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Clinical utility of fluoride-18 positron emission tomography/CT in temporomandibular disorder with osteoarthritis: comparisons with ^{99m}Tc -MDP bone scan

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Objectives: The purpose of this study was to compare the clinical utility of fluoride-18 positron emission tomography (^{18}F -PET)/CT with that of conventional ^{99m}Tc -methylene diphosphonate (MDP) bone scan in temporomandibular disorder (TMD) with osteoarthritis.

Methods: 24 patients with TMD who underwent both ^{18}F -PET/CT and ^{99m}Tc -MDP bone scans for diagnostic work-up were enrolled. The temporomandibular joint (TMJ)-to-skull uptake ratio, TMJ-to-muscle uptake ratio and TMJ-to-spine uptake ratio on ^{18}F -PET/CT and the TMJ uptake ratio on bone scan were measured.

Results: Of the 48 TMJs in 24 patients, 35 TMJs were diagnosed as TMD with osteoarthritis, 8 TMJs as TMD with anterior disc displacement (ADD), and the remaining 5 TMJs showed no evidence of TMD (NED). All three uptake ratios on ^{18}F -PET/CT and the TMJ uptake ratio on the bone scan tended to be higher in TMD with osteoarthritis than in TMD with ADD or NED. Receiver operating characteristic (ROC) curve analysis for detecting TMD with osteoarthritis indicated that the TMJ-to-skull uptake ratio, TMJ-to-muscle uptake ratio and TMJ-to-spine uptake ratio on PET/CT (0.819, 0.771 and 0.813, respectively) showed higher area under the ROC curve value than the TMJ ratio on bone scan (0.714). The TMJ-to-skull uptake ratio on PET/CT showed the highest sensitivity (89%) and accuracy (81%) of all uptake ratios.

Conclusions: ^{18}F -PET/CT can help diagnose TMD with osteoarthritis with superior diagnostic ability and is a suitable alternative modality to a conventional ^{99m}Tc -MDP bone scan.

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Introduction

Temporomandibular disorder (TMD) is a generic term used for any clinical problems that concern the

temporomandibular joint (TMJ) and produce orofacial pain and mandibular dysfunction.^{1,2} TMD manifests as headaches, jaw pain, pain of the TMJ and limited mouth opening.^{1,2} Previous studies have reported a prevalence of 20–25% for TMD, and TMD is most common among individuals aged 20–40 years.^{2–4} To standardize the diagnosis and classification of TMD,

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the research diagnostic criteria for temporomandibular disorder (RDC/TMD) were introduced, and the RDC/TMD guidelines classify TMD as associated with a muscle disorder, disc displacement or osteoarthritis.^{5,6} TMD with osteoarthritis is characterized by deterioration and abrasion of articular cartilage and local thickening and remodelling of the underlying bone, frequently accompanied by superimposition of secondary inflammatory changes.⁷ TMD with osteoarthritis can induce physical, behavioural, psychological and social problems; hence, accurate diagnosis and early treatment are essential.⁸

TMD has been evaluated using non-invasive imaging modalities such as planar bone scan and single photon emission CT (SPECT) as well as skeletal radiography, CT and MRI.^{8–12} Because the bone scan can detect the alteration in bone metabolic activity before structural or anatomical bony alterations occur, it can be used for early detection of TMD and has been shown to have high sensitivity for detection of TMD and TMD with osteoarthritis.^{8,10,12} However, recently, the problem of the worldwide shortage of molybdenum-99 has arisen,^{13,14} and fluoride-18 positron emission tomography (¹⁸F-PET) has attracted attention as an alternative modality that has both greater sensitivity and better image quality than those of a conventional bone scan.^{15,16}

In this study, we compare the clinical utility of ¹⁸F-PET/CT with that of a conventional ^{99m}Tc-methylene diphosphonate (MDP) bone scan for detection of TMD with osteoarthritis for using ¹⁸F-PET/CT as an alternative to bone scan.

Materials and methods

Patients

This study was approved by the institutional review board (approval number 2011-39) in our medical centre. 24 patients (3 male and 21 female; mean age, 32 ± 14 years) who underwent ¹⁸F-PET/CT and a conventional ^{99m}Tc-MDP bone scan for diagnostic work-up of TMD were enrolled in this study. Patients with metabolic bone disease or metastatic bone disease were excluded from the study. All patients were willing to participate and provided their written informed consent. Based on symptoms, signs and conventional radiographic images of the patients, all 48 TMJs of the enrolled patients were clinically assessed according to the RDC/TMD guidelines.^{5,6} After clinical assessment, all patients were categorized to three groups: Group 1, myofascial pain only; Group 2, disc displacements only; and Group 3, arthralgia, osteoarthritis or osteoarthrosis. Because there were no patients with arthralgia in the enrolled patients, the TMJ of each patient was classified as TMD with osteoarthritis, TMD with anterior disc displacement (ADD) or as showing no evidence of TMD (NED). The diagnosis of myofascial pain was excluded because myofascial pain is related to soft-tissue pathology.

^{99m}Tc-methylene diphosphonate bone scan

All bone scan images were acquired 4 h after an intravenous injection of 740 MBq (20 mCi) of ^{99m}Tc-MDP. Anterior, right lateral and left lateral view images of the TMJ with a 500 000 count were obtained using a dual-head gamma camera (Vertex V60; ADAC, Milpitas, CA) equipped with a low-energy parallel-hole collimator.

Fluoride-18 positron emission tomography/CT

All ¹⁸F-PET/CT scans were performed using a dedicated PET/CT scanner (Biograph™ 40, Siemens Medical Solutions, Hoffman Estates, IL). The protocol for the ¹⁸F-PET/CT scan was based on the practice guideline of the Society of Nuclear Medicine for ¹⁸F-PET/CT.¹⁷ There was no special preparation of patients before the ¹⁸F-PET/CT scan. PET/CT scanning was performed 40 min after an intravenous injection of 185–370 MBq (5–10 mCi) of ¹⁸F-sodium fluoride. The patients were examined in a supine position with their arms at their sides, and scanning was performed from the skull to the upper thigh. First, CT images were acquired with 50 mA, 120 kV and 5 mm section width parameters. Thereafter, ¹⁸F-PET images were acquired at 2 min per bed position. The CT images were reconstructed on a 512 × 512 matrix and converted using 511 keV equivalent attenuation factors for attenuation correction. The PET images were reconstructed onto a 128 × 128 matrix using the ordered-subsets expectation maximization with an attenuation correction. All ¹⁸F-PET/CT images were reconstructed into transaxial, coronal and sagittal images.

Quantitative analyses of the bone scan and fluoride-18 positron emission tomography/CT images

In order to quantify uptake in the TMJ on the ^{99m}Tc-MDP bone scan, TMJ uptake ratios were calculated for all patients based on the method reported by Lee *et al*.¹⁸ Square regions of interest (ROIs) of 13 × 13 pixels were manually drawn at the right and left TMJs and the parietal skull areas and uptake for each ROI were measured (Figure 1a). Using the ipsilateral parietal skull uptake as the background uptake, we calculated the TMJ uptake ratios as follows:

$$(\text{TMJ uptake ratio}) = (\text{TMJ uptake} - \text{parietal skull uptake}) / (\text{parietal skull uptake})$$

Because the use of quantitative indices such as a standardized uptake value (SUV) has not been validated for the ¹⁸F-PET/CT scan,¹⁷ the TMJ uptake ratios on ¹⁸F-PET/CT scans were calculated using various background regions. Skull uptake, spine uptake and muscle uptake were used to determine background uptake. The TMJ uptake was measured by placing a circular ROI at the site of maximum ¹⁸F uptake on the transaxial images (Figure 1b). To measure the skull uptake, spheroid ROIs were manually drawn at the right and left parietotemporal bones (Figure 1c) and the

Figure 1 Images of a 39-year-old patient who had a diagnosis of temporomandibular disorder with osteoarthritis in the left temporomandibular joint (TMJ) and no evidence of disease in the right TMJ. (a) ^{99m}Tc -methylene diphosphonate bone scan image showed intense uptake in the left TMJ. Square regions-of-interest (ROIs) are drawn in the right and left TMJs and parietal skull areas to calculate uptake ratios. Fluoride-18 positron emission tomography/CT images (b–e) also showed intense uptake in the left TMJ (b). The circles in (b–e) show examples of drawn ROIs to measure the uptake of the left TMJ, skull, spine and muscle, respectively

mean uptake of the ROIs was measured. The average value of the mean uptake at the right and left parieto-temporal bones was used as the skull uptake. The mean uptake of a spheroid ROI at the vertebral body of the cervical spine was used as the spine uptake (Figure 1d). Furthermore, spheroid ROIs were drawn at the right and left gluteus muscles, and the average value of the mean uptake of the right and left gluteus muscles was used as the muscle uptake (Figure 1e). The SUV was

used as a purely descriptive indicator of the uptakes of the TMJ, skull, spine and muscle¹⁷ and was calculated as follows:

$$\frac{[\text{decay corrected activity (kBq) per tissue volume (ml)}]}{[\text{injected fluoride-18 activity (kBq) per body mass (g)}]}$$

Using the uptakes at the TMJ, skull, spine and muscle, the TMJ-to-skull uptake ratio, TMJ-to-spine uptake

Figure 2 ^{99m}Tc -methylene diphosphonate bone scan image (a) and fluoride-18 positron emission tomography (PET) and fused PET/CT images (b) of a 48-year-old female patient who had a diagnosis of temporomandibular disorder (TMD) with osteoarthritis in the right temporomandibular joint (TMJ) and TMD with anterior disc displacement in the left TMJ. Both the bone scan and fluoride-18 PET/CT images show focal intense uptake in the right TMJ, whereas only mild uptake is shown in the left TMJ

Figure 3 Distribution of temporomandibular joint (TMJ) uptake ratio on ^{99m}Tc -methylene diphosphonate bone scan (a), TMJ-to-skull uptake ratio (b), TMJ-to-spine uptake ratio (c) and TMJ-to-muscle uptake ratio (d) on fluoride-18 positron emission tomography/CT in TMJs categorized as temporomandibular disorder (TMD) with osteoarthritis, TMD with anterior disc displacement, and no evidence of TMD. ADD, anterior disc displacement; NED, no evidence of TMD

ratio and TMJ-to-muscle uptake ratio were calculated for each TMJ for all patients.

Statistical analyses

The TMJ uptake ratios in the bone scans and the TMJ-to-skull uptake ratios, TMJ-to-spine uptake ratios and TMJ-to-muscle uptake ratios in the ^{18}F -PET/CT scans were compared between TMJs categorized as TMD with osteoarthritis, TMD with ADD and NED using a Kruskal–Wallis test. Furthermore, Spearman's correlation coefficients were calculated for the three types of TMJ uptake ratios of ^{18}F -PET/CT with regard to the TMJ uptake ratio on the bone scan. Thereafter, the diagnostic accuracy of the TMJ uptake ratio on the bone scan and the TMJ-to-skull, TMJ-to-spine and TMJ-to-muscle uptake ratios on ^{18}F -PET/CT for detecting TMD

with osteoarthritis were compared using receiver operating characteristic (ROC) curve analysis with a calculation of the area under the ROC curve (AUC). All these analyses were performed using SPSS[®] software for Windows (SPSS Inc., Chicago, IL) and *p*-values less than 0.05 were considered statistically significant.

Results

Characteristics of patients

Of the 24 enrolled patients, 19 patients had bilateral TMD and the remaining 5 patients had unilateral TMD. Among the 48 TMJs of the enrolled 24 patients, 35 TMJs were diagnosed as TMD with osteoarthritis, 8 TMJs as TMD with ADD (Figure 2) and 5 TMJs as

NED. Of the five patients with unilateral TMD, three patients had TMD with osteoarthritis and the remaining two patients had TMD with ADD.

The mean SUVs (g ml^{-1}) of skull, spine and muscle uptake on ^{18}F -PET/CT of all patients were 1.27 ± 0.52 (range 0.73–3.12; median 1.21), 5.49 ± 1.51 (range 3.44–9.99; median 5.11) and 0.74 ± 0.12 (range 0.47–0.99; median 0.74), respectively.

The TMD with osteoarthritis had a high TMJ uptake ratio on ^{18}F -PET/CT and on bone scan. The TMJ uptake ratio on bone scan and the TMJ-to-skull uptake ratio, TMJ-to-spine uptake ratio and TMJ-to-muscle uptake ratio on ^{18}F -PET/CT for all enrolled patients are shown in Table 1 (Figure 3). A Kruskal–Wallis test with *post hoc* analysis revealed that all three uptake ratios on ^{18}F -PET/CT were significantly higher in TMJ categorized as TMD with osteoarthritis than in that categorized as TMD with ADD ($p < 0.05$). Furthermore, the TMJ-to-spine uptake ratio in TMD with osteoarthritis was also significantly higher than that in NED ($p < 0.05$). However, the TMJ-to-skull uptake ratio and the TMJ-to-muscle uptake ratio in TMD with osteoarthritis tended to be higher than that in NED, but this difference was not statistically significant ($p > 0.05$). By contrast, only a marginal significance was shown in the TMJ uptake ratio on bone scan ($p = 0.07$), although the TMJ uptake ratio in TMD with osteoarthritis tended to be higher than that in TMD with ADD or NED.

The relationship between uptake ratios on bone scan and fluoride-18 positron emission tomography/CT

There were significant correlations between the TMJ uptake ratio on bone scan and the three uptake ratios on ^{18}F -PET/CT. The TMJ-to-skull uptake ratio on ^{18}F -PET/CT and the TMJ uptake ratio on the bone scan showed the strongest correlation [$p < 0.0001$; Spearman's correlation coefficient $\rho = 0.652$; 95% confidence interval (CI) 0.451–0.790] (Figure 4). The TMJ-to-spine uptake ratio ($p = 0.001$; $\rho = 0.474$; 95% CI 0.220–0.668) and TMJ-to-muscle uptake ratio ($p = 0.01$; $\rho = 0.359$; 95% CI 0.083–0.583) were significantly but weakly correlated with the TMJ uptake ratio.

Receiver operating characteristic curve analysis for the detection of temporomandibular disorder with osteoarthritis

The results of the ROC curve analysis of the uptake ratio on bone scan and on ^{18}F -PET/CT for detecting TMD with osteoarthritis are shown in Table 2 (Figure 5).

Figure 4 Scatter plot showing the correlation between the temporomandibular joint (TMJ) uptake ratio on $^{99\text{m}}\text{Tc}$ -methylene diphosphonate bone scan and TMJ-to-skull uptake ratio on fluoride-18 positron emission tomography/CT. The TMJ-to-skull uptake ratio was significantly correlated with the TMJ uptake ratio

All uptake ratios on ^{18}F -PET/CT had higher AUC values and better accuracy than the TMJ uptake ratio on bone scan (Figure 6). The TMJ-to-skull uptake ratio on ^{18}F -PET/CT had the highest AUC value of all uptake ratios (0.819; 95% CI 0.681–0.915), and, in addition to an optimal cut-off value of 3.3 (sensitivity 89% and specificity 62%), by using a cut-off value of 4.9, the specificity for detecting TMD with osteoarthritis was 100% with a sensitivity of 54%. Furthermore, the TMJ-to-spine uptake ratio had a similar but slightly lower AUC value than the TMJ-to-skull uptake ratio and, in addition to an optimal cut-off value of 0.7 (sensitivity 86% and specificity 54%), by using a cut-off value of 1.0, the specificity was 100% with a sensitivity of 60%.

Discussion

To the best of our knowledge, this study is the first study to evaluate the clinical utility of ^{18}F -PET/CT in patients with TMD. The TMJ-to-skull, TMJ-to-spine and TMJ-to-muscle uptake ratios on ^{18}F -PET/CT tended to be higher in TMJs categorized as TMD with osteoarthritis than in TMJs categorized as TMD with ADD or NED. Furthermore, all three uptake ratios on ^{18}F -PET/CT showed higher AUC values and accuracy

Table 1 The values of the temporomandibular joint (TMJ) uptake ratio on bone scan and the TMJ-to-skull uptake ratio, TMJ-to-spine uptake ratio and TMJ-to-muscle uptake ratio on fluoride-18 positron emission tomography/CT in 48 TMJs of the enrolled 24 patients

Variables	TMD with osteoarthritis (n = 35)	TMD with ADD (n = 8)	NED (n = 5)	p-value
TMJ uptake ratio	2.55 ± 0.72 (median: 2.55)	1.93 ± 0.66 (median: 1.94)	2.05 ± 0.64 (median: 2.15)	0.07 ^a
TMJ-to-skull uptake ratio	5.69 ± 2.89 (median: 5.06)	2.98 ± 1.16 (median: 2.81)	3.64 ± 1.12 (median: 4.08)	0.003 ^a
TMJ-to-spine uptake ratio	1.23 ± 0.52 (median: 1.26)	0.75 ± 0.21 (median: 0.72)	0.74 ± 0.19 (median: 0.71)	0.004 ^a
TMJ-to-muscle uptake ratio	9.14 ± 4.97 (median: 7.83)	5.35 ± 1.47 (median: 5.54)	5.86 ± 2.09 (median: 5.60)	0.02 ^a

ADD, anterior disc displacement; NED, no evidence of TMD.

^aKruskal–Wallis test.

Figure 5 Receiver operating characteristic curves of temporomandibular joint (TMJ) uptake ratio on ^{99m}Tc -methylene diphosphonate bone scan (a), TMJ-to-skull uptake ratio (b), TMJ-to-spine uptake ratio (c) and TMJ-to-muscle uptake ratio (d) on fluoride-18 positron emission tomography/CT for detecting temporomandibular disorder with osteoarthritis. The TMJ-to-skull uptake ratio showed the highest area under the curve (AUC) value among the uptake ratios

for detecting TMD with osteoarthritis than the TMJ ratio on the ^{99m}Tc -MDP bone scan, suggesting that ^{18}F -PET/CT could be more helpful than conventional bone scan for diagnosing TMD with osteoarthritis.

Previous studies using conventional bone scan have shown that bone scan may help diagnose TMD with osteoarthritis.^{8,19,20} A recent study by Kim *et al*⁸ showed that the uptake ratio in TMD with osteoarthritis was significantly higher than that in TMD without osteoarthritis. Furthermore, ROC curve analysis for detecting TMD with osteoarthritis revealed an AUC value of 0.690, and the sensitivity and specificity of the bone scan were

72% and 58%, respectively. These results are similar to those achieved with the bone scan in our study but still indicate the lower diagnostic ability of the bone scan than that of ^{18}F -PET/CT in our study. Because the uptake ratio in a planar image is potentially affected by the superimposition of activity from adjacent and opposite structures,¹¹ other previous studies have used bone SPECT to evaluate TMD and treatment response of TMD.^{10,11,21} However, comparative analyses between ^{18}F -PET/CT and bone SPECT cannot be achieved because there is no previous study demonstrating the diagnostic performance of bone SPECT for detecting TMD with osteoarthritis.

Figure 6 The comparisons of the sensitivity, specificity and accuracy of the temporomandibular joint (TMJ) uptake ratio on ^{99m}Tc -methylene diphosphonate bone scan and TMJ-to-skull uptake ratio, TMJ-to-spine uptake ratio and TMJ-to-muscle uptake ratio on ^{18}F -positron emission tomography/CT for detecting temporomandibular disorder with osteoarthritis

^{18}F uptake in bone is dependent on blood flow and almost all delivered ^{18}F is retained by the bone after a single pass of blood.^{22,23} The high bone uptake early after injection and the rapid blood and renal clearance in ^{18}F -PET result in higher target-to-background ratios and better sensitivity than those of conventional bone scan using ^{99m}Tc -labelled phosphonates.²⁴ Furthermore, because of the rapid blood clearance, ^{18}F -PET/CT imaging can be performed less than 1 h after ^{18}F injection, whereas patients who undergo bone scan have to wait for 3–4 h after the injection of bone scanning agents.^{15,17} Given these advantages of ^{18}F -PET/CT, previous studies have shown its clinical usefulness in evaluating bone metastases,^{25,26} sacroiliitis¹⁶ and orthopaedic problems.^{27,28} The results of our study also showed a high diagnostic performance of ^{18}F -PET/CT in the detection of TMD with osteoarthritis, with a high sensitivity of 89% and an accuracy of 81%. The results of our study suggest that ^{18}F -PET/CT can help diagnose TMD with osteoarthritis and that it could be an excellent alternative to conventional bone scan. Furthermore, the TMJ ratio of the bone scan and the three uptake ratios of ^{18}F -PET/CT were significantly correlated, indicating that the bone scan and ^{18}F -PET/CT would show similar patterns of TMJ uptake in pathological conditions.

Because the quantitative indices used for ^{18}F -PET/CT scans have not been validated, many previous studies using ^{18}F -PET/CT have used visual analyses or lesion-to-background uptake ratios.^{15–17} We also used the TMJ-to-background uptake ratio for quantitative analysis rather than the pure TMJ uptake value, and we measured the skull, spine and muscle uptake to determine the background uptake value. Lesion-to-skull and lesion-to-spine uptake ratios have already been used for quantitative analyses in previous studies using bone scan or bone SPECT,^{11,18,29} and can be measured in patients who undergo ^{18}F -PET/CT scanning of only the head and neck area. However, the skull and spine uptake values varied among the patients enrolled in our study, possibly because of differences in age, sex and metabolic condition.¹¹ By contrast, muscle uptake, representing soft-tissue uptake, had the least variance among the three background uptakes, suggesting that muscle uptake is more effective in determining background uptake than skull or spine uptake. Nevertheless, the TMJ-to-skull and TMJ-to-spine uptake ratios had higher diagnostic ability than that of the TMJ-to-muscle uptake ratio, indicating that the skull and spine can be used for determining background uptake in TMD patients despite the wide variance.

There are several limitations in our study. First, we separately analysed the right and left TMJ uptake in the same patients, treating these values as if the TMJ uptake was not influenced by the disease status of the contralateral TMJ. However, TMJ uptake could be affected by abnormality of the contralateral TMJ, and these abnormalities might have confounded the TMJ uptake value.¹⁸ Second, we compared the diagnostic performance of ^{18}F -PET/CT with that of a bone scan. Further comparison studies with CT or MRI are required. Finally, only a small number of patients were enrolled in this pilot study and further studies with more patients are needed to elucidate the clinical usefulness of ^{18}F -PET/CT in TMD.

In conclusion, ^{18}F -PET/CT showed high TMJ uptake ratios in TMD with osteoarthritis and demonstrated higher sensitivity and accuracy than those of a conventional bone scan for detecting TMD with osteoarthritis. ^{18}F -PET/CT can be more helpful than a conventional bone scan for the diagnosis of TMD with osteoarthritis and can be an alternative modality to a bone scan in times of molybdenum shortage.

Table 2 The results of receiver operating characteristic curve analysis of the temporomandibular joint (TMJ) uptake ratio on bone scan and the TMJ-to-skull uptake ratio, TMJ-to-spine uptake ratio and TMJ-to-muscle uptake ratio on fluoride-18 positron emission tomography (PET)/CT for detecting TMD with osteoarthritis

Variables	AUC (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)	Accuracy (%)
TMJ uptake ratio	0.714 (0.566–0.835)	2.0	77	46	69
TMJ-to-skull uptake ratio	0.819 (0.681–0.915)	3.3	89	62	81
TMJ-to-spine uptake ratio	0.813 (0.671–0.911)	0.7	86	54	77
TMJ-to-muscle uptake ratio	0.771 (0.628–0.880)	6.4	71	85	75

AUC, area under the curve; CI, confidence interval.

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