[18F]Fluorodeoxyglucose positron emission tomography/computed tomography for diagnosing polymyositis/dermatomyositis

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Abstract. [18F]fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) is useful for diagnosing cancers and inflammatory diseases. A polymyositis/dermatomyositis (PM/DM) lesion is an inflammatory heterogeneous disease of the striated muscle. In the present study, the maximum standardized uptake value (SUV_{max}) was compared between 22 cases with definite or probable PM/DM (PM/DM group) that underwent [18F]FDG-PET/CT examination and the same number of patients with no myopathy. The average proximal muscle FDG uptake value (SUV_{average}) for each patient was represented by calculating the average of the SUV_{max} for these muscles bilaterally. The correlation between creatine kinase (CK), serum creatine kinase isoenzyme, myodynamia of the proximal limb girdle muscle and SUV_{max} of each muscle group were analyzed. The results indicated that the SUV_{max} was markedly different between the PM/DM group and the non-myopathy group. It was demonstrated that [18F]FDG-PET/CT has a diagnostic value for PM/DM. The serum CK levels and the SUV_{average} were negatively correlated with myodynamia. [18F]FDG-PET/CT may be used for examination to assess the severity of myositis. Furthermore, it may provide detection sites for muscle biopsy in patients with myositis.

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Introduction

Dermatomyositis (DM), polymyositis (PM) and inclusion body myositis are the major categories of idiopathic inflammatory myopathy (1). PM/DM may affect any striated muscle of the body. The associated pathological changes are mainly associated with inflammatory or degenerative processes of muscle fibers and adjacent connective tissue (2). The diagnostic criteria are based on the standards set by Bohan and Peter (3) in 1975. The changes in laboratory parameters feature elevation of serum muscle enzymes, including creatine kinase (CK), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), which are major non-invasive diagnostic measures of PM/DM (3). However, since laboratory indicators do not accurately distinguish between inflammatory and non-inflammatory myopathies, results of muscle biopsy and electromyography are still important for PM/DM diagnosis (2). A limitation of biopsy is that the results do not always reflect the disease activity and severity in patients with PM/DM, as the distribution of muscle lesions is frequently patchy. In addition, muscle biopsy frequently causes trauma in patients (4,5). [18F]fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) is a non-invasive hybrid imaging modality that combines metabolic evaluation and morphological correlation of pathophysiological processes. The most commonly used radiotracer, FDG, is an analogue of glucose, the uptake of which is proportional to cellular metabolic activity. It is widely used in cancer imaging due to its sensitivity in detecting most malignant cells (6). The uptake of FDG is similar between malignant cells and inflammatory cells. In recent years, PET/CT has also been used to investigate inflammatory diseases, including inflammatory and infectious vascular disease, and inflammatory bowel disease (7,8). The common histopathological presentation of PM/DM includes infiltration of inflammatory cells, and degeneration and regeneration of muscle fibers, with the major muscles involved being the limb girdles, neck and pharynx, although the dominant inflammatory cell types and the typical site of infiltration within the muscle are different between PM and DM (9,10).

It has been suggested that PET/CT imaging has limited value for the evaluation of myositis in patients with PM/DM due to its low sensitivity, although it may be useful for detection of occult malignancies, including bronchogenic carcinoma

and thymic carcinoma in PM/DM patients (11-13). However, muscle biopsy may cause pain and other complications. According to this previous study, the application and benefits of ¹⁸F-FDG PET/CT for detecting PM/DM remain controversial. The present study aimed to investigate the diagnostic value of ¹⁸F-FDG PET/CT in DM and determined its ability to distinguish PM/DM from non-myopathy. In addition, the location of FDG uptake in PM/DM and its ability to indicate muscle biopsy sites were determined.

Materials and methods

Patients. A total of 22 patients (16 females, 6 males) diagnosed with definite or probable PM/DM (the PM/DM group) who underwent ¹⁸F-FDG PET/CT examinations prior to receiving an initial corticosteroid treatment at Tianjin Medical University General Hospital from October 2013 to August 2016 were included in the present study. The same number of age- and sex-matched individuals were included in the non-myopathy control group, who did not exhibit myasthenia, movement disorders, skin rashes, myalgia or elevated levels of serum muscle enzymes. PM/DM was diagnosed according to the criteria published by Bohan and Peter (3) in 1975. The Ethics Committee of Tianjin Medical University General Hospital (Tianjin, China) approved this retrospective study.

PET/CT imaging. PET/CT imaging was performed with a combination PET/CT scanner (Discovery LS; GE Healthcare, Little Chalfont, UK). Case and control groups were examined after fasting for 6 h, and blood glucose was controlled at ≤11.1 mmol/l. PET/CT scans from the skull to the proximal thigh were performed at 60 min after the intravenous administration of 5.5 MBq/kg of FDG. During the 60-min uptake period, the patients were advised to take a rest and remain calm to minimize any non-specific FDG uptake in muscles. PET images were reconstructed with the use of CT data for attenuation correction. Image fusion was performed after transverse, coronal and sagittal section image display. Local delayed imaging was performed at 3 h after radiopharmaceutical uptake on suspicious lesions. One of the experienced nuclear physicians and a radiologist reviewed the images separately. To assess the presence of abnormal ¹⁸F-FDG uptake, the highest level of radioactive concentration was selected to map the region-of-interest and the maximum standardized uptake value (SUV_{max}) was automatically measured. SUV_{max} represented the FDG uptake of seven muscle groups, including the cervical, thoracic, lumbar, upper arm, shoulder, pelvic and thigh regions (14). Areas where the FDG uptake was increased in other anatomical structures were not included. The SUV_{max} was calculated with the following formula: SUV (g/ml) = regional radioactive concentration (Bq/ml)/[injection dose (Bq)/body weight (g)]. The average SUV_{max} of the bilateral muscles was calculated to represent the average FDG uptake of the proximal muscle of the individual patient, and it was referred to as the $SUV_{average}$.

Clinical data. Clinical data from all patients, including sex, age, limb muscle strength, laboratory results, muscle SUV_{max} and $SUV_{average}$ were recorded. Myodynamia (MD) was measured using Manual Muscle Testing (MMT), and

Table I. Diagnostic data of the patients with polymyositis/dermatomyositis.

Parameter	n (%)
Lung manifestations (n=22)	
ILD	16 (72.73)
Lca	1 (4.55)
NR	3 (13.63)
IA	2 (9.09)
Muscle biopsy (n=14)	
MYO	13 (92.86)
IA	1 (7.14)
Electromyography (n=17)	
MI	11 (64.71)
MSI	5 (29.41)
NI	1 (5.88)

ILD, interstitial lung disease; Lca, lung cancer; NR, normal; IA, information absent; MYO, myositis; MI, myogenic injury; MSI, mixed source injury; NI, neurogenic injury.

evaluated with Daniels and Worthingham's Muscle Testing (0-5 scale) (15). In order to locate the muscles that were often involved in PM/DM, the SUV_{max} was measured in the seven aforementioned muscle groups.

Statistical analysis. Statistical analysis was performed using SPSS (version 20; IBM Corp., Armonk, NY, USA) and Graphpad Prism (version 5.0; GraphPad Software, Inc., La Jolla, CA, USA) software. Data fitting a normal distribution are expressed as the mean ± standard deviation and independent-samples t-tests were applied for statistical comparisons. Data that did not follow a normal distribution were expressed as the median and interquartile range (IQR), and the differences between groups were compared using the non-parametric Mann-Whitney U test. Correlation analysis was performed by determining Spearman's correlation coefficients. P<0.05 was considered to indicate a statistically significant difference. Receiver operating characteristic (ROC) curve analysis for the SUV_{average} of the proximal muscle was performed to discriminate between PM/DM and control groups.

Results

Patient characteristics. Of the 22 patients, dermatomyositis was associated with interstitial lung disease in 16, no lung damage in 3 and lung cancer in 1 patient, and for 2 patients, data were not available. Of these patients, 14 cases were subjected to muscle biopsy and 17 received electromyography (EMG). Among the patients with muscle biopsy, myositis-associated changes were detected in 13 and for 1 patient, data were not available. In the patients assessed by EMG, myogenic injury (n=11), mixed-source injury (n=5) and neurogenic injury (n=1) were detected (Table I).

Representative PET/CT images of patients with DM and non-muscular disease are displayed in Figs. 1 and 2 presents the distribution of $SUV_{average}$ in the proximal muscles in the case

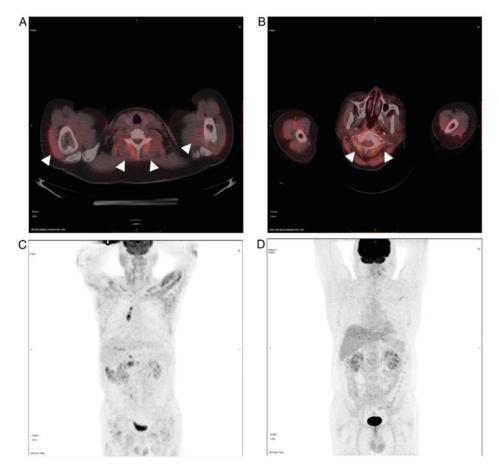


Figure 1. PET/CT images of patients with dermatomyositis and non-muscular disease. (A and B) Representative PET/CT images of different cases are presented. Arrowheads indicate the abnormal uptake of FDG in paravertebral muscles and upper arm regions. (C) MIP image of a representative patient with dermatomyositis. (D) MIP image of a control patient. FDG uptake in the proximal muscle groups is present in the patient with myositis, but not in the control patient. MIP, maximum intensity projection; FDG, [18F]fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

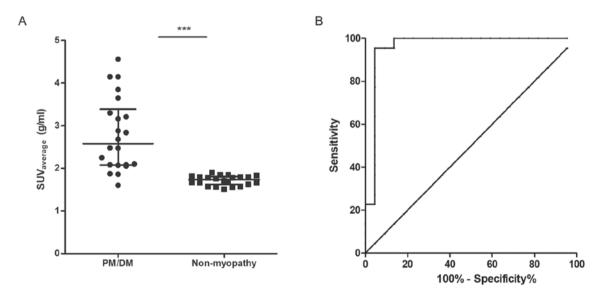


Figure 2. Distribution of $SUV_{average}$ in the proximal muscles compared between the case group and the control group. (A) Comparison of mean proximal muscle SUVs between PM/DM patients and subjects with non-muscular diseases. The horizontal bars represent the median, Q1 and Q3. ***P<0.001. (B) Receiver operating characteristics curve analysis demonstrated an area under the curve of 0.96 (95% confidence interval, 0.89-1.03) for $SUV_{average}$ to discriminate PM/DM patients from subjects without myopathy. An optimal cut-point of $SUV_{average}$ was at 1.86 g/ml, giving the sensitivity of 95.5% and the specificity of 95.5%. The Youden Index was 0.910. $SUV_{average}$, average of the maximum standardized uptake value; PM/DM, polymyositis/dermatomyositis; Q, quartile.

group and the control group. $SUV_{average}$ in the proximal muscle was significantly (P<0.001; Table II) greater in PM/DM patients

(median, 2.58 g/ml; IQR, 2.08-3.39 g/ml) compared with that in patients with non-muscular diseases (median, 1.74 g/ml; IQR,

Table II. Clinical data of the PM/DM patients and non-myopathy group.

Parameter	PM/DM (n=22)	Non-myopathy (n=22)	Normal range	P-value
Age (years)	52.8±13.1	50.1±11.1		0.46
Sex (male/female)	6/16	6/16		1.00
CK (U/l)	211.00 (IQR 1588.75)	60.50 (IQR 36.75)	30-170	< 0.001
CK-MB (U/l)	16.50 (IQR 34.00)	15.50 (IQR 9.25)	0-24	0.072
LDH (U/l)	313.50 (IQR 229.25)	141.00 (IQR 81.00)	94-250	< 0.001
AST (U/l)	40.50 (IQR 70.25)	32.50 (IQR 19.25)	15-46	0.011
SUV _{average} (g/ml)	2.58 (IQR 1.31)	1.74 (IQR 0.19)		< 0.001

Values are expressed as the mean \pm standard deviation, n or the median (IQR). PM, polymyositis; DM, dermatomyositis; IQR, interquartile range; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; SUV_{average}, average of the maximum standardized uptake value.

Table III. Correlation analysis of the SUV_{average} and MD vs. serum enzyme.

Value	CK	CK-MB	LDH	AST	MD
SUV _{average}	r=0.264	r=0.175	r=0.074	r=0.157	r=-0.641
	P=0.235	P=0.437	P=0.757	P=0.509	P=0.004a
CK	/	/	/	/	r=-0.493
					P=0.038b
CK-MB	/	/	/	/	r=-0.056
					P=0.825
LDH	/	/	/	/	r=-0.026
					P=0.918
AST	/	/	/	/	r=-0.126
					P=0.618
CR	r=0.489	r=0.253	r=0.131	r=0.110	r=-0.566
	P=0.021b	P=0.257	P=0.562	P=0.625	P=0.014b
TR	r=0.457	r=0.424	r=0.094	r=0.086	r=-0.622
	P=0.032b	P=0.049b	P=0.679	P=0.704	$P=0.006^{a}$
LR	r=0.503	r=0.442	r=0.212	r=0.416	r=-0.580
	$P=0.017^{b}$	P=0.039b	P=0.344	P=0.054	P=0.012 ^b
UAR	r=0.329	r=0.488	r=0.299	r=0.278	r=-0.341
	P=0.135	P=0.021 ^b	P=0.176	P=0.210	P=0.166
SR	r=0.305	r=0.185	r=0.060	r=0.119	r=-0.619
	P=0.167	P=0.410	P=0.789	P=0.597	$P=0.006^{a}$
PR	r=0.166	r=0.125	r=0.089	r=0.280	r=-0.482
	P=0.460	P=0.580	P=0.695	P=0.207	P=0.043b
Thigh region	r=0.357	r=0.282	r=0.080	r=0.355	r=-0.466
	P=0.103	P=0.204	P=0.722	P=0.105	P=0.051

^aP<0.01, ^bP<0.05. CR, TR, LR, UAR, SR, PR and thigh region represented the values of FDG uptake in regional location. MD was evaluated with Daniels and Worthingham's Muscle Testing (0-5 scale). CR, cervical region; TR, thoracic region; LR, lumbar region; UAR, upper arm region; SR, shoulder region; PR, pelvic region; MD, myodynamia; CK, serum creatine kinase; CK-MB, serum creatine kinase isoenzyme; LDH, serum lactate dehydrogenase; AST, serum aspartate aminotransferase; SUV_{average}, average of the maximum standardized uptake value.

1.62-1.81 g/ml). ROC analysis for the SUV_{average} to discriminate between PM/DM and non-myopathy conditions revealed an area under the curve of 0.96 (95% confidence interval, 0.89-1.03). The optimal cut-point of SUV_{max} was at 1.86 g/ml, giving the sensitivity of 95.5% and the specificity of 95.5%. The Youden

Index was 0.910. The detailed clinical data for the PM/DM and non-myopathy groups are summarized in Table II.

Correlation analysis. Next the correlations between FDG uptake values (SUV_{max} and $SUV_{average}$), serum muscle enzyme

levels and MD were investigated. The SUV_{max} in the cervical, thoracic and lumbar regions all correlated with CK levels in the serum (P<0.05). Similarly, the SUV_{max} in the upper arm, thoracic and lumbar regions was significantly correlated with serum CK-MB levels (P<0.05). However, the $SUV_{average}$ did not correlated with the levels of any serum enzymes (P>0.05). The CK levels in the serum were negatively correlated with muscle strength, which was presented as MD (r=-0.493; P=0.038). However for the other muscle enzymes, no correlation was identified. In addition, the $SUV_{average}$ was significantly negatively correlated with muscle strength (r=-0.641; P=0.004). SUV_{max} in the cervical, thoracic, lumbar, shoulder and pelvic regions was negatively correlated with MD, but that in the upper arm and thigh regions was not (Table III).

Discussion

PM and DM are a group of systemic, non-suppurative inflammatory diseases of the striated muscle. Clinical manifestations include symmetrical limb proximal MD with tenderness (5), increased serum CK and erythrocyte sedimentation rate, and myogenic damage on EMG; furthermore, a good response to glucocorticoid treatment is observed. In the present study, the SUV_{max} of the proximal limb muscles was measured. At the same time, in order to evaluate the overall muscle condition, SUV_{average} on both sides of the seven muscle groups was determined. The present study indicated that the FDG uptake value of PM/DM patients was significantly higher than that of the non-myopathy patients, which is in accordance with the study by Tanaka et al (5). However, in the aforementioned study, mean proximal muscle SUVs were significantly correlated with serum levels of CK (P=0.015). The serum levels of CK and CK-MB were not correlated with the mean SUV_{max} of the proximal muscle in the present results. In the present study, the inflammatory response in each muscular site of the human body was identified to be different; similarly the clinical manifestations in PM/DM tissues were different. The SUV_{average} is not representative of the activity and severity of muscles specifically affected by myositis in patients with PM/DM. The serum CK levels and SUV_{average} were all negatively correlated with MD, which is similar to the results of the study by Tanaka et al (5). It may be inferred that, compared with AST and LDH levels, the serum CK levels and FDG uptake value are more representative and effective to reflect the severity of myositis in patients with PM/DM.

Regarding the comparison between the local muscle groups, the present study indicated that in the PM/DM group, the disease severity was not identical. In addition, SUV_{max} in the cervical, thoracic and lumbar regions was correlated with the CK levels in the serum (P<0.05). This was consistent with the study by Streib *et al* (16), which concluded that, for any patient suspected of having a myopathy, EMG examination should include the paraspinal muscles. A recent study has revealed that anti-M2 antibodies appear to be biomarker associated with the distribution of affected muscles (17). The histological features were compared between myositis patients positive and negative for anti-M2 antibodies (17). It was revealed that inflammation appeared to be more intense in the trunk and to a lesser degree in weak limb muscles (17). The present study is a retrospective analysis, which cannot

be further verified, since the experimental data remains incomplete. Pathology is the bridge of clinical work and basic research. In the diagnosis of muscle disease, muscle biopsy is the major method to determine the nature of the disease, and it is also irreplaceable. However, FDG uptake reflects metabolically active sites, and muscle biopsy may not provide results that are representative of the most affected lesions. The most important advantage of PET/CT is that the entire body may be imaged in one scan. It may directly assess the scope and patterns of muscle lesions, including structures that are not routinely screened in pathological analysis. In the present study, active regions were identified in the paraspinal muscles. Although PET/CT cannot replace muscle biopsy, it may provide novel and more suitable locations for muscle biopsy.

In the present study, serum CK-MB levels were associated with FDG uptake in the muscles of the upper arm, as well as thoracic and lumbar regions, which was inconsistent with the results of Pei et al (18). CK-MB is one of the isoforms of CK and the MB type is mainly present in cardiomyocytes, accounting for >5% of total serum CK. However, there are still 2% CK-MB in skeletal muscle, and total CK is >6% in the case of myocardial damage and <6% in the case of skeletal muscle damage. The increase in CK also leads to an increase in the corresponding proportion of CK-MB. The correlation between CK-MB, CK and SUV_{max} was consistent in two of three regions. One of the positions was inconsistent with regard to the examination of the measurement error of SUV_{max} . In one case of the case group, CK-MB was significantly higher than normal (501 U/l), but total CK was <6% (8,973 U/l), and no complains of palpitation, precordial discomfort or chest pain were reported. Therefore, it was inferred that PM/DM is rarely involves the myocardium.

DM patients frequently have a high risk of occult malignant tumors (10). The present study reviewed PM/DM patients who had been subjected to PET/CT examination to exclude tumors. Of the 22 patients, one had been diagnosed with lung cancer. In this patient, it was observed that the SUV_{max} at each site was significantly higher than that for other myositis patients. This result is similar to that of Selva-O'Callaghan *et al* (19). This may provide a predictive means for patients with myositis combined with tumors, or for patients with myositis who gradually develop tumors (20). However, the sample size in the present study was limited and it is necessary to perform further studies with larger samples in order to provide statistically significant results.

One limitation of the present study was the small number of patients included. This is due to PET/CT not being a common method to diagnose myositis, high cost of examination and shortcomings including low specificity. Magnetic resonance imaging (MRI), may be a suitable method, which may detect muscle edema in diseased muscle, including inflammatory myopathies, with sufficient sensitivity (21). MRI has its limitations, including low specificity and local imaging. Furthermore, certain patients are not suitable for MRI examination, including those with pacemakers. The distribution patterns of the abnormal signals of MRI and PET/CT are different. MRI detects inflammatory edema and PET/CT detects FDG uptake by active inflammatory cells. PET/CT directly assesses the scope and patterns of muscle lesions. As indicated above, PET/CT allows for scanning large areas,

non-invasive examination and relatively high-contrast imaging for evaluation of the muscle status in the whole body. These advantages may indicate its potential clinical application for improving the diagnostic accuracy in DM/PM.

In conclusion, [18F]FDG-PET/CT has a diagnostic value for distinguishing PM/DM from non-myopathy cases, and it may be used for examination to assess the severity of myositis. Furthermore, it may indicate novel and more suitable locations for muscle biopsy in patients with myositis.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

WW and QC designed the study. LS drafted the manuscript. NZ performed the data analysis and interpretation. YD, QC and LS acquired the data. LS, QC, XL and WW revised and reviewed the manuscript. LS, YD, NZ, XL, QC and WW researched the literature. XL also contributed in the analysis of the results. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work.

Ethical approval and consent to participate

The Ethics Committee of Tianjin Medical University General Hospital (Tianjin, China) approved this retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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