[18F]FDG uptake in proximal muscles assessed by PET/CT reflects both global and local muscular inflammation and provides useful information in the management of patients with polymyositis/dermatomyositis

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Abstract

Objective. This study aimed to determine whether [18F]fluorodeoxyglucose-PET/CT ([18F]FDG-PET/CT) discriminates PM/DM from non-muscular diseases and also whether FDG uptake in proximal muscles reflects the activity and severity of muscular inflammation in PM/DM.

Methods. Twenty treatment-naïve PM/DM patients who underwent [18F]FDG-PET/CT were retrospectively identified by reviewing medical records. The same number of age- and sex-matched control patients with non-muscular diseases were also identified. Standardized uptake value (SUV) was calculated for each of the seven proximal muscles. For patient-based assessment, mean proximal muscle SUV was calculated by averaging the SUVs for these proximal muscles bilaterally.

Results. Mean proximal muscle SUVs were significantly greater in PM/DM patients than in control patients (median 1.05 vs 0.69, \(P < 0.001\)). Mean proximal muscle SUVs significantly correlated with mean proximal manual muscle test scores (\(r = 0.49, P = 0.028\)) and serum levels of creatine kinase (\(r = 0.54, P = 0.015\)) and aldolase (\(r = 0.64, P = 0.002\)). Furthermore, SUVs in proximal muscles from which biopsy specimens were obtained significantly correlated with histological grade for inflammatory cell infiltration (\(r = 0.66, P = 0.002\)).

Conclusion. Our results suggest that [18F]FDG-PET/CT is useful in the diagnosis of PM/DM when inflammation in proximal muscles is globally assessed with quantitative measurements. Our results also indicate that local FDG uptake in a proximal muscle reflects the activity of inflammation in the same muscle and provides useful information in determining the region for muscle biopsy.

Key words: [18F]FDG-PET/CT, polymyositis, dermatomyositis, muscle biopsy, MRI, manual muscle test, creatine kinase, aldolase.

Introduction

Idiopathic inflammatory myopathy is a heterogeneous condition characterized by symmetrical muscle weakness and elevated serum levels of skeletal muscle-derived enzymes. PM and DM are the major disease subgroups of idiopathic inflammatory myopathy, which have common and also distinct clinical and histological features [1, 2]. Although some genetic and environmental factors are considered to be involved in the pathogenesis of chronic muscle inflammation, the aetiology of PM/DM remains largely unknown [3, 4].

Muscle enzymes such as creatine kinase (CK) and aldolase and EMG provide information that indicates myogenic pathologies and are the major noninvasive diagnostic measures in PM/DM. However, since these
measures do not accurately discriminate inflammatory and non-inflammatory myopathies, muscle biopsy remains the gold standard in the diagnosis of PM/DM despite its invasiveness, which can cause pain and other complications. Infiltration of inflammatory cells and degeneration and regeneration of muscle fibres are the common histopathological findings of PM/DM, although the dominant inflammatory cell types and the typical site of infiltration within the muscle are different between PM and DM [5]. The limitation of histopathological assessment of myositis is that a biopsy specimen does not always reflect the presence of inflammation or the global activity and severity of myositis in patients with PM/DM because the distribution of muscle lesions is frequently patchy [6]. Imaging can supplement the weakness of conventional measures. MRI detects inflammatory oedema in the affected muscle and has been increasingly used for diagnosis, guidance of biopsy and assessment of disease activity in the management of PM/DM [7-10]. However, a routine MRI does not cover all the proximal muscles that are frequently involved in PM/DM due to the limitation in the size of the field of view (FOV). Although several groups recently reported the utility of whole-body MRI in the assessment of inflammatory myositis [11, 12], the length of the procedure and the limited resolution are issues for its use in clinical practice.

$[^{18}\text{F}]$FDG-PET/CT is a metabolic imaging technique originally developed for detecting malignancies. Although the utility of $[^{18}\text{F}]$FDG-PET in the management of rheumatic or inflammatory diseases has been increasingly reported [13-20], its applications and benefits in the management of PM/DM are still controversial [21, 22]. In this study, we used a novel quantitative method for the global assessment of FDG uptake in the proximal muscles and aimed to determine whether $[^{18}\text{F}]$FDG-PET/CT discriminates PM/DM from non-muscular diseases. We also investigated whether the muscular FDG uptake reflects the activity and severity of muscular inflammation at an individual patient level and also at each muscle level.

**Patients and methods**

**Patients**

Patients who fulfilled the criteria for either definite or probable PM/DM proposed by Bohan and Peter [1] and underwent $[^{18}\text{F}]$FDG-PET/CT before receiving initial corticosteroid treatment for myositis from April 2009 to July 2012 were retrospectively identified by reviewing medical records in the Department of Allergy and Clinical Immunology, Chiba University Hospital. Patients with clinically amyopathic DM, a disease subset of DM with typical skin manifestations but minimal evidence of myositis, were not included in this study according to the criteria used. Clinical, laboratory, electrophysiological, histological and imaging data were collected. Age- and sex-matched control patients were also identified in patients without muscular diseases who underwent $[^{18}\text{F}]$FDG-PET/CT during the same period in the Diagnostic PET Imaging Center, Department of Radiology, Sanno Medical Center. All patients gave written consent for their clinical information to be published. The study was approved by the ethics committee of Chiba University.

**Muscle strength evaluation**

Muscle strength was evaluated by manual muscle test (MMT) and was graded using Kendall’s 0–10-point grading scale as previously described [23, 24]. In order to focus on the muscles that are frequently involved in PM/DM and large enough for the method to evaluate $[^{18}\text{F}]$FDG uptake described below, seven proximal muscle groups (trapezius, deltoid, biceps, iliopsoas, gluteus medius, gluteus maximus and quadriceps) were chosen for the muscle evaluation. MMT in this set of proximal muscle groups was validated in the previous study [25].

**MRI**

MRI was performed using a 1.5T MR unit (GE Medical Systems, Milwaukee, WI, USA). T2-weighted images and short T1 inversion recovery (STIR) images of the proximal limbs with weakness were obtained. Images were assessed by two experienced rheumatologists (M.Y. and K.S.) and proximal muscles with inflammatory oedema were identified.

**PET/CT imaging**

Patients fasted overnight or for at least 6 h before the examination. Blood glucose levels were confirmed to be within normal limits before the injection of 4.0 MBq/kg of $[^{18}\text{F}]$FDG. Images were acquired at 60 min after injection. Patients rested during the uptake period in order to minimize non-specific FDG uptake in muscles. An integrated PET/CT (Discovery ST, GE Medical Systems, Milwaukee, WI, USA) was used for image acquisition. CT scanning was performed with 140 kV, 50 mA, a pitch of 1.75, a section thickness of 3.75 mm, an FOV of 50 cm and a matrix size of 512 x 512. Immediately after the unenhanced CT scan, a PET scan was performed with a section of thickness 3.27 mm, a matrix size of 128 x 128 and an acquisition time of 2 min. PET data sets were reconstructed iteratively with an ordered subsets expectation maximization algorithm and segmented attenuation correction (2 iterations, 21 subsets) and the CT data.

SUV was calculated by the following formula: SUV (g/ml) = regional radioactivity concentration (Bq/ml)/[injected dose (Bq)/body weight (g)]. Region of interest (ROI) (20 mm diameter) was manually placed by a single trained radiologist (K.U.) at the region with the highest FDG uptake in each muscle, excluding the region obviously influenced by FDG uptake in other anatomical structures. In order to avoid noise and obtain the value representing a certain volume of muscle tissue, SUV was calculated as the mean value of ROI instead of the maximum value at a single pixel. Seven proximal muscles (trapezius, deltoid, biceps, iliopsoas, gluteus medius, gluteus maximus and quadriceps) were evaluated bilaterally.
corresponding to the muscle groups where MMT was performed. The size of these muscles was large enough to place the ROI (supplementary Fig. S1, available at Rheumatology Online). For patient-based assessment, a mean proximal muscle SUV for an individual patient was calculated by averaging the SUVs for these muscles bilaterally (14 muscles).

**Histological assessment of inflammation**

Infiltration of inflammatory cells in the muscle was assessed with haematoxylin and eosin (HE)-stained samples and was graded with a previously described 5-point grading system: 0, no inflammatory cells present; 1, slight inflammation; 2, moderate; 3, obvious; 4, strong [10]. Stained samples were evaluated by three examiners (T.I., Y.S. and A.O.) who were blinded to the clinical and imaging data, and the mean values of the three independent grades were presented.

**Statistical analysis**

Statistical analysis was performed using SPSS version 16.0J (IBM Japan, Tokyo, Japan). Data were summarized with the median and interquartile range (IQR) and analysed for statistical significance by using a Mann-Whitney U test or Spearman’s correlation coefficient. P-values <0.05 were considered statistically significant.

**Results**

**Characteristics of patients with PM/DM and control diseases**

Twenty Japanese patients with new-onset PM/DM who underwent [18F]FDG-PET/CT before receiving initial corticosteroid therapy were identified. [18F]FDG-PET/CT was performed primarily for malignancy screening. Either muscle biopsy (n = 19) or EMG (n = 19) was performed in all patients to confirm the diagnosis. Demographics and disease characteristics of these patients are shown in Table 1. Female (n = 16, 80%) and DM patients (n = 15, 75%) predominated. Median age was 62 years (IQR 41–67 years) and the median duration of muscle symptoms was 5 months (IQR 3–6.25 months). One patient (case 9) had only rash and minimal myalgia when [18F]FDG-PET/CT was performed, but later developed proximal muscle weakness with elevated muscle enzymes and was diagnosed with conventional DM instead of amyopathic DM. Another patient (case 16) had a chronic onset of weakness in the proximal muscles and rash and had a disease duration of 60 months when she was diagnosed with DM. The muscle biopsy specimen revealed histological findings consistent with DM with no inclusion bodies. One patient (case 5) had gastric cancer. Anti-Jo-1 antibody was negative in all patients and other myositis-related autoantibodies were not investigated in this study. All patients achieved clinical remission of myositis with either corticosteroid therapy alone or combination therapy with immunosuppressive agents. No patients have received any alternative diagnosis for their muscle weakness for a median follow-up period of 19 months (IQR 8–28 months).

Twenty age- and sex-matched Japanese patients with non-muscular diseases were also identified. The proportion of females and the median age were identical to PM/DM patients. Diagnoses of these control patients were malignant tumours (n = 15), benign tumours (n = 3) and inflammatory diseases (n = 2).

**Discrimination between PM/DM and non-muscular diseases using mean FDG uptake in proximal muscles**

Fig. 1 shows the representative [18F]FDG-PET/CT images in patients with a non-muscular disease and DM (case 18). As shown in Fig. 2A, mean proximal muscle SUVs were significantly greater in PM/DM patients than those in patients with non-muscular diseases (median 1.05 vs 0.69, P < 0.001). The values were comparable between PM [median 0.98 (IQR 0.801.42)] and DM [median 1.06 (IQR 0.90–2.16)]. Receiver operator characteristic (ROC) analysis demonstrated a large area under the curve (AUC) [0.95 (95% CI 0.88, 1.02)] for the mean proximal muscle SUV to discriminate PM/DM from non-muscular diseases (Fig. 2B). When the optimal cut-point was determined by the ROC curve, a mean proximal muscle SUV >0.83 g/ml gave a sensitivity of 90% and a specificity of 100%. MRI for symptomatic arms or legs was performed in eight [18F]FDG-PET/CT-positive (i.e. mean proximal muscle SUV >0.83 g/ml) patients and three (38%) had no abnormal findings suggestive of inflammatory myositis. These results indicate that [18F]FDG-PET/CT can discriminate PM/DM from non-muscular diseases and can be more sensitive than MRI to detect muscle inflammation, at least in some patients with PM/DM.

**Correlation of mean proximal muscle FDG uptake with global disease activity and severity of myositis**

We next assessed whether the mean FDG uptake in proximal muscles correlates with the disease activity and severity of myositis. As shown in Fig. 3, mean proximal muscle SUVs significantly correlated with mean proximal MMT scores (r = 0.49, P = 0.028) and serum levels of CK (r = 0.54, P = 0.015) and aldolase (r = 0.64, P = 0.002). In case 1, [18F]FDG-PET/CT revealed intensive inflammation in the erector muscles of the spine, which was reflected in the extremely elevated serum level of CK (54 318 U/l) but not the mean proximal muscle SUV (0.88 g/ml) because erector muscle of the spine was not included in the seven proximal muscles assessed in this study. These results suggest that [18F]FDG-PET/CT not only detects the presence of inflammatory myositis, but also reflects the global activity and severity of myositis in PM/DM patients.

**Correlation between regional FDG uptake and corresponding muscle weakness**

We next investigated whether the regional FDG uptake in each proximal muscle correlates with corresponding muscle weakness. As shown in Fig. 4A, SUVs in proximal muscles significantly correlated with the corresponding
**Table 1** Demographics and clinical, laboratory and imaging data of the patients with PM/DM

<table>
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<th>Case no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>PM/DM</th>
<th>Duration of muscle weakness (months)</th>
<th>Mean proximal MMT score</th>
<th>CK (U/l)</th>
<th>AST (U/l)</th>
<th>ALT (U/l)</th>
<th>LDH (U/l)</th>
<th>Aldolase (U/l)</th>
<th>Skin lesions characteristic of DM</th>
<th>Interface dermatitis on skin biopsy</th>
<th>Interstitial lung disease</th>
<th>ANA titre and pattern</th>
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GS: Gottron’s sign; SS: shawl sign; MH: mechanic’s hand; NFB: nail fold bleeding; PUE: periangual erythema; PD: poikiloderma; HR: heliotrope rash; VNS: V-neck sign; NR: not reported; NA: not applicable; sp: speckled; nu: nucleolar; homo: homogeneous. <sup>a</sup>Elbow; <sup>b</sup>knee; <sup>c</sup>forehead; <sup>d</sup>thigh; <sup>e</sup>scalp; <sup>f</sup>malar region; <sup>g</sup>neck; <sup>h</sup>back; <sup>i</sup>gluteal region; <sup>j</sup>upper arm.
Fig. 1 Representative [$^{18}$F]FDG-PET/CT images in patients with a non-muscular disease and dermatomyositis.

(A) A maximum intensity projection (MIP) image of a control patient. (B) A MIP image of a representative patient with dermatomyositis (case 18). Diffuse FDG uptake in the proximal muscles is present in the patient with dermatomyositis, but not in the control patient. (C-E) Representative PET/CT images of the same patient with dermatomyositis are shown. Arrowheads indicate the abnormal accumulation of FDG in deltoid (C), iliopsoas (D) and quadriceps (E) muscles.

Fig. 2 Discrimination between PM/DM and non-muscular diseases using mean FDG uptake in proximal muscles.

(A) Comparison of mean proximal muscle SUVs between PM/DM and non-muscular diseases. A horizontal bar represents the median. ***P < 0.001. (B) ROC analysis for mean proximal muscle SUV to discriminate between PM/DM and control diseases resulted in an AUC of 0.95 (95% CI 0.88, 1.02) and an optimal cut-point at 0.83 g/ml.
MMT scores \((n=280, \rho=0.34, P<0.001)\). In subgroup analysis, SUVs in the trapezius \((\rho=-0.50, P<0.001)\), deltoids \((\rho=-0.42, P=0.007)\), gluteus maximus \((\rho=-0.43, P=0.006)\) and quadriceps \((\rho=-0.46, P=0.003)\) significantly correlated with the corresponding MMT scores (supplementary Table S1, available at Rheumatology Online). These results indicate that the regional muscular FDG uptake reflects inflammation that causes weakness in the same muscle. The lack of significant correlation in gluteus medius \((\rho=-0.27, P=0.089)\) was probably due to the lack of statistical power. For biceps \((\rho=-0.19, P=0.231)\), the muscle strength seemed to be affected by arthralgia in the hands and wrists in some cases, which could have confounded the analysis.

Correlation between regional FDG uptake and inflammatory cell infiltration

Finally, we assessed whether the muscular FDG uptake correlates with the intensity of inflammatory cell infiltration at a biopsy site. As shown in Fig. 4B, SUVs in proximal muscles from which biopsy specimens were obtained significantly correlated with the histological grade for the infiltration of inflammatory cells \((n=19, \rho=0.58, P=0.009)\). Disease type-specific analysis showed similar trends both in PM \((n=5, \rho=0.78, P=0.033)\) and in DM \((n=14, \rho=0.48, P=0.086)\). These results demonstrate that the regional FDG uptake in a muscle reflects the infiltration of inflammatory cells in the same muscle.

Discussion

In this study, we developed a novel quantitative method for the assessment of mean FDG uptake in the proximal muscles that represents the global inflammatory activity of myositis. By using this method, we demonstrated that \([^{18}F]FDG\)-PET/CT can discriminate PM/DM from non-muscular diseases and can be more sensitive than MRI to detect muscle inflammation, at least in some patients with PM/DM. A previous Japanese study reported the low sensitivity of \([^{18}F]FDG\)-PET/CT to detect muscle inflammation in patients with PM/DM [21]. However, as they discussed in their article, the sensitivity of \([^{18}F]FDG\)-PET/CT was decreased, probably because of their too strict definition for the presence of abnormal muscular FDG uptake, by which a muscle with FDG uptake equal to or higher than physiological liver uptake was interpreted as positive. In fact, when we applied the same definition in our cases, only 10 cases (50%) were positive for \([^{18}F]FDG\)-PET/CT (data not shown). Since PM/DM is a systemic condition that unevenly affects multiple muscles, discriminating PM/DM from non-muscular diseases based on a single most inflamed muscle might be difficult, irrespective of the threshold. On the other hand, the mean proximal muscle SUV we employed in this study includes all major proximal muscles and actually demonstrated a superior discriminating capacity. Further studies
are needed, however, to investigate whether $^{18}$F-FDG-PET/CT is capable of accurately discriminating PM/DM from noninflammatory myopathies or other inflammatory conditions such as polyarthritis or systemic vasculitis.

We also demonstrated that mean proximal muscle SUV reflects the global activity and severity of myositis in PM/DM patients. Pipitone et al. [22] reported that although muscular FDG uptake was significantly higher in patients with PM/DM than in those with non-muscular diseases, the correlation between muscular FDG uptake and the disease activity of PM/DM was not statistically significant. The lack of significant correlation might have been due to the small number of cases ($n = 12$), the influence of immunosuppressive therapy, which was given to most of the patients, or the different method employed in the evaluation of muscular FDG uptake. The maximum SUVs from four proximal limb muscles were averaged in their study. The method is semiquantitative but does not thoroughly assess all the proximal muscles as our method does. The practical implication of our positive result is that $^{18}$F-FDG-PET/CT may be utilized not only for diagnosis but also for monitoring disease activity or predicting prognosis in the management of PM/DM. Although $^{18}$F-FDG-PET/CT involves high cost and modest but substantial exposure to ionizing radiation and further assessment for the responsiveness of muscular FDG uptake is necessary, discretionary use of this tool for monitoring purposes in difficult cases or in clinical trials may be beneficial.

The most important and novel finding in our study is that the regional FDG uptake reflects the corresponding weakness of the same muscle group and correlates with the infiltration of inflammatory cells in the biopsy specimen obtained from the same muscle. Although previous studies have already shown that FDG uptake is increased in inflammatory lesions due to the presence of metabolically active cells such as lymphocytes [26, 27], no studies have actually demonstrated the direct association between FDG uptake and inflammation in the same muscle in PM/DM. Our muscle-based data on histopathology and function provide the theoretical basis for the use of $^{18}$F-FDG-PET/CT in the management of PM/DM. For practical purposes, our data indicate that $^{18}$F-FDG-PET/CT provides useful information in determining the optimal muscle for tissue biopsy. Some studies reported the utility of MRI for that purpose [9, 10]. However, MRI does not necessarily allow for comprehensive assessment for all proximal muscles and our data showed that $^{18}$F-FDG-PET/CT was more sensitive than MRI, at least in some patients, in detecting muscular inflammation that was confirmed by histological assessment.

$^{18}$F-FDG-PET/CT also provides additional benefits in the evaluation of patients with PM/DM. The increased prevalence of malignancy in patients with PM/DM has been well documented [1], which necessitates screening investigations at the time of PM/DM diagnosis. A previous study showed that $^{18}$F-FDG-PET/CT is as capable of detecting occult cancers in patients with PM/DM as conventional screening [28]. In fact, the advanced gastric cancer in one of our patients (case 5) was clearly depicted with marked FDG uptake by PET/CT (supplementary Fig. S2, available at Rheumatology Online). In addition, $^{18}$F-FDG-PET/CT can be useful in determining the activity of ILD, which is a possibly critical complication in PM/DM [21]. In our study, FDG uptake was increased in the lung lesions in five of nine patients with ILD (data not shown) (supplementary Fig. S3, available at Rheumatology Online). The independent prognostic value for the $^{18}$F-FDG-PET/CT-positive lung lesions in PM/DM needs to be determined in future studies.

The major limitation of this retrospective study is that MRI was performed in less than half of the patients and the comparison between $^{18}$F-FDG-PET/CT and MRI was incomplete. In order for $^{18}$F-FDG-PET/CT to become routine care in the management of PM/DM, its clear advantage over MRI needs to be demonstrated by a direct comparison in a prospective study since MRI is much less expensive than $^{18}$F-FDG-PET/CT [insurance reimbursement for a single scan from the Japanese government, $165 vs $1014 (1 U.S. dollar = 85 Japanese yen)] and MRI does not produce exposure to ionizing radiation. However, considering the additional benefits of $^{18}$F-FDG-PET/CT discussed above and the limited number of muscles evaluated in a single MRI scan, the overall cost-effectiveness should be assessed on a case-by-case basis, taking into account the disease manifestation and the risk for malignancy.

In conclusion, our study demonstrated that $^{18}$F-FDG-PET/CT enables quantitative evaluation of muscle inflammation both at the individual patient level and at each muscle level. Therefore $^{18}$F-FDG-PET/CT can play significant roles in the diagnosis, in determining the site of muscle biopsy and in the evaluation of disease activity and severity of PM/DM. Considering its additional benefits in malignancy screening and ILD assessment, $^{18}$F-FDG-PET/CT is a potent tool with multifaceted information in the assessment of patients with possible PM/DM.

### Rheumatology key messages

- Assessment of global muscular inflammation with $^{18}$F-FDG-PET/CT discriminates PM/DM from non-muscular diseases.
- FDG uptake in proximal muscles reflects the activity and severity of muscular inflammation in PM/DM.
- Regional FDG uptake is informative in determining the site for muscle biopsy in PM/DM.

### Acknowledgements

We thank Dr Yoshihisa Kobayashi, Dr Hirotoshi Kawashima, Dr Junichi Hosokawa, Dr Mieko Yamagata, Dr Kazuyuki Meguro and Dr Ayako Matsuki for the care and management of PM/DM patients enrolled in the study.

**Disclosure statement:** The authors have declared no conflicts of interest.
Supplementary data

Supplementary data are available at Rheumatology Online.

References