

PET/computed tomography shows association between subjective pain in knee joints and fluorine-18-fluorodeoxyglucose uptake

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Objective The aim of this study was to evaluate the capability of fluorine-18-fluorodeoxyglucose (¹⁸F-FDG)-PET/computed tomography (CT) in screening for musculoskeletal inflammation and injury in the knee region.

Methods The study included 12 subjects (6 men and 6 women) who complained of knee pain at rest and 94 controls who did not. Maximum standardized uptake value (SUV)_{max} was calculated for the right and left knees and compared via a 4-point numerical rating scale (NRS) for subjective knee pain. Correlations between SUV values were also evaluated.

Results SUV_{max} was significantly higher in knee joints with resting and/or walking pain than in pain-free knee joints. SUV_{max} in knee joints with walking pain were significantly correlated with NRS category ($\beta = 0.129$, $P < 0.001$).

Conclusion ¹⁸F-FDG-PET/CT may be useful in screening for musculoskeletal inflammation and injury in the knee region. As knee pain is common, especially among elderly individuals, we should consider conducting further examinations when ¹⁸F-FDG uptake is identified in knee joints. *Nucl Med Commun* 41:241–245 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Nuclear Medicine Communications 2020, 41:241–245

Keywords: ¹⁸F-FDG-PET/CT, knee joint, pain, standardized uptake value

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Received 30 October 2019 Accepted 25 November 2019

Introduction

In older people, musculoskeletal pain is common, particularly in the knees. Joint pain is associated with functional limitations and impaired quality of life [1], and knee pain is a major public health issue. It has been suggested that the number of patients with knee pain is increasing in Japan with the advancing age of the population [2,3]. Chronic knee pain associated with aging is generally considered to be an unavoidable consequence of aging, and disrupts basic activities of daily living such as walking and ascending stairs [4].

In the evaluation of early-stage knee disorders, a simple physical examination is performed and radiographs are obtained. These examinations can now be complemented by ultrasound and MRI studies, both of which enable more detailed evaluation [5–11].

Fluorine-18-fluorodeoxyglucose (¹⁸F-FDG)-PET is a recently developed imaging technique that can detect

the rate of glucose metabolism [12,13], which is especially high in tumors [14–16] and in inflammatory cells [17–19]. ¹⁸F-FDG-PET/computed tomography (CT) is a single imaging technique that reveals the morphological and metabolic features of neoplastic lesions, and performs better than MRI for differentiating symptomatic lesions from among the various other lesions present within a particular region [20]. This is because ¹⁸F-FDG-PET reflects the difference in ¹⁸F-FDG uptake between the various tissues and bones based on their activity, and can therefore detect osteoblast activity or increased vascularity of clinical abnormal tissue. The technique also has the advantage of detecting any pathological lesion at a very early stage [21–24].

Furthermore, it has been suggested that incidental uptake of ¹⁸F-FDG may also represent musculoskeletal inflammation and/or injury and may be a marker for joint disease [25]. Our previous study reported that the maximum standardized uptake value (SUV)_{max} was significantly higher in shoulder joints with mild and severe pain at rest compared with those without pain at rest, and that SUV_{max} was significantly higher in shoulder joints with moderate and severe pain during motion compared with

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those without pain during motion [26]. Because knee pain frequently indicates musculoskeletal inflammation and injury, we recruited participants from a general population who participated in an ^{18}F -FDG-PET/CT screening program, and evaluated the relationship between the clinical symptoms and the SUVmax (a semiquantitative parameter of radiotracer uptake: the regional ^{18}F -FDG concentration normalized with the injected tracer dose and subject bodyweight) of knee joints. The aim of the study was to evaluate the capability of ^{18}F -FDG-PET/CT in screening for musculoskeletal inflammation and injury in the knee region.

Materials and methods

Study participants and questionnaire

We initially included 106 consecutive noncancer subjects who underwent PET/CT screening for a cancer check-up at the Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center (Isahaya, Japan) between January 2015 and September 2016. The characteristics of the study participants are listed in Table 1. The age of participants ranged from 27 to 84 years (mean age: 56.7 years). Written informed consent was obtained from all 106 subjects.

The demographic characteristics (e.g. sex, age and medical history) of all study participants were obtained by self-reported questionnaires. Participants also answered questions regarding pain (resting pain and walking pain) in the right and left knees.

Of the 106 subjects, 12 (6 men and 6 women) who complained of joint pain at rest were assigned to the 'rest pain (+) group', and 94 subjects (54 men and 40 women) without pain at rest were assigned to the 'rest pain (-) group'. The participants assigned to these groups were not asked whether they had joint pain on walking. The 212 knees of the 106 subjects were included in further analysis.

Of the 106 subjects, 30 (15 men and 15 women) who complained of joint pain on walking were assigned to the 'walk pain (+) group', and 76 subjects (45 men and 31 women) without joint pain on walking were assigned to the 'walk pain (-) group'. The participants assigned to these groups were not asked whether they had resting pain.

Of the 106 subjects, 35 (19 men and 16 women) with resting pain and/or walking pain were assigned to the 'rest and/or walk pain (+) group'. This group contained the participants with resting pain only, walking pain only, or both. In addition, 71 subjects (41 men and 30 women) without resting or walking pain were assigned to the 'rest and/or walk pain (-) group'.

Among the 212 knees, 19 had resting pain [rest pain (+) knee], whereas 193 knees did not [rest pain (-) knee]; 44 knees had walking pain [walk pain (+) knee], whereas 168 knees did not [walk pain (-) knee]. Furthermore, 52 knees had resting pain and/or walking pain [rest and/or walk pain (+) knee], whereas 160 knees had no pain on resting or walking [rest and/or walk pain (-) knee].

Each participant who complained of knee pain was asked to indicate their perceived degree of pain via a 10-point numerical rating scale (NRS) comprising the following four categories: none (NRS 0), mild (NRS 1–3), moderate (NRS 4–6), and severe (NRS 7–10).

Before the study, ethical approval was obtained from the Ethics Committee of Nagasaki University Graduate School of Medicine (project registration number 14090932-2).

Fluorine-18-fluorodeoxyglucose-PET/computed tomography

The PET/CT study was performed on a PET/CT scanner (Discovery ST; GE Healthcare, Milwaukee, Wisconsin, USA). Imaging was started 50 min after intravenous injection of ^{18}F -FDG through an anterior cubital vein. The injected ^{18}F -FDG dose was determined according to bodyweight (4 MBq/kg), with individual doses ranging from 182.1 to 400 MBq. The subjects fasted for at least 6 h before ^{18}F -FDG injection and the glucose level of each participant was measured by hexokinase UV method before ^{18}F -FDG injection. Participants with a glucose level higher than 200 mg/dL were excluded from the study. The median glucose level of the 106 participants included in the study was 93 mg/dL (range 75–150 mg/dL). All participants were scanned in the supine position with the arms placed along the sides of the body. The image acquisition time was 2.5 min per bed position,

Table 1 Characteristics of the study participants

Variable	Men	Women	All	P value
Age (y)	55.2 ± 11.6	58.7 ± 12.4	56.7 ± 12.0	0.14
Subjects with resting pain, n (%)	6 (10)	6 (13)	12 (11.3)	0.62
Knee joints with resting pain, n (%)	8 (6.7)	11 (12)	19 (9)	0.18
Subjects with walking pain, n (%)	15 (25)	15 (32.6)	30 (28.3)	0.39
Knee joints with walking pain, n (%)	20 (16.7)	24 (26.1)	44 (20.8)	0.23
Subjects with resting and/or walking pain, n (%)	19 (31.7)	16 (34.8)	35 (33)	0.74
Knee joints with resting and/or walking pain, n (%)	26 (21.7)	26 (28.3)	52 (24.5)	0.3
R-SUVmax	1.04 (0.91–1.39)	1.0 (0.84–1.37)	1.03 (0.91–1.37)	0.56
L-SUVmax	1.05 (0.95–1.26)	0.99 (0.84–1.29)	1.03 (0.89–1.27)	0.19

Values are mean ± SD, number (percentage), or median (25th–75th percentile).

L-SUV, left-standardized uptake value; R-SUV, right-standardized uptake value; SUVmax, the maximum standardized uptake value.

with 7–8 bed positions, covering the whole body in three-dimensional mode. The acquisition parameters for dual-detector helical CT were 140 kV, 30 mA, 3.75-mm slice thickness, and pitch of 1.5. Attenuation correction of the PET data was performed with the acquired CT data. The PET/CT images were displayed in the coronal, sagittal, and transaxial planes and viewed on an Xeleris workstation (GE Healthcare, Tokyo). Details of this procedure have been described elsewhere [27,28].

Evaluation of fluorine-18-fluorodeoxyglucose uptake in knee joints

The PET and CT images of each participant were analyzed using a dedicated image analysis program on a personal computer. The PET and CT images were superimposed to form a fused PET/CT image using the Metavol software (www.metavol.org). ¹⁸F-FDG uptake was then quantitatively examined as an index of glucose metabolic activity in the knee joints. The spherical volume of interest (VOI) of 60 mm in diameter was manually placed to roughly enclose the medial, lateral and front side of knee joint. Using a dedicated workstation, the ¹⁸F-FDG uptake in each joint was evaluated and the SUVmax (maximum SUV value within each VOI) of each joint was calculated automatically.

Statistical analysis

Results are expressed as the mean \pm SD or median (25th–75th quartiles). Differences in continuous values between men and women were compared using the *t*-test or the Mann–Whitney U test, and differences between categorized values such as frequency of joint pain were evaluated using the χ^2 test. SUVmax of resting and walking pain were adjusted for age and compared by analysis of covariance (ANCOVA). The correlations of SUVmax with walking pain, adjusted for age, were evaluated by multivariate linear regression analysis. A *P*-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software (v. 22.0 for Windows; SPSS Japan, Tokyo, Japan).

Results

There was no significant difference in average age between men and women (55.2 \pm 11.6 years vs. 58.7 \pm

12.4 years, *P* = 0.14, Table 1). There was no significant difference in the frequencies of resting or walking pain between men and women [6/60 (10.0%) vs. 6/46 (13.0%), *P* = 0.62; and 15/60 (25.0%) vs. 15/46 (32.6%), *P* = 0.39, respectively]. There was no significant difference in the number of knee joints with both resting and walking pain between men and women [8/120 (6.7%) vs. 11/92 (12.0%), *P* = 0.18; and 20/120 (16.7%) vs. 24/92 (26.1%), *P* = 0.23, respectively]. Also, there was no significant difference in the number of knee joints with resting and/or walking pain between men and women [26/120 (21.7%) vs. 26/92 (28.3%), *P* = 0.30].

There was no significant difference in the SUVmax of right knee joints (R-SUVmax) or SUV of left knee joints (L-SUVmax) between men and women [1.04 (0.91–1.39) vs. 1.0 (0.84–1.37), *P* = 0.56; and 1.05 (0.95–1.26) vs. 0.99 (0.84–1.29), *P* = 0.19, respectively]. The SUVmax of knee joints with resting and/or walking pain were significantly higher than those of knee joints without resting and/or walking pain, and remained significant even after adjustment for age. In addition, the SUVmax of knee joints with walking pain were significantly higher than those of knee joints without walking pain, whereas there was no significant difference in the SUVmax of knee joints between those with and without resting pain (Table 2).

Multivariate linear regression analysis adjusted for age and sex revealed that SUVmax of knee joints with walking pain was significantly correlated with NRS category (β = 0.129, *P* < 0.001) (Table 3).

Discussion

PET is commonly used for diagnosing cardiac diseases and tumors, and it is also useful for determining the grade of tumor malignancy. Skeletal muscle activity has been

Table 3 Multivariate regression analysis of standardized uptake value max of knee joints

Variable	β	95% CI	<i>P</i> value
NRS category	0.129	0.072, 0.185	<0.001
Sex	-0.093	-0.174, -0.011	0.026
Age	0.007	0.004, 0.011	<0.001

β , standardized regression coefficient; CI, confidence interval; NRS, numerical rating scale.

Table 2 Types of knee pain and standardized uptake values

Type of pain	SUVmax ^a	<i>P</i> value	<i>P</i> value, age-adjusted		
			Men	Women	All participants
Rest and/or walking pain					
(+)	1.31 (1.02–1.58)	<0.001	<0.001	0.001	<0.001
(-)	1.0 (0.88–1.2)				
Rest pain					
(+)	1.24 (0.97–1.37)	0.17	0.81	0.32	0.5
(-)	1.03 (0.89–1.27)				
Walk pain					
(+)	1.35 (1.0–1.59)	<0.001	<0.001	0.002	<0.001
(-)	1.0 (0.88–1.21)				

SUVmax, the maximum standardized uptake value.

^aMedian (25th–75th percentiles).

examined in vivo by determining the FDG uptake [13], and it has been shown that there is little accumulation of FDG in the muscles, in case that the patient is adequately prepared before injection. Therefore, the combination of FDG-PET and CT imaging in PET/CT assists in the localization of anatomic lesions and may increase the specificity of a diagnosis when compared with using PET or CT alone [29]. The increase in glucose metabolism is not confined to the tumor cells; as it is also apparent in inflammatory cells such as leukocytes, granulocytes, and macrophages, enhanced uptake of the radionuclide helps diagnose infective and inflammatory disorders much more effectively [17,18,30]. Consequently, PET/CT is a highly effective and accurate method for detecting anatomic lesions.

In the present study, SUVmax was significantly higher in knees with resting and/or walking pain than in those without. Takiguchi *et al.* [31] previously reported that SUVmax was significantly lower in the trapezius muscle in subjects with neck/shoulder pain compared with the pain-free group. In contrast, Kubota *et al.* [21] demonstrated that in patients with rheumatoid arthritis, SUVmax was significantly higher in painful/swollen large joints throughout the whole body than in nonpainful/swollen joints. Our previous study reported that SUVmax was significantly higher in shoulder joints that had rest and/or motion pain than in pain-free shoulder joints [26]. To our knowledge, our study is the first to report ^{18}F -FDG uptake in knee joints in participants with knee pain but without rheumatic disorders. The uptake values probably reflect local inflammation and accompanying metabolic activity. When identifying the uptake of ^{18}F -FDG in participants with nonrheumatic disorders, we should consider conducting further examinations, including clinical evaluation of signs and symptoms, radiography, ultrasound, and MRI.

Using the NRS values, we showed that to some extent, the SUV reflects the participant's perception of knee pain, which suggests that the degree of subjective pain may be evaluated by ^{18}F -FDG uptake in the knee region. Masala *et al.* [32] recently reported no significant correlation of changes in SUVmax and intensity of pain in patients with metastatic bone lesions. In addition, Takiguchi *et al.* [31] found a negative correlation between SUVmax in the trapezius muscle and intensity of pain in the neck/shoulder region. In contrast, our previous study demonstrated significantly higher SUVs associated with mild and severe pain at rest in shoulder joints compared with those associated with absence of pain at rest, and significantly higher SUVmax associated with moderate and severe pain on motion in shoulder joints compared with those associated with absence of motion pain [26]. The current results are consistent with those of our previous study, which reported the same trend in a different joint. The NRS value indicates the degree of pain, which suggests that the SUVmax value reflects the degree of

pain. Further studies are needed to clarify the relationship between the perceived degree of knee pain and the SUVmax value.

Several limitations of this study warrant mention. Because we enrolled individuals who participated in cancer screening by PET/CT, selection bias might have occurred at this stage. We did not obtain the final diagnosis of knee pain by conducting further examinations such as knee radiography and MRI. As we used NRS values to evaluate the severity of knee pain, the data are subject to differing perceptions between individuals. In addition, we did not evaluate inflammation markers (such as metalloproteinase-3, tumor necrosis factor- α , and C-reactive protein). Further studies are needed to clarify the mechanism of ^{18}F -FDG uptake in knee joints.

In conclusion, the present findings suggest that ^{18}F -FDG-PET/CT might be useful in screening for musculoskeletal inflammation and injury in the knee region. As knee pain is common, especially among elderly individuals, we should consider undertaking further examinations if ^{18}F -FDG uptake is identified in knee joints, even in patients with nonrheumatic disorder.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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