Utility of positron emission tomography as a new tool for muscle involvement in patients with idiopathic inflammatory myositis: a controlled study

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Abstract

Objective

Idiopathic inflammatory myositis (IIM) represents a rare group of disease that can affect multiple organs in addition to the muscles. 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is an emerging scanning method that is widely used in diagnosing, staging and response to treatment in patients with cancer. In this study, we aimed to evaluate the muscle involvement in PET/CT which was performed for malignancy screening and its correlation with myositis-specific antibodies (MSA) and/or myositis-associated antibodies (MAA) in patients with IIM.

Methods

IIM patients who fulfilled 2017 EULAR/ACR classification criteria and had PET-CT scans during the active phase of myositis (within two weeks of starting steroids) were included into the study. Age and sex matched participants with history of malignancy (non-IIM patients) were defined as control group.

Results

Data of 160 IIM patients were evaluated and 34 patients (of 64.7% female) whose PET/CT results were available, included into the study. Fourteen patients with diagnosis of malignancy without IIM (non-IIM patients) defined as the control group. Sensitivity and specificity of a positive FDG muscle uptake were 37.1% and 100%, 65.7% and 92.9%, 91.4% and 7.1% compared to liver, mediastinum and LTM uptakes, respectively. In multivariate analysis, higher baseline CRP (p=0.017, confidence interval [CI] 95%: 1.03-1.36, OR:1.18) and LDH (p=0.029, CI 95%:1.001-1.017, OR:1.01) levels were associated with muscle PET/CT positivity.

Conclusion

In patients with active IIM, median muscle FDG uptake with PET/CT was higher compared to non-IIM. PET/CT may be used for the evaluation of extent and activity in patients with IIM.

Key words

idiopathic inflammatory myositis, muscle FDG uptake, positron emission tomography (PET-CT), myositis-specific antibody, myositis-associated antibody

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Introduction

Idiopathic inflammatory myositis (IIM) represents a rare group of diseases that can affect multiple organs in addition to the muscles and may lead to a severe decline in the quality of life (1). IIM were classified into several distinct subgroups such as dermatomyositis (DM), polymyositis (PM), immune-necrotising myopathy and inclusion body myositis (IBM). Historically, clinical features can include muscle weakness, skin disease and can involve internal organs, such as lung and heart (2). A large variety of autoantibodies, directed against cytoplasmic or nuclear components, can now be identified in these patients and many specific clinic-serological syndromes have been described (3, 4). Muscle inflammation can also occur in other connective tissue diseases, including systemic sclerosis, systemic lupus erythematosus and Sjögren's syndrome, in addition to rheumatoid arthritis, the so-called myositis overlaps syndromes. While myositis-associated antibodies (MAA) including anti-Pm-Scl, anti-U1-RNP and anti-Ku are typically associated with myositis-overlap, myositis-specific antibodies (MSA) have also been identified in this patient group (5). In systemic sclerosis, patients with anti-Pm-Scl autoantibodies often have a phenotype similar to the ASS and more likely to have limited cutaneous disease, muscle disease, interstitial lung disease (ILD) and calcinosis (6).

In addition to clinical findings, laboratory findings such as muscle enzymes, histological examination and autoantibodies, imaging methods also play an important role in the diagnosis and management of IIM. Skeletal muscle magnetic resonance imaging (MRI) is a commonly used diagnostic tool to identify muscle inflammation, is also useful to guide muscle biopsy and may demonstrate the pattern of affected muscles beyond clinical appearance, which helps to exclude muscular dystrophies (1). In IIM, muscle oedema is thought to occur early in the disease course, while the appearance of muscle atrophy and fatty replacement are generally late manifestations (7). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is an emerging scanning method that is widely used in diagnosing, staging and response to treatment in patients with cancer. Furthermore, the clinical utility of ^{18}F FDG PET/CT is increasing in large vessel vasculitis (8). ^{18}F-FDG PET/CT is being used to detect malignancy (9, 10), and may be an emerging diagnostic method for muscle involvement in patients with IIM (11-14). Theoretically, ^{18}F-FDG PET/CT has multiple diagnostic purposes for IIM patients: (1) to detect or exclude malignancy, (2) to evaluate the activity of myopathy, (3) to identify interstitial lung disease (15). However, muscle involvement in PET/CT has not been standardised in patients with IIM and has not been validated, so far. Furthermore, association between muscle uptake in PET/CT and MSA and/or MAA is unclear.

In this study, we aimed to evaluate the muscle involvement in PET/CT which was performed for malignancy screening and its correlation with MSA and / or MAA in patients with IIM.

Material and methods

Patients and data

IIM patients who fulfilled 2017 EULAR/ACR classification criteria and had PET-CT scans during the active phase of myositis (within two weeks of starting corticosteroid treatment) were included into this retrospective observational study. Age and sex matched participants with a history of malignancy (non-IIM patients) was defined as the control group. Baseline demographic and clinical features including clinical diagnosis, other organ/system involvement, baseline muscle strength, history of malignancy during to the follow up and laboratory results including muscle enzymes [creatinine kinase (CK; reference value <220 U/L), lactate dehydrogenase (LDH; reference value <250 U/L)], troponin T (reference value <14pg/mL), inflammatory markers [erythrocyte sedimentation rate (ESR; reference value <20 mm/hour), C-reactive protein (CRP; reference value <5 mg/L)], autoantibodies including antinuclear antibody (ANA), MSAs and MAAs as well as muscle

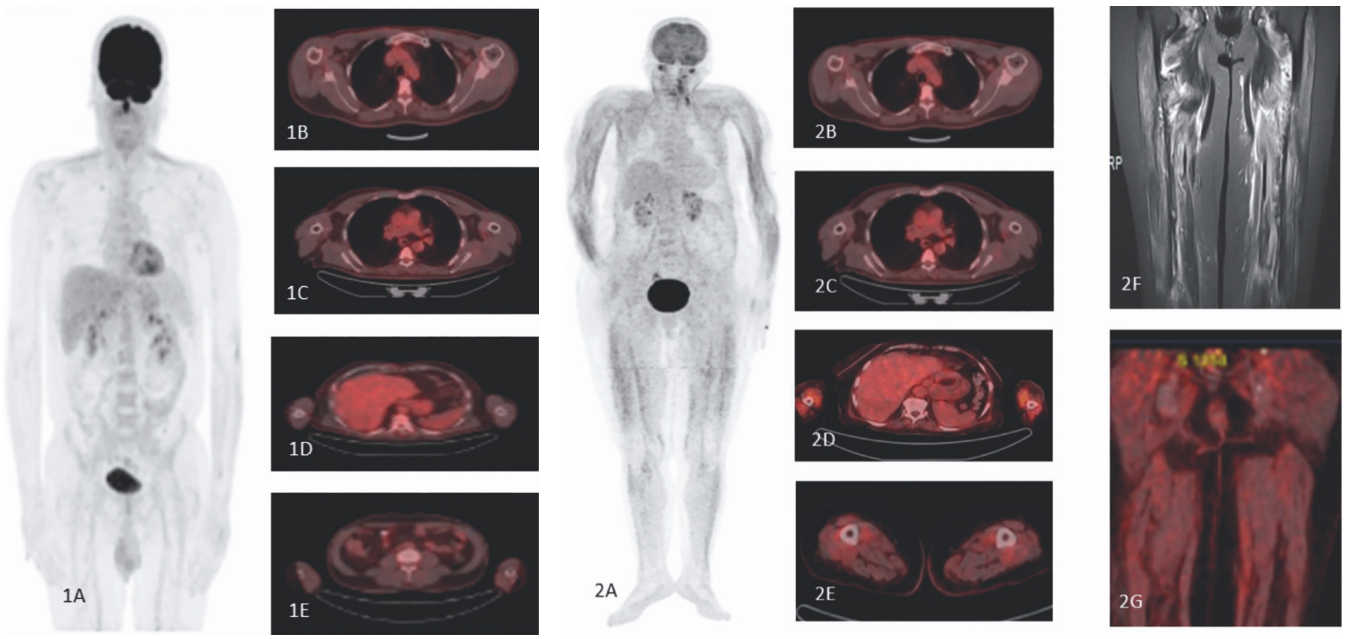

Fig. 1. Negative PET-CT scan for muscle involvement.
A: Axial image of PET-CT. **B**: Deltoid muscle. **C**: Mediastinal blood pool. **D**: Liver. **E**: Lumbal longus muscle.
Fig. 2. Positive PET-CT scan for muscle involvement.
A: Axial image of PET-CT. **B**: Deltoid muscle. **C**: Mediastinal blood pool. **D**: Liver. **E**: Positive PET-CT scan for lower limb (horizontal). **F**: Positive muscle MRI. **G**: Positive PET-CT scan for lower limb (axial).

biopsy, electromyography (EMG) and muscle MRI results during PET-CT scans were obtained from patients charts. EMG positivity was defined as the presence of proximal muscle irritability features compatible with myositis. Muscle strength was evaluated by manual muscle testing (16). Anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-KS, anti-OJ, anti-Ha, and anti-Zo antibodies target aminoacyl tRNA synthetases as well as anti-Mi-2, anti-MDA5 (anti-CADM140), anti-TIF1-gamma (anti-155/140, anti-p155), anti-NXP-2 (anti-MJ), anti-signal recognition particles (anti-SRP), and anti-SAE antibodies were classified as MSAs. ANA, anti-Ro, anti-Ku, anti-U1RNP, and anti-Pm-Scl were considered as MAAs. MSA and MAA assays were performed by using a commercial kit for immunoblot.

Local ethics committee approval and individual written participant consent were obtained for this study (date-number: 22/11/2019-19).

^{18}F-fluorodeoxyglucose PET/CT scan

All patients were fasted at least 6 hours before imaging, and the blood glucose of the patients was controlled below 200 mg/dL. ^{18}F-FDG was injected intravenously at a body weight-adjusted dose (2.5 MBq/kg±10%). Sixty minutes later, the patients lay in a supine position in the examination bed with both upper limbs being placed at the sides of the body. The images between the head and the middle of thigh were acquired by the Discovery IQ Gen2 4 Ring PET/CT Scanner (GE Healthcare, Milwaukee, Wisconsin, USA). After transmission scan, 3-dimensional PET acquisition was obtained for 3 min per bed position for 6–8 bed positions. The image was reconstructed with ordered subset expectation maximisation. The reconstruction parameters of PET were as follows: 2 iterations and 8 subsets and slice thickness of 5 mm. CT acquisition was performed on a six-slice spiral CT with a slice thickness of 4 mm (120–150 kV, 80 mA). Three-dimensional PET, CT, and fusion images were reviewed using dedicated software (Advance Workstation 4.7, GE healthcare).

Definition of muscle involvement

PET/CT scans of IIM patients and non-IIM patients with malignancy as controls were assessed cross-sectionally by two experienced nuclear medicine specialists (EGI and ZGÖ) and decisions were made by consensus. Muscle FDG results were evaluated separately for each muscle compartments such as upper proximal and distal extremity as well as lower proximal and distal extremity. Positive PET/CT for myositis was defined as higher FDG muscle uptake compared to liver, mediastinal blood pool (mediastinum) and longissimus thoracis muscle (LTM) for each muscle compartment. Involvement in any muscle in the relevant compartment was considered positive muscle PET/CT scan. Univariate and multivariate analysis were performed according to FDG uptake compared to mediastinum which was found to have highest diagnostic accuracy. PET/CT results expressed by maximum standardised uptake value (SUV-max) (Fig. 1 and 2).

Statistical analysis

SPSS (Statistical Package for the Social Sciences) 21.0 version (IBM, Armonk, NY, USA) was used for statistical analysis. Descriptive statistics, discrete and continuous numerical variables were expressed as mean, ± standard deviation or median. Categorical variables

were expressed as number of cases and percentages. Cross table statistics were used to compare categorical variables. Normally distributed parametric data were compared with Student's t-test and non-parametric data that did not meet normal distribution were compared with Mann-Whitney U-and Kruskal-Wallis tests. Kaplan-Meier and log-rank methods were used for survival analysis. Multivariable analysis was performed by using logistic regression. Cohen's kappa test was performed to measure agreement between MRI and PET/CT scanning. Receiver operating characteristics (ROC) analysis was performed for sensitivity and specificity analysis. $p<0.05$ value was considered statistically significant.

Results

Data of 160 IIM patients were evaluated and 34 patients (of 64.7% female) whose PET/CT results were available included into the study. Fourteen patients with a diagnosis of malignancy without IIM (non-IIM patients) defined as the control group. Mean age of IIM patients was 55±13 (range: 25-85) years in the study group. Mean patient age and gender distribution were not significantly different between the study and control groups. Median disease duration of IIM patients was 12 (interquartile range [IQR]; 11.5) months. Of those 34 patients, clinical diagnosis of DM was in 25 (73.5%), PM in 8 (23.5%) and immune-necrotising myopathy in one patient (3%). Clinical and laboratory features of the patients with IIM were described in Table I.

In PET-CT evaluation, mean background liver, mediastinum and LTM uptakes were similar in patients with IIM and non-IIM groups. Higher muscle uptake was observed in proximal and distal upper extremities ($p=0.001$ and $p=0.036$, respectively) and lower extremity ($p=0.003$ and $p<0.001$, respectively) in patients with IIM compared to control group (Table II). Seven malignancies were observed in 6 patients (17.7%) after PET/CT scan, and all were in DM patients. Lung cancer in two patients, Chronic lymphocytic leukaemia and prostate cancer in one patient, breast, endometrium, and parotid cancer were detected in one patient. All 3 patients with antibody results were anti-TIF_1 gamma positive (Supplementary Table S1).

Sensitivity and specificity of positive FDG muscle uptake were 37.1% and 100%, 65.7% and 92.9%, 91.4% and7.1 % compared to liver, mediastinum and LTM uptakes, respectively. In univariate analysis; baseline median CK [568 (IQR: 3430) *vs*. 76 (IQR: 75) U/L; $p=0.026$], LDH [568 (IQR: 3430) *vs*.

Table I. Baseline clinical and laboratory characteristics of patients with idiopathic inflammatory myositis.

Variables	Results
Age (years) [mean ± SD (range)]	55±13 (25-85)
Gender, female (n, %)	22 (64.7)
Age of diagnosis [mean ± SD (range)]	52.8±13.7 (24-82)
Disease duration [median (IQR)]	12 (12.75)
Clinical characteristics (n, %)	
Muscle weakness (n=30)	22 (73.3)
Dysphagia (n=32)	11 (34.4)
Respiratory muscle weakness (n=32)	2 (6.3)
Arthritis (n=32)	6 (18.8)
Raynaud phenomenon (n=32)	4 (12.5)
Constitutional symptoms (n=32)	11 (34.4)
Lung involvement (n=32)	4 (12.5)
Malignancy (n=32)	8 (25)
Baseline CK levels [median (IQR)]	203 (2296)
Baseline ESR levels [median (IQR)]	22 (18)
Baseline CRP levels [median (IQR)]	7.5 (11.75)
Baseline LDH levels [median (IQR)]	316 (564)
Baseline troponin levels [median (IQR)]	124 (941)
CK levels at last visit [median (IQR)]	58 (74.5)
Positive electromyography (n=25)	20 (80)
Positive muscle MRI (n=24)	19 (79.2)
Positive Muscle biopsy (n=13)	10 (76.9)
Diagnosis (n, %)	
Dermatomyositis	25 (75.8)
Classical	19 (76)
ASS/overlap myositis	1 (4)
Amyopathic	5 (20)
Juvenile	0
Polymyositis	8 (24.2)
Classical	6 (75)
ASS/overlap myositis	2 (25)
Necrotising myositis	1 (2.9)
Autoantibodies (n, %)	
Myositis-associated antibodies (MAA)	
Anti-nuclear antibody (n=30)	17 (56.7)
Anti-SSA (n=31)7	(22.6)
Anti-Ku (n=18)	2 (11.1)
Anti-PM-SCL (n=18)	0
Myositis-specific antibodies (MSA)	
Anti-Jo1 (n=31)	3 (9.7)
Anti-Mi2 (n=18)4	(22.2)
Anti-TIF1 gamma (n=18)	8 (44.4)
Anti-MDA5 (n=18)	0
Anti-NXP2 (n=18)	1 (5.6)
Anti-SAE1 (n=18)	1 (5.6)
Anti-SRP (n=18)1	(5.6)
Anti-PL7 (n=18)0	
Anti-PL12 (n=18)	0
Anti-EJ (n=18)	0
Anti-OJ (n=18)	0
Relapse (n=32)	7 (21.9)
Mortality (n=34)	6 (17.6)

SD: standard deviation; IQR: inter quartile range; CK: creatinine kinase; LDH: lactate dehydrogenase; ESH: erythrocyte sedimentation rate; CRP: C-reactive protein; EMG: electromyography; MRI: magnetic resonance imaging; ASS: anti synthetase syndrome, ANA: anti-nuclear antibody; MAA: myositis-associated antibodies; MSA: myositis-specific antibodies.

Table II. Comparison of PET-CT findings between patients with IIM and control group.

Variables	IIM (n=34)		Control (n=14)		*p*-value
Age (mean±SD; range)	55±13	(25-85)	49.2±10.7	(34-72)	0.2
Gender, female (n, %)	22	(64.7)	8	(57.1)	0.6
Liver (SUV-max) (mean±SD; range)	3.1±1.2	(0.38-7.30	3.6±0.55	(2.6-4.6)	0.14
Mediastinum (SUV-max) (mean±SD; range)	2±0.85	(0.3-5.2)	2.1±0.36	(1.4-2.8)	0.7
Longissimus thoracic muscle (SUV-max) (mean±SD; range)	1.28±0.6	(0.15-2.7)	1.13±0.3	(0.7-1.6)	0.4
Proximal upper extremity (SUV-max) (median; IQR)	1.7	(1.36)	1.15	(0.35)	***0.001****
Distal upper extremity (SUV-max) (median; IQR)	1.7	(1.28)	1.2	(0.3)	***0.036****
Proximal lower extremity (SUV-max) (median; IQR)	1.8	(1.28)	1.3	(0.42)	***0.003****
Distal lower extremity (SUV-max) (median; IQR)	1.9	(2.2)	1.2	(0.4)	***<0.001****
Liver (n, %)	13	(37.1)	0		***0.01***§ ***(OR:7.1)***
Proximal upper extremity	5	(15.6)	0		0.1
Distal upper extremity	6	(18.8)	0		0.16
Proximal lower extremity	7	(21.9)	0		0.083§
Distal lower extremity	4/23	(17.4)	0		0.3
Mediastinum (n, %)	23	(65.7)	1	(7.1)	***<0.001***§ ***(OR:13.7)***
Proximal upper extremity	14	(43.8)	0		***0.004***§ ***(OR:8.8)***
Distal upper extremity	12	(37.5)	1	(7.7)	0.07§
Proximal lower extremity	14/32	(43.8)	0		***0.004***§ ***(OR:8.8)***
Distal lower extremity	12/23	(52.2)	0		0.053§
Longissimus thoracic muscle (n, %)	32	(91.4)	13	(92.9)	0.9
Proximal upper extremity	28	(87.5)	7	(50)	***0.01***§ ***(OR:7.5)***
Distal upper extremity	26	(81.3)	7/13	(53.8)	0.076§
Proximal lower extremity	28/32	(87.5)	12	(85.7)	0.9
Distal lower extremity	20/23	(87)	2/5	(40)	***0.05***§ ***(OR:5.4)***
PET positivity (n, %)					
Liver	13	(37.1)	0		***0.01***§ ***(OR:7.1)***
Mediastinum	23	(65.7)	1	(7.1)	***<0.001***§ ***(OR:13.7)***
Longissimus thoracic muscle	32	(91.4)	13		0.9
Overall (Liver and/or mediastinum)	23	(67.6)	1	(7.1)	***<0.001 (OR:14.5)***

*Mann-Whitney U-test; §Fisher's exact test.
IIM: idiopathic inflammatory myositis; SD: standard deviation; IQR: inter quartile range; PET: positron emission tomography.

76 (IQR: 75) U/L; *p*=0.026], and CRP [8.5 (IQR: 26) *vs*. 1.9 (IQR: 7.3) mg/L; *p*=0.032] levels and positive muscle MRI [89 % (n=16) *vs*. 50% (n=3); *p*=0.04; OR:4.1] were higher in patients who had PET/CT positivity than those without. Although PET-CT positivity was higher in patients with positive muscle biopsy [80% (n=8) *vs*. 33% (n=1); *p*=0.1], it did not reach statistical significance. Muscle FDG uptake did not differ between patients with positive EMG and those without [79% (n=15) *vs*. 83.3% (n=5); *p*=0.8]. PET/CT positivity did not differ according to clinical diagnosis (DM *vs*. PM [60% (n=15) *vs*. 87.5% (n=7); *p*=0.15], presence of malignancy [70% (n=7) *vs*. 70 % (n=16); *p*=1], development of relapse [57.1% (n=4) *vs*. 72% (n=18); *p*=0.45] and mortality [100% (n=6) *vs*. 60% (n=17); *p*=0.15]. Significant agreement was observed between PET-CT positivity and positive lower proximal extremity MRI (kappa=0.412; *p*=0.04) (Table III). PET/CT positivity was not different among certain autoantibody profile such as ANA, anti-Jo1 and other MAA and MSAs (Table III, and Suppl. Tables S2 and S3).

In correlation analysis, age of diagnosis (r=0.620, *p*<0.001), LDH levels were positively (r=0.393, *p*=0.035) and baseline muscle strength (r=-0.411, *p*=0.04) was negatively correlated with muscle FDG uptake in upper extremity. Only age at diagnosis was correlated with FDG uptake in upper and lower proximal extremity (r=0.566, *p*=0.001 and r=0.463, *p*=0.01, respectively). Age of diagnosis (r=0.382, *p*=0.037) and baseline troponin levels were correlated with highest FDG uptake (r=619, *p*=0.01). There was no correlation between FDG uptake and baseline CK, CRP and ESR levels (Table IV).

In multivariable analysis, higher baseline CRP (*p*=0.017, confidence interval [CI] 95 %: 1.03–1.36, OR:1.18) and LDH (*p*=0.029, CI 95 %: 1.001–1.017, OR:1.01) levels were associated with muscle PET/CT positivity. Survival analysis revealed no difference between patients with PET/CT positivity and others (Log-Rank: *p*=0.15).

In ROC analysis, although there was no significant cut-off value of FDG uptake for upper proximal extremity (Area under curve [AUC]:0.883, *p*=0.052, 95% CI: 0.678–1.0) (Fig. 3); a cut-off value 1.2 SUV-max (AUC: 0.933, *p*=0.028, 95% CI: 0.79–1) with 90% sensitivity and 66.7% specificity (LR: 2.7) for lower proximal extremity (Fig. 4) was calculated for muscle FDG uptake. Additionally, cut-off values of CRP (Suppl. Fig. S1) 4.5 mg/L (AUC: 0.811, *p*=0.007, 95% CI: 0.64–0.98) with 72.2% sensitivity and 70% specificity (LR: 2.4) and CK 1316 U/L (AUC: 0.760, *p*=0.016, 95% CI: 0.59–0.94) (Suppl. Fig. S2) with 45.5% sensitivity and 91% specificity (LR: 5) for predicting muscle PET/CT positivity were calculated. No cut-off value was observed in LDH, ESR and troponin levels for predicting muscle PET/CT positivity.

Discussion

Imaging methods are frequently used in patients with IIM for detecting muscle inflammation, differentiation from metabolic myopathies and assessment of interstitial lung disease and/or heart involvement as well as malignancies. ^{18}FDG-PET/CT is an emerging imaging method and is widely used for screening malignancy in patients with IIM

Table III. Univariate analysis of clinical and laboratory characteristics of patients with IIM according to PET-CT findings.

Variables	Overall PET/CT positivity			Liver			Mediastinum		
	Yes (n=23)	No (n=11)	*p*value	Yes (n=13)	No (n=21)	*p*value	Yes (n=23)	No (n=11)	*p*value
Age (years) (mean±SD; range)	54.3±11.9	56.5±15.4	0.6	54.4±12.1 (49-72)	55.4±13.8 (25-85)	0.8	54.3±11.9 (49-74)	56.5±15.4 (25-85)	0.6
Gender (n, %)									
Female	13 (59.1)	9 (40.9)	0.15	7 (31.8)	15 (68.2)	0.3	13 (59.1)	9 (40.9)	0.15
Male	10 (83.3)	2 (16.7)		6 (50)	6 (50)		10 (83.3)	2 (16.7)	
Baseline CK levels (U/L) (median; IQR)	568 (3430)	76 (75)	***0.015***	434 (3874)	115 (1908)	0.08	568 (3430)	76 (75)	***0.015***
Baseline LDH levels (U/L) (median; IQR)	318 (612)	236 (496)	0.5	316 (452)	388 (630)	1	318 (612)	236 (496)	0.5
Baseline ESH levels (mm/hour) (median; IQR)	21.5 (20)	23 (11)	0.9	28.5 (21.3)	22 (18)	0.2	21.5 (20)	23 (11)	0.9
Baseline CRP levels (mg/L) (median; IQR)	8.5 (26)	1.9 (7.3)	***0.006***	13.5 (42)	4 (7)	***0.01***	8.5 (26)	1.9 (7.3)	***0.006***
Baseline troponin levels (pg/mL) (median; IQR)	519 (1150)	24 (61)	0.13	833 (2429)	72 (540)	0.1	519 (1150)	24 (62)	0.13
CK levels at last visit (U/L) (median; IQR)	66 (153)	45 (91)	0.14	72 (667)	54.5 (67)	0.5	66 (153)	45 (91)	0.14
Positive muscle MRI (n, %)									
Yes	16 (88.9)	2 (11.1)	***0.412** (OR:4.1) (p=0.04)***	10 (90)	1 (10)	0.2** (p=0.2)	16 (89)	2 (11)	***0.412** (OR:4.1) (p=0.04)***
No	3 (50)	3 (50)		1 (20)	4 (80)		3 (50)	3 (50)	
Mortality (n, %)									
Yes	6 (100)	0	0.15*	5 (83)	1 (17)	0.02* ***(OR:6.3)***	6 (100)	0	0.15
No	17 (60.7)	11 (39.3)		8 (29)	20 (71)		17 (60)	11 (40)	

SD: standard deviation; IQR: inter quartile range; CK: creatinine kinase; LDH: lactate dehydrogenase; ESH: erythrocyte sedimentation rate; CRP: C-reactive protein; MRI: magnetic resonance imaging.
*Fisher's exact test, **kappa test.

Table IV. Correlation analysis between clinical and laboratory features and PET findings.

Variables	Regions of muscle uptake									
	upper extremity proximal		upper extremity distal		lower extremity proximal		lower extremity distal		Highest uptake	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Age of diagnosis	0.620	***<0.001***	0.566	***0.001***	0.463	***0.01***	-0.056	0.8	0.382	***0.037***
Baseline CK levels	0.222	0.2	0.238	0.2	0.143	0.4	0.199	0.4	0.275	0.13
Baseline LDH levels	0.393	***0.035***	0.334	0.077	0.283	0.1	0.270	0.2	0.334	0.077
Baseline ESR levels	-0.047	0.8	-0.015	0.9	-0.086	0.7	-0.004	1	-0.109	0.6
Baseline CRP levels	0.207	0.3	-0.05	0.8	0.112	0.6	0.091	0.7	0.143	0.5
Baseline troponin levels	0.373	0.15	0.368	0.2	0.360	0.2	0.146	0.1	0.619	***0.01***
Muscle strength										
upper extremity	-0.411	***0.04***	-0.154	0.5					-0.129	0.5
lower extremity					-0.103	0.6	-0.001	1	-0.04	0.8

CK: creatinine kinase; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

(15) (17). Furthermore, it has recently also been used for evaluation of muscle inflammation in patients with IIM (11). The potential advantage of PET/CT is to evaluate whole-body inflammatory muscle lesions and other organ involvement in addition to malignancy screening. Despite its advantages, it is still unclear which structures should be used for comparison of FDG uptake in the evaluation of muscle involvement. Some organs and/or compartments are potential candidates for reference values such as liver, mediastinal blood pool and LTM. Different reference points were used previously and currently there is no consensus on this issue. Martis *et al*. (18), suggested a proximal muscles/LTM SUV-max ratio had a diagnostic accuracy of 50% sensitivity and 83.3% specificity whereas mediastinal blood pool was used by Tateyama *et al*. (11) and liver was used as a reference point by Matuszak *et al*. (19). The main limitation of these studies was the lack of comparison of different reference points. Firstly, we

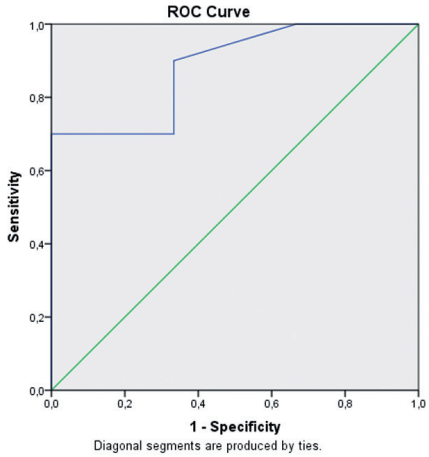

Fig. 3. ROC curve of muscle FDG uptake in upper proximal extremity according to muscle biopsy.
AUC: 0.883, p=0.052, 95% CI: 0.678-1.0.

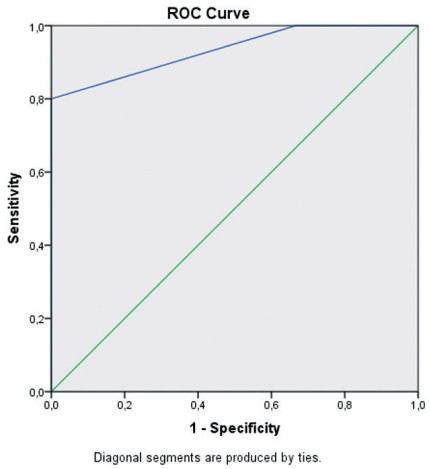

Fig. 4. ROC curve of muscle FDG uptake in lower proximal extremity according to muscle biopsy.
AUC: 0.933, p=0.028, 95% CI: 0.794-1.0.

evaluated the potential candidate reference structures (liver, mediastinal blood pool and LTM) that previously described and thereafter, we performed further analysis based on mediastinal blood pool that had the highest diagnostic accuracy in our study.

MRI has been a standard method for the assessment of muscle inflammation and also useful to assess the disease activity (activity *vs*. damage) and guiding for muscle biopsy in patients with IIM. Despite lack of standardisation, muscle MRI is used widely in daily practice in patients with IIM (20). On the other hand, comparison of muscle MRI and PET/CT for detection of myositis is an emerging issue and there are few studies with conflicting results. In the Tanaka *et al*. study, sensitivity of PET/CT for reflecting muscle inflammation was higher than muscle MRI (12). In a study by Owada *et al*., sensitivity of PET/CT (33%) was lower than muscle MRI (51%), EMG (74%) and muscle biopsy (100%) (14) which was contrary to the former study. In our study, we found a significant agreement of PET/CT positivity with muscle MRI. Significant concordance between PET/CT and muscle MRI was also established in another study (11). Pipitone *et al*. could not show correlation between PET/CT and muscle strength, muscle enzymes and MRI findings; possibly due to low number patients included into the study (21). We also assessed the relationship with muscle pathology and PET/CT finding, however no association was observed. There were inconsistent results in association between muscle PET/CT and muscle pathology findings in the literature. A significant correlation was reported between PET/CT and muscle pathology findings in only one study (12). Furthermore, muscle FDG uptake values were correlated with myositis histological scores in another study (r=0.60, p=0.0002) (11). On the other hand, no association was observed between PET/CT results and muscle histological findings in the study by Owada *et al*. (14) which were compatible with our results. This issue still needs to be answered in the future.

In this study, we found higher baseline CK and CRP levels in patients with PET/CT positivity for myositis in the univariate analysis; however only CRP and LDH levels were associated with PET/CT positivity in patients with IIM in multivariable analysis. Correlation of muscle FDG uptake with muscle strength as well as muscle enzymes and CRP in our study are also compatible with these findings. In the Tanaka *et al*. study, serum CK and aldolase levels as well as muscle strength were significantly correlated with PET/CT positivity which were consistent with our results (12). In the Motegi *et al*. study, CK (r=0.478, p<0.05) but not CRP levels were correlated with muscle FDG uptake in patients with DM (22). Furthermore, in the Li *et al*. study, PET/CT positivity was negatively correlated with muscle strength (r=-0.605, p<0.001) which was consistent with our results (15). In Matuszak *et al*., the authors also concluded that PET/CT may be a good biomarker for monitoring disease activity in patients with IIM (19). It is not surprising that high CRP values are associated with PET/CT positivity as a reflection of muscle inflammation in our study. These results indicate that PET/CT may be useful in screening disease activity in addition to its diagnostic role in IIM patients.

In our study we also established a cut-off value of 1.2 SUV-max for positive muscle inflammation by PET/CT in lower proximal extremities. In Sun *et al*. study, a cut-off value of SUV-max was 1.86 with 95.5% sensitivity and 95.5% specificity (AUC: 0.96, 95% CI: 0.89–1.03) (23). A median SUV-max threshold of 0.66 differentiated high muscle disease activity from low or no muscle disease activity with 92.3% sensitivity in another study (19). Various cut-off values for muscle FDG uptake in different studies may be due to difference in the definition of muscle PET/CT positivity according to various reference points such as liver, mediastinal blood pool and LTM. Further studies are needed to establish the best reference point for the highest most diagnostic performance.

In our study, we observed no association between various autoantibodies such as ANA, MSAA and MSAs and pattern of PET/CT positivity. This finding may be due to the presence of relatively few patients with autoantibody results. The association of muscle PET/CT involvement and autoantibody status is unknown in patients with IIM. Moreover, current study revealed lack of association between muscle PET/CT involvement and presence of malignancy, relapse as well as mortality. In the Owada *et al*. study, there was no significant relationship between FDG muscle uptake and the presence of ILD, anti-Jo-1 positivity and malignancy which were consistent with our results (14). The literature contains limited evidence about these issues and future studies are needed.

This study has some strengths and limitations. Comparison of clinical and laboratory findings including broad

autoantibody profiles with PET/CT results is an advantage. Providing cut-off values for CRP and CK levels to predict PET/CT positivity as well as cut-off value for FDG muscle uptake are other strengths of our study. Furthermore, comparison of various candidate reference structures and different limbs of muscle FDG uptake were performed for the best diagnostic accuracy. The main limitation is the retrospective design of the study. Additionally, presence of low number of patients who had MSAs and MAAs is another limitation to make it difficult in comparison among relevant subgroups. Since PET/CT has been implemented in our daily clinical practice in recent years, in this retrospective study, it could not be possible to screen all patients with PET/CT prior of induction therapy. The inclusion of patients in the study over a long period may have led to missing information in the patient histories and variations in the standard of care. However, patient assessment and follow-up were performed by the same rheumatologists (MI and AG) during this period, and data were collected using a predefined protocol to minimise these disadvantages.

Conclusion

In patients with active IIM, median muscle FDG uptake with PET/CT was higher compared to non-IIM reflecting muscle inflammation. Muscle FDG values compared to mediastinal blood pool had the highest diagnostic accuracy for myositis compared to liver and longissimus thoracis muscle. PET/CT positivity were associated with biomarkers of inflammation and elevated muscle enzymes and correlated with muscle enzyme levels and clinical activity. PET/CT may be used for the evaluation of extent and activity in patients with IIM although further prospective research is needed.

Take home messages

- PET-CT may be helpful for evaluation of muscle inflammation beyond screening for malignancy in patients with idiopathic inflammatory myositis.
- Mediastinal blood pool had the best diagnostic accuracy compared to liver and longissimus thoracis muscle.

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