethics committee.

Provenance and peer review

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Data sharing statement

No additional data are available.

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Figure legends

Figure 1. FDG PET and MRI findings in a patient with dermatomyositis (Patient 11). Serial sections of FDG PET/CT (A). Using FDG uptake in mediastinum blood vessels as a positivity criterion, positive regions were found in the paraspinal muscles, shoulders, upper arms, and lumbar girdles in a predominantly symmetrical distribution. An FDG PET image of the upper arm level (B). Frontal view of an FDG PET image indicating FDG uptake in the shoulders, upper arms, and iliopsoas (C). MRI of the thighs (D) showing high signal areas in the bilateral quadriceps femoris (T2-weighted images with fat suppression).

Figure 2. The numbers of vFDG-positive muscle regions are correlated with the mean SUVmax in four extremities (A). Serum values of creatinine kinase (CK) were higher in patients with more than two vFDG-positive muscle regions than in those with two or less regions (B). The number of vFDG-positive muscle regions correlated with the total histological scores (C). The mean SUVmax in four extremities correlated with the total histological scores (D). There were no differences in SUVmax in corresponding muscles between muscles with abnormal MRI signals and those without (E). In muscle regions examined by MRI, SUVmax in the corresponding muscles was higher in vFDG-positive muscles than in vFDG-negative ones (F).

Figure 3. FDG PET (A) and MRI findings (B) for both thighs in a patient with PM (Patient 14). Distribution patterns of high signal on MRI and FDG PET are different. The FDG uptake is localized and predominantly within the muscles.

Figure 4. The mean SUVmax in four extremities was higher in patients with PM/DM than in those with ALS (A). In patients with PM/DM, SUVmax of bilateral muscles was highly correlated,

suggesting symmetrical muscle lesions (B). Correlation coefficients: bilateral quadriceps femoris, $\rho = 0.91$, $p < 0.0001$; bilateral medial and posterior compartments of the thighs, $\rho = 0.88$, $p < 0.0001$; right quadriceps femoris and right medial and posterior compartments of the thighs, $\rho = 0.58$, $p = 0.0004$; left quadriceps and left medial and posterior compartments of the thighs, $\rho = 0.69$, $p < 0.0001$. In patients with ALS, only a moderate correlation was found between bilateral muscles (Spearman rank correlation) (C).

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Table 1 Summary of patients with PM/DM

Clinical findings							Visually identified FDG uptakes in muscles§								FDG uptakes in other organs				Muscle biopsy findings¶			MRI findings**		
	Age	Sex	Clinical diagnosis	Dur*	CK†	Therapy at PET‡	SCM	PC	S	U	PT	PL	B	T	Lung	Lymph nodes.	Malig-nancy.	others	Sites	Cell inf	Nec/reg	Sites	High signals	Consistency with vFDG
PM/DM without other collagen diseases																								
1	24	M	DM	1	3000	5d P80	■	■	■	■	■	■	■	■		↑			BB	2	3	thigh	(+)	P (+)
2	82	M	DM	1	4307	5d P50	■	■	■	■	■							porta hepatis	BB	0	1	thigh	(+)	(-)
3	52	F	DM	4	436	(-)		■	■	■			■	■					BB	3	3	thigh	(+)	P (+)
4	20	F	DM	3	312	(-)										↑			BB	0	1	thigh	(+)	(-)
5	37	F	DM ILD	1	783	7d P20			■						↑				BB	1	1	thigh	(+)	(-)
6	33	F	DM	3	51	(-)			■							↑		stomach,.uterus	BB	1	1	Not done		
7	33	F	DM	2	274	(-)							■			↑		marrow,spleen	BB	0	0	Not done		
8	73	F	DM	1	182	(-)	■	■	■	■	■	■				↑		stomach	BB	3	3	Not done		
9	66	M	DM	4	239	(-)													BB	0	2	should.br	(+)	(-)
10	65	M	DM	2	377	(-)										↑		lung	Deltoid	1	2	brachium	(+)	(-)
11	53	M	DM	4	2488	(-)	■	■	■	■	■	■	■						BB	2	2	thigh	(+)	(-)
12	25	F	PM	4	926	(-)													BB	2	0	thigh	(+)	(-)
13	76	F	PM ILD	2	1343	(-)					■	■	■		↑				BB	1	3	thigh	(+)	(-)
14	54	M	PM ILD	14	6347	2d P60			■	■			■	■	↑				Gastro	1	1	thigh	(+)	P (+)
15	56	F	PM ILD	8	362	(-)									↑	↑		joints	QF	2	1	thigh	(+)	(-)
16	55	F	PM	12	1019	(-)		■	■	■					↑	↑		spleen	BB	1	1	Not done		
17	69	F	PM	60	758	(-)	■											myocardium	Deltoid	1	2	Not done		
18	79	F	PM	7	9627	(-)			■	■			■					lung	BB	0	2	thigh	(+)	(-)
19	52	M	PM	60	3372	9d P60													Deltoid	2	1	thigh	(+)	(-)
20	40	F	PM	2	1842	7d P60													BB	1	2	Not done		

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21	50	F	PM	36	7182	(-)												BB	0	2	brachium	(-)	N(+)
22	73	M	PM ILD	1	1377	13d P55			■			■					diaphragm	BB	2	1	Not done		
PM/DM with other collagen diseases																							
23	27	F	MCTD	7	200	8d P50									↑		salivary gland	BB	2	1	thigh	(-)	N(+)
24	72	F	PM, SSC	18	1442	(-)									↑	↑	pudenda	BB	2	1	brachium	(+)	(-)
25	73	F	PM, SSC	14	126	(-)										↑	thyroid gland.	BB	0	0	thigh	(-)	N(+)
26	70	F	PM RA Sjs	24	761	(-)									↑	↑		BB	2	2	thigh	(+)	(-)
27	72	F	PM CREST	36	386	(-)		■				■				↑	joints	QF	2	1	thigh	(+)	(-)
28	42	M	MCTD	3	5585	(-)				■			■			↑		BB	3	3	thigh	(+)	(-)
29	65	F	PM Sjs	2	1764	(-)			■		■	■	■		↑	↑	joints	BB	2	2	thigh	(-)	N(+)
30	70	F	PM RA	3	1050	(-)									↑	↑		QF	2	1	Not done		
31	63	M	PM SSC	7	1396	(-)		■										BB	1	2	brachium	(-)	N (+)
32	52	F	PM SSC	1	1142	(-)		■							↑	↑		BB	0	1	brachium	(+)	(-)
33	75	F	MCTD	7	2123	(-)		■	■		■		■	■			peritoneum	BB	2	2	brachium	(+)	P (+)

*Duration of illness (months).

†Serum creatine kinase (CK) levels (IU/L).

‡Duration (days, d) and daily dose (mg) of prednisolone (P) at the time of the PET study.

§The regions of positive vFDG at least in either side of the region are filled. vFDG-positivity criterion is described in Material and Methods.

¶The criteria for grading of pathological findings is described in Material and Methods.

**P (+), both PET and MRI showed positive findings; N (+), both PET and MRI were negative; (-), either PET or MRI showed positive findings.

B, buttock; BB, biceps brachii; cell inf, mononuclear cell infiltration; CREST, CREST syndrome; DM, dermatomyosiits; Gastro, gastrocnemius; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; nec/reg, muscle fiber necrosis and regeneration; PC, paraspinal muscles at cervical levels; PL, paraspinal muscles at lumbar levels; PM, polymyositis; PT, paraspinal muscles at thoracic levels; QF, quadriceps femoris; RA, rheumatoid arthritis; S, shoulders; SCM, sternoclidomastoid muscles; Sjs, Sjögren syndrome; SSC, systemic sclerosis; T, thighs.