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¹⁸F-Fluorodeoxyglucose positron emission tomography for the assessment of myositis: a case series

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ABSTRACT

Objective. To establish whether ¹⁸F-Fluorodeoxyglucose (FDG) positron emission computerised tomography (FDG-PET/CT) might reveal active disease in patients with myositis.

Methods. We studied 12 patients with active myositis (2 polymyositis, 10 dermatomyositis). The controls consisted of 14 randomly chosen subjects without muscle disease. FDG uptake was expressed as the ratio of maximum proximal muscle to liver standardised uptake value. Magnetic resonance of the thigh and pelvic floor muscles was performed on a 1.0 or 1.5T scanner using a surface coil. Oedema (1 = present, 0=absent) was assessed by fat suppressed sequences in 17 muscles and a score (0-17) calculated by adding the separate scores. Muscle strength was evaluated in 12 muscle groups by manual muscle test and graded according to the extended Medical Research Council scale (0-5).

Results. FDG uptake in proximal muscles was significantly higher in patients with myositis (median 0.58, interquartile range 0.52) than in those without (median 0.30, interquartile range 0.09; p<0.001 Mann-Whitney U-test). FDG muscle uptake in patients with myositis did not correlate with disease duration, creatine kinase levels, muscle strength, or magnetic resonance scores.

Conclusions. FDG-PET/CT can reveal FDG uptake by affected muscles of patients with myositis and might potentially be useful to assess myositis activity.

Introduction

The idiopathic inflammatory myopathies (IIM) are chronic inflammatory muscle disorders that comprise dermatomyositis (DM) and polymyositis (PM). Assessing IIM disease activity is challenging because there are no fully validated measures to capture disease activity and because muscle weakness may result from disease activity, chronic damage, or a combination of both. FDG-PET/CT is a nuclear medicine technique that detects increased uptake of a fluorine-labelled glucose analogue

(FDG) by metabolically active cells at sites of neoplasm, infection, and inflammation (1). This study aimed to establish whether FDG-PET/CT could reveal active disease in patients with myositis. To this end, we a) compared FDG uptake in proximal muscles of patients with active IIM with that of patients without muscle disease and b) looked for correlations between FDG-PET/CT findings and imaging, clinical, and laboratory data.

Patients and methods

We studied 12 patients with active IIM (2 PM and 10 DM, three with an associated neoplasm) diagnosed using the Bohan and Peter criteria (2) (Table I). Median disease duration was 10 months (interquartile range [IQR] 19). The controls consisted of 14 randomly chosen patients without apparent muscle disease, 4 of whom turned out to have a localised tumour on FDG-PET/CT. Patients and controls had similar ages (median 59.8 vs. 63.5 years, respectively). Eleven patients and 6 controls were female (p=0.015, Fisher's exact test).

All subjects were kept fasting for ≥ 6 hours before FDG injection. Blood glucose levels before FDG injection were ≤120 mg/ml in all cases. Mean time from injection to acquisition was 60±10 minutes. During this uptake period patients were kept resting to minimise non-specific FDG muscle uptake. Just before acquisition the patients were invited to void the urinary bladder. 3D whole-body FDG-PET/CT was performed (mid-femora to external auditory meatus; bed acquisition time: 3.5') using a Discovery GE-DSTE PET/CT system (GE Healthcare, Milwaukee, Wisconsin, US). Transaxial, coronal and sagittal images were reconstructed using standard company reconstruction algorithms.

A semiquantitative evaluation of the images was performed by means of maximum Standardised Uptake Value (SUV) bilaterally in the proximal muscles of upper limbs, lower limbs, and in the liver, and the muscle/liver SUV ratio was calculated. The volume used to measure SUV (660 mm³) was selected automatically by the PET/CT software. To increase the accuracy of the measurements, approximately five different areas of each proximal mus-

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Table I. Bohan and Peter criteria for the classification of DM and PM (2).

- Symmetrical weakness of the limb girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement
- Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemmal nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and inflammatory exudate, often perivascular
- Elevation in serum of skeletal muscle enzymes, particularly the CK and often aldolase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) and lactate dehydrogenase (LDH)
- 4. Electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre, high frequency repetitive discharges
- 5. Any one of the characteristic dermatologic features of the rash of DM

The Bohan and Peter criteria require the presence of two of the first four items for a diagnosis of "possible" PM, three for a diagnosis of "probable" PM, and four for a diagnosis of "definite" PM. A diagnosis of "possible", "probable", and "definite" DM can be made if item 5 is fulfilled plus one, two, and three of the first four items, respectively.

Table II. Clinical, laboratory, and imaging data of patients with idiopathic inflammatory myopathies. FDG-PET/CT proximal muscle uptake was expressed as muscle/liver SUV ratio averaged over the four limbs. For further details, see *Patients and methods*.

Diagnosis	FDG muscle uptake	MR score	MMT (0-5)	CK (U/l)	ANA	ENA	Immuno- suppressive treatment	Treatment duration before FDG-PET/CT
PM	0.58	10	4.49	4326	NEG	NEG	MTX 7.5 mg/week	1 month
РМ	0.57	8	4.38	1662	1/1260 Fs.	NEG	MTX 15 mg/week	1 week
DM	0.43	9	3.76	69	1/80 Gran.	NEG	MP 4 mg day	34 months
DM	0.53	5	4.03	343	1/160 Fs.	NEG	PDN 50 mg/day	5 days
DM	0.92	4	4.56	1821	NEG	NEG	nil	n.a.
DM	0.62	17	4.318	137	NEG	NEG	PDN 5 mg - MTX 10 mg/week	PDN 12 months MTX 3 months
DM	0.35	2	4.33	98	1/160 Hom.	NEG	MP 8 mg/day	2 months
DM	1.23	8	4.31	61	1/320 Hom.	NEG	nil	n.a.
DM	1.40	3	4.17	37	NEG	NEG	MP 24 mg/day	7 months
pDM	0.24	0	4.5	41	1/320 Hom.	NEG	PDN 6.25 - MMF 2 g/day	PDN 31 months MMF 13 months
pDM	0.97	9	3.7	765	1/640 Hom.	NEG	PDN 50 mg/day	1 week
pDM	0.46	4	4.34	172	NEG	NEG	PDN 18.75 mg/day	4 months

CK: creatine kinase; ENA: extractable nuclear antigens; FDG: ¹⁸F-Fluorodeoxyglucose; FDG-PET/ CT: ¹⁸F-Fluorodeoxyglucose positron emission computerised tomography; FS: fine speckled: Gran: granular; Hom.: homogeneous; MMF: mycophenolate mofetil; MMT: manual muscle testing; MP: methylprednisolone; MR: magnetic resonance; MTX: methotrexate; n.a.: not applicable; NEG: negative; pDM: paraneoplastic DM; PDN: prednisone.

cle group were sampled and the SUV thus obtained was averaged for each proximal muscle group. A total SUV was then calculated by averaging the values found in the four proximal limb muscles and expressed as the ratio of muscle to liver SUV. Coronal images were used for SUV evaluation because they allow to visualise at the same time the limbs and the liver, while the CT image on the same screen was used to choose the correct muscle regions.

MR of the thigh muscles was performed on a 1.0 or 1.5T scanner (Philips) using a surface coil (Sense-Flex-M). Oedema (1=present, 0=absent) was assessed bilaterally by fat-suppressed sequences in 17 thigh and pelvic floor muscles, i.e. gluteus maximus, quadratus femoris, vastus lateralis, vastus medialis, tensor fasciae latae, rectus femoris, sartorius, gracilis, pectineus, adductor longus, adductor brevis, adductor magnus, short head biceps femoris, long head biceps femoris, semimembranous, semitendinous, and ileopsoas. A MR global oedema score (0–17) was calculated by adding the separate scores bilaterally and dividing them by two (3).

Muscle strength was evaluated in 12 muscle groups (head flexors, head extensors, shoulder abductors, elbow flexors, elbow extensors, wrist flexors, wrist extensors, finger flexors, hip flexors, knee extensors, ankle extensors, and ankle flexors) by manual muscle test (MMT). Muscle strength was graded using the extended 0-5 (0 = no movement, 5=normal strength) Medical Research Council scale (4), translating intermediate points of the scale in decimals as follows: 4+=4.5, 4-=3.66, 3+=3.33, 3-=2.66, 2+=2.33, 2-=1.66 as detailed elsewhere (5).

Creatine kinase (CK) values were expressed in U/l (range 25-140).

Antinuclear antibodies (ANA) were measured by indirect immunofluorescence, while a screen for extractable nuclear antigens (ENA) was performed by ELISA followed (if ELISA was positive) by immunoblot to identify the antibodies to the specific ENA.

FDG-PET/CT, MR, MMT and CK measurement were performed within a week. FDG-PET/CT and MMT were performed by a single examiner, respectively. MR images were blindly scored by two Radiologists, who reached full agreement.

Statistical analysis was done using SPSS version 14.0.

Informed consent was obtained by the patients of the study, which was approved by the local Ethics Committee (Comitato Etico Provinciale di Reggio Emilia, protocol n. 60/2008).

Results

FDG muscular uptake in myositis

FDG uptake was significantly higher in patients with IIM (median 0.58, IQR 0.52) (Table II, Fig. 1-2) compared with subjects without muscle disease (median 0.30, IQR 0.09; p<0.001 Mann-Whitney U-test). Sensitivity and specificity for

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a SUV muscle/liver ratio of 0.45 were 75% and 100%, respectively.

Proximal muscle FDG uptake grade was similar in the proximal muscles of the upper (median 0.64, IQR 0.89) and lower (median 0.55, IQR 0.42) limbs.

Correlation of muscle FDG uptake with parameters of disease activity in myositis

We next sought to establish whether FDG muscle uptake in IIM patients might correlate with disease duration or with parameters of disease activity, including serum CK levels and MMT and MR scores. We found no significant correlation between muscle FDG uptake and any of the above parameters (Spearman's rho p>0.05, Table II).

Discussion

Evaluating disease activity in the IIM is challenging. Serum CK levels do not always reliably reflect disease activity (6), while muscle weakness may result from disease activity, but also from chronic damage. In active myositis, MRI can show inflammatory muscle oedema (7). However, muscle oedema may be absent in patients with active myositis, while patients with inactive myositis may have muscle oedema related to causes different from inflammation (7).

In this pilot prospective study, we aimed to establish whether FDG-PET/CT might have a role in assessing disease activity in patients with myositis. Our main finding is that FDG-PET/CT can accurately distinguish patients with active IIM from subjects without muscle disease. Our results are in agreement with the limited data published so far, which comprise one patient with active DM (8) and one with active PM (9), both of whom had high FDG uptake in proximal limb muscles.

Increased FDG uptake can be observed in normal muscles following physical exercise. However, we believe that the increased FDG uptake seen in our myositis patients truly reflects disease activity for a number of reasons. First, none of our patients engaged in major physical activities prior to undergoing FDG-PET/CT. Second, proximal muscle FDG uptake is distinctively unusual

Fig. 1. Box plot of muscle to liver SUV ratios in patients with myositis and in the controls (median and 95% confidence intervals). For further details, see Patients and methods.



Patients with myositis

Fig. 2. FDG-PET/ CT, Coronal images. Left: patient with dermatomyositis; right: control without myositis. Note the diffuse proximal muscle FDG uptake in the patient with dermatomyositis, but not in the control subject. Also note the different position of the patients (patients undergoing PET/CT are routinely scanned in the "arms up' position, but myositis patients have been scanned arms down to better visualise the muscles).



in healthy subjects, being typically observed only following heavy exercise, e.g. in the thigh muscles after intensive cycling (10). Third, our patients with IIM consistently showed a significantly higher muscular FDG uptake compared with unaffected controls. Mean proximal muscle FDG uptake was similar in the upper and lower limb muscles, consistent with the diffuse and symmetrical involvement of proximal muscles in myositis.

Increased FDG uptake in proximal muscles has also been reported in one patient with statin-related necrotising myopathy (11) and in two patients with chronic sarcoidosis (12, 13). In line

with these observations, we have noted moderately elevated muscle FDG uptake in six patients with heterogeneous muscle complaints (HIV-associated myositis, paraneoplastic myalgia, paraneoplastic myopathy, necrotising myopathy, focal myopathy, and inclusion body myositis, respectively; data not shown). These data suggest that FDG muscle uptake is not specific for myositis, but probably simply reflects the intensity of metabolic activity within the affected muscles including that of infiltrating inflammatory cells.

In our study population, 4 out of the 14 controls and 3 out of the 12 patients with myositis had a tumour. Theoreti-

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cally, tumours might affect muscle SUV determination in two ways: a) by avidly taking up FDG, thus reducing the uptake of FDG by muscles ("steal phenomenon") or b) by causing abnormal FDG uptake in primary tumour lesions or metastases close to the muscles, thus spuriously increasing muscle SUV. However, we think that the presence of tumours is unlikely to have significantly affected our results for a number of reasons. First, only 4 out the 14 patients without myositis were eventually diagnosed as having cancer by FDG-PET/ CT, none of whom had widespread cancer that might have caused a significant "steal effect". Second, in the group of patients with myositis, no significant difference in muscle SUV was found comparing patients with paraneoplastic and non-paraneoplastic myositis (data not shown). Third, we normalised muscle for liver SUV, which reduces the risk that muscle SUV could have been affected by any "steal effect", if present at all. As for point b), none of the patients with tumours had primary tumour lesions or metastases close to the muscles except one patient with paraneoplastic DM, who had a few, scattered bone metastases. However, in this isolated case, the use of PET/CT fusion images allowed us to accurately discriminate FDG uptake by the bone from that by the muscle.

One patient with DM and two patients with non-IIM muscle disorders were taking potentially myotoxic drugs (statin and colchicine). However, they had been taking these drugs for a while without noticeable side effects, while they tended to have lower than average FDG uptake values. Therefore, it is unlikely that intake of these drugs affected FDG-PET/CT muscle findings.

We found no significant correlations between muscle FDG uptake, on the one hand, and disease duration, serum CK levels, and MMT and MR scores, on the other. This lack of correlations could be due to the fact that different disease activity parameters capture different aspects of myositis that are only partially interrelated (3, 6, 14, 15). However, it is just as plausible that we could not find significant correlations because of the small number of patients investigated. These two hypotheses are not mutually exclusive.

In addition to the small sample size, this study has other limitations. Our patients had clinically active myositis, therefore our study cannot address the question of whether FDG-PET/CT might reveal mild muscle inflammation. Negative FDG-PET/CT muscle findings have been reported in a patient with chronic sarcoidosis (16), in one patient with inclusion body myositis, and two patients with the anti-synthetase syndrome (11). These observations may suggest that FDG-PET/CT might have a limited capacity to detect mild degrees of muscle inflammation, however, our study cannot shed light on this point.

In addition, FDG-PET/CT was not repeated after treatment onset in newly diagnosed patients (or after treatment change in relapsing patients), except in one patient suspected to have paraneoplastic DM despite an initial negative screen. In this patient, FDG muscle uptake normalised in parallel with the clinical response to therapy (data not shown). Apart from this anecdotal case, sensitivity to change of FDG muscle uptake could not be evaluated in our patients' cohort.

In conclusion, our findings showed increased FDG uptake by the affected skeletal muscles of IIM patients but not by muscles of patients without muscle disease. These findings suggest that FDG-PET/CT might potentially be useful to assess myositis activity. Larger studies with adequate longitudinal follow-up are required to confirm our findings, to establish whether FDG-PET/CT muscle findings correlate with other measures of disease activity, to compare the performance of FDG-PET/CT to that of MR, and to evaluate sensitivity to change of muscle FDG uptake before and after treatment.

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