의학석사 학위논문

^{18}F-FDG PET/CT findings of radiographic lesions suggesting old healed tuberculosis

치유된 결핵의 흔적으로 판단되는 흉부 방사선 병변의 ^{18}F-FDG PET/CT 소견

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^{18}F-FDG PET/CT findings of radiographic lesions suggesting old healed tuberculosis

by
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A thesis submitted to the Department of Internal Medicine in partial fulfillment of the requirements for the Degree of Master of Philosophy in Internal Medicine at Seoul National University College of Medicine

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ABSTRACT

Introduction : The presence of radiographic lesions suggesting old healed tuberculosis (TB) is one of the strongest risk factors for the subsequent development of active TB. We elucidated the metabolic activity of radiographic lesions suggesting old healed TB using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and compared the uptake with the results of the tuberculin skin test (TST) and interferon-γ release assay (IGRA).

Methods: This cross-sectional study included 63 participants with radiographic lesions suggesting old healed TB and with available ^{18}F-FDG PET/CT scans. The maximum standardized uptake value (SUV_{max}) was measured in the lesions, and the clinical characteristics and results of the TST and IGRA were analyzed.

Results : The SUV_{max} in old healed TB was 1.5 or higher among nine (14.3%) participants. Age [adjusted odds ratio (aOR), 1.23; 95% CI, 1.03-1.46], history of previous TB (aOR, 60.43; 95% CI, 1.71-2131.65), and extent of the lesions (aOR, 1.34; 95% CI, 1.02-1.75) were associated with higher SUV_{max}. The positive rates for the TST and IGRA were not different between groups with and without increased FDG uptake.

Conclusions : Increased FDG uptake on ^{18}F-FDG PET/CT was observed in a subset of patients with radiographic lesions suggesting old healed TB. The clinical meaning of the increased FDG uptake should be determined in future studies.

Key words: ^{18}F-FDG PET/CT; tuberculosis; pulmonary; SUV_{max}

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INTRODUCTION

Old healed tuberculosis (TB) can be defined as radiographic lesions suggesting TB sequelae without clinical or microbiological evidence of active pulmonary TB. Old healed TB usually presents as pulmonary nodules in the hilar area or upper lobes with fibrotic scars and volume loss. Also, bronchiectasis and pleural scarring may be combined.(1) Nodules and fibrotic scars from old healed TB may contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. In previous studies, the presence of radiographic lesions consistent with old healed TB was one of the strongest risk factors for the development of active TB.(2) However, there is no information on the metabolic states in such lesions.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely used for differentiation of malignant from benign pulmonary lesions because FDG uptake was significantly increased in malignant pulmonary lesions.(3) However, FDG accumulates in not only malignant tumors but also inflammatory lesions of both infectious and noninfectious origins, including pulmonary TB, sarcoidosis, histoplasmosis, and others.(4-7) The inflammatory cells such as neutrophils and activated macrophages at the site of inflammation or infection may be responsible for the accumulation of FDG.(8, 9) Reports have suggested the usefulness of ^{18}F-FDG PET/CT for the evaluation of inflammatory lesions.(6, 10)

Because active pulmonary TB in the acute state has intense glucose hypermetabolism,(11) strong uptake of FDG was observed in pulmonary TB(3, 12-14) as well as in pulmonary tuberculoma.(15-17) Subsequently, ^{18}F-FDG PET/CT was proposed as a tool for determining the activity of pulmonary tuberculomas(16) and for evaluating the therapeutic response of TB.(18, 19) However, there are no

reports on PET findings in radiographic lesions suggesting old healed TB. In the present study, we elucidated the metabolic activity of old healed TB using ^{18}F-FDG PET/CT and compared the uptake with the results of the tuberculin skin test (TST) and interferon (IFN)-γ release assay (IGRA).

MATERIALS AND METHODS

Participants and study design

This was a cross-sectional study based on a previous prospectively enrolled trial of 193 participants with radiographic lesions suggesting old healed TB at Seoul National University Hospital (Seoul, Republic of Korea), a tertiary referral hospital, between 1 January 2010 and 31 January 2011.(20) From the cohort, 63 participants with radiographic lesions suggesting old healed TB and available ^{18}F-FDG PET/CT scans were included in this study. The maximum Standardized Uptake Value (SUV_{max}) was measured in the radiographic lesions suggesting old healed TB, and the demographic data, clinical characteristics, and results of the TST and IGRA were analyzed. The study protocol was approved by the Ethics Review Committee of Seoul National University Hospital.

Interpretation of computed tomography of the chest

The presence of old healed TB was defined based on criteria proposed by Linh et al.(21) and the Centers for Disease Control and Prevention guidelines.(22) The extent of lesions suggesting old healed TB (cm^2) was determined by multiplying the major and minor axes (cm) measured on coronal images of the chest computed tomography (CT), where the major axis was the longest axis.

Whole blood IGRA and TST

The QuantiFERON-TB Gold In-Tube test (QFT-GIT) was performed according to the manufacturer's instructions. Test results were interpreted as negative, indeterminate, or positive (cut off, 0.35 IU/mL) using the manufacturer's software.(23) TST was performed according to the Mantoux method using a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark). After 48-72 hours, any induration was measured in millimeters using the ballpoint method. A positive TST result was defined as an induration of ≥10 mm.

^{18}F-FDG PET/CT imaging

All patients fasted for at least 6 h prior to the study. ^{18}F-FDG PET/CT imaging studies were conducted 60 min after intravenous injection of F-18 FDG (5.18 MBq/kg). Patients were examined using dedicated PET/CT scanners (Gemini, Philips; Biograph 40, Siemens). Emission scans were conducted in a three-dimensional mode following a CT scan for attenuation correction. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and were reoriented in axial, sagittal, and coronal slices. PET/CT images were analyzed in three different planes: transverse, coronal, and sagittal.

Two board-certified nuclear medicine physicians, unaware of the demographic/clinical data and laboratory results, interpreted the ^{18}F-FDG PET/CT scans. FDG uptake was measured as the standardized uptake value (SUV) on the emission images, using a vendor-supplied analysis tool package (Syngo.via, Siemens). After visually finding the area of highest FDG uptake in lesions suggesting old healed TB, the region of interest (ROI) was outlined. A SUV normalized for the injected dose and body weight was obtained in each pixel using

a standard method: SUV = ROI activity/(injected dose/body weight), where the ROI activity is measured in mCi/mL, the injected dose is measured in mCi, and body weight is measured in g. The maximum pixel value in the ROI was chosen as the maximum SUV (SUV_{max}). We assumed a SUV_{max} of 1.5 as a cut-off value of significant FDG uptake in old healed TB, based on the fact that the SUV of normal lung tissue is usually between 0.4 and 0.5.(24)

Statistical Analysis

Data are expressed as median values with minimum and maximum values. Comparisons of demographic characteristics, TST and IGRA results, and radiographic findings between patients with and without meaningful SUV uptake were performed using Pearson's χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. To elucidate the predictors for meaningful SUV increase, we selected clinical variables through univariate comparison and performed subsequent multiple logistic regression. In regression, backward elimination was used to select variables to be maintained in the final model. A *P* value of 0.10 was the criterion for statistical significance of association. All statistical analyses were performed with PASW software (ver. 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics of the participants

The median age of the 63 participants was 65 years (range, 36-88 years), and 43 (68.3%) were male. The presence of a BCG scar was confirmed in 22 patients (38.6%), and 30 (47.6%) had a history of TB treatment. In total, 66.7% of

participants had a positive TST, and 77.8% had a positive QFT-GIT. The median extent of the lesions on chest CT was 3.52 cm^2 (range, 0.12–32.86 cm^2) (Table 1).

Comparison between participants with and without meaningful SUV uptake

In participants, ^{18}F-FDG PET/CT scans were performed for the diagnosis or staging work up of malignant diseases. 58 (92.1%) of them were diagnosed as having malignant diseases, most commonly lung cancer.

The SUV_{max} was 1.5 or higher in nine (14.3%) participants out of 63 participants. The median age of this group was higher than that of the group without increased FDG uptake (72 *vs.* 63.5 years, P = 0.03). Body mass index and the presence of a BCG scar were not different between the two groups. In addition, the positive rates of TST and QFT-GIT were not different. However, the extent of the radiographic lesions suggesting old healed TB was larger in the participants with increased SUV_{max} compared with those with lower SUV_{max} (8.33 *vs.* 2.78 cm^2, P = 0.01) (Table 1).

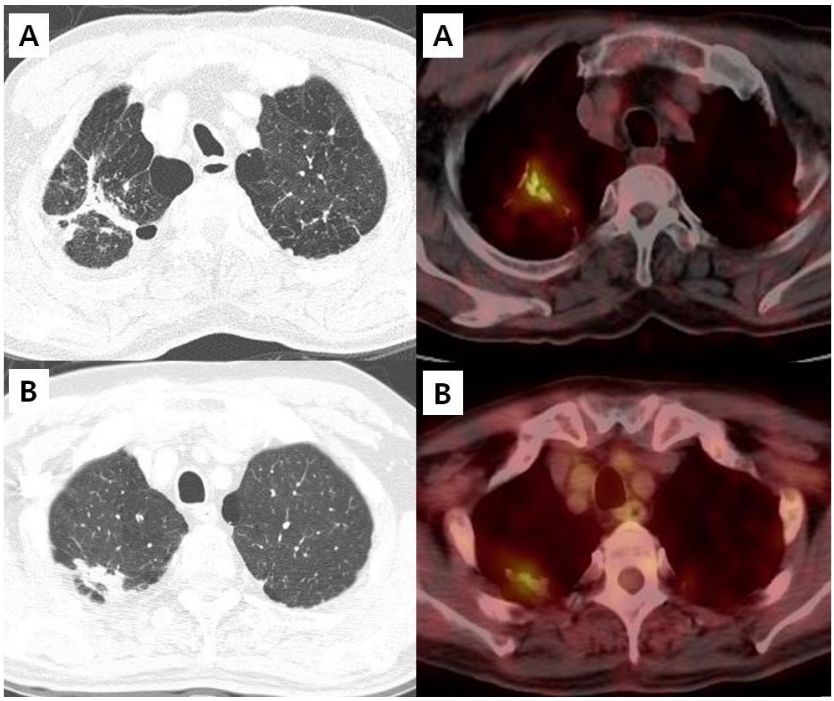

Figure 1. Chest CT and ^{18}F-FDG PET/CT findings of two participants with old healed TB, showing increased FDG uptake.

A. Fibrotic scar and calcified nodules suggesting old healed TB in the right upper lobe was observed on the chest CT of a 76-year-old man without a history of TB. The SUV_{max} of the lesions was measured as 4.0 by ^{18}F-FDG PET/CT. Both the TST and IGRA were negative.

B. Fibrotic scar and nodules in the right upper lobe were observed on the chest CT of a 71-year-old man. He had been treated for pulmonary TB 25 years earlier. The SUV_{max} of the lesions was measured as 2.2 by ^{18}F-FDG PET/CT. Both the TST and IGRA were positive.

Table 1. Demographic, clinical, and radiographic characteristics of 63 participants with old healed TB

Characteristic	Total (N = 63)	FDG uptake ≥1.5 SUV_{max} (N = 9)	FDG uptake <1.5 SUV_{max} (N = 54)	*P* value
Age, years	65 (36-88)	72 (48-79)	63.5 (36-88)	0.03
Male	43 (68.3)	8 (88.9)	35 (64.8)	0.25
Body mass index, g/m^2	22.2 (17.6-28.3)	24.0 (17.6-25.8)	22.1 (17.8-28.3)	0.24
Presence of BCG scar	*22 (38.6)	1 (12.5)	21 (42.9)	0.13
History of TB treatment	30 (47.6)	7 (77.8)	23 (42.6)	0.07
Ex or current smoker	38 (60.3)	8 (88.9)	30 (55.6)	0.08
Comorbidities				
Diabetes	5 (7.9)	0	5 (9.3)	1.00
Chronic liver disease	3 (4.8)	0	3 (5.6)	1.00
Chronic renal failure	0	0	0	
Malignancy	58 (92.1)	9 (100)	49 (90.7)	1.00
Positive TST (>10 mm)	†38 (66.7)	5 (62.5)	33 (67.3)	1.00
Diameter of induration (mm)	12.0 (0-24)	13.0 (0-24)	11.0 (0-18)	0.50
Positive IGRA	49 (77.8)	8 (88.9)	41 (75.9)	0.67
Titer of TB antigen-nil (IU/mL)	1.12 (0.06-10.0)	1.1 (0.32-7.8)	1.14 (0.06-10.0)	0.73
Chest CT findings				
Extent (cm^2)	3.52 (0.12-32.86)	8.33 (2.90-32.86)	2.78 (0.12-21.93)	0.01
Fibrotic scar	54 (85.7)	8 (88.9)	46 (85.2)	1.00
Calcified nodule	44 (69.8)	8 (88.9)	36 (66.7)	0.26
Non-calcified nodule	22 (34.9)	3 (33.3)	19 (35.2)	1.00
Fibrotic scar with volume loss	5 (7.9)	2 (22.2)	3 (5.6)	0.15
Nodules with volume loss	1 (1.6)	1 (11.1)	0	0.14
Upper lobe bronchiectasis	12 (19.0)	3 (33.3)	9 (16.7)	0.35
Pleural thickening & calcification	51 (81.0)	8 (88.9)	43 (79.6)	1.00

Results are presented as number (percentage) or median (range).

*The presence of BCG scar could be evaluated in 58 patients.

†The result of the TST could be assessed in 57 patients.

Characteristics associated with higher SUV in old healed TB

In the final model of multiple logistic regression, age, history of previous TB, extent of radiographic lesions, smoking history, TST result, and QFT-GIT result were included. Among them, age [adjusted odds ratio (aOR), 1.23; 95% confidence interval (CI), 1.03-1.46], history of previous TB (aOR, 60.43; 95% CI, 1.71-2131.65), and extent of the lesions (aOR, 1.34; 95% CI, 1.02-1.75) were associated with higher SUV on ^{18}F-FDG PET/CT scans. (Table 2).

Table 2. Predictors of increased FDG uptake among patients with radiographic lesions suggesting old healed TB

Factor	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age*	1.07 (0.99-1.16)	0.74	1.23 (1.03-1.46)	0.02
History of TB treatment	4.72 (0.90-24.85)	0.07	60.43 (1.71-2131.65)	0.02
Extent of lesions on CT	1.18 (1.04-1.33)	0.01	1.34 (1.02-1.75)	0.03
Presence of smoking history	6.40 (0.75-54.78)	0.09	2.09 (0.15-29.12)	0.59
Positive TST	0.81 (0.17-3.81)	0.79	3.35 (0.24-47.82)	0.37
Positive IGRA	2.54 (0.29-22.23)	0.40	1.21 (0.06-23.41)	0.90

*x+1 years *vs.* x years

Subsequent development of active TB

In total, 55 participants were followed for at least 3 months. The median follow-up period was 27.2 (interquartile range, 19.3-30.8) months. During the follow-up period, no one had clinical or radiological evidence of the development of active TB.

DISCUSSION

In this study, we demonstrated increased FDG uptake in radiographic lesions suggesting old healed TB in a subset of patients. Increased FDG uptake was more frequent among older patients, in patients with a history of treatment for TB, or in patients with more extensive radiographic lesions.

Latent TB infection is not simply a state of bacterial stasis, but rather a state of dynamic bacterial and immunological equilibrium.(25) It has been observed in mouse models that a subpopulation of bacteria continues to replicate, although the size of the bacterial population remains stable.(26) In addition, a recent study using a non-human primate model showed that *Mycobacterium tuberculosis* accumulated mutations during latency.(27) Given that at least a subset of old healed TB includes *M. tuberculosis* in dormancy, the increased FDG uptake in old healed TB in our study may represent active immunological and metabolic processes.

In the present study, age, history of previous TB, and the extent of lesions were associated with higher SUV on ^{18}F-FDG PET/CT scans. The incidence of TB is higher in the older population than in the younger population partly because of the reactivation of dormant *M. tuberculosis*(28) due to age-related waning of anti-mycobacterial host immunity.(29) In addition, the incidence of TB among patients with a history of past TB treatment is higher compared with those without a history

of TB.(30-32) Furthermore, the higher incidence of active TB among patients with a larger extent of old healed TB lesions has been reported previously.(33) Given that the factors associated with increased FDG uptake are known risk factors for TB development, participants with old healed TB lesions with higher SUV on ^{18}F-FDG PET/CT scans might be at higher risk for active TB. Long-term close monitoring for clinical or radiological evidence of the development of active TB among participants would reveal the clinical meaning of the increased FDG uptake on radiographic lesions suggesting old healed TB.

Interestingly, there was no correlation between increased FDG uptake and positive TST or IGRA results in our study. This observation can be explained by the limited predictive value of TST and IGRA for the progression to active TB(34, 35) when increased FDG uptake in old healed TB could represent the risk for subsequent TB development. Otherwise, the role of increased FDG uptake, TST, and IGRA in predicting active TB may be complementary.

CONCLUSIONS

In conclusion, some of the lesions suggesting old healed TB showed increased FDG uptake on ^{18}F-FDG PET scans. FDG uptake within lesions suggesting old healed TB may imply the presence of active metabolic activity in the lesions. The possibility that ^{18}F-FDG PET/CT imaging of old healed TB lesions could be exploited as a biomarker for the development of active TB should be tested in a future study.

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국문 초록

서론: 치유된 폐결핵 흔적을 시사하는 방사선 병변이 있는 경우, 향후 결핵 발병의 강력한 위험인자 가운데 하나로 간주된다. 그러나 치유된 결핵의 흔적의 대사 활성도에 대해서는 밝혀진 바가 거의 없다. 이 연구에서는 치유된 폐결핵을 시사하는 방사선 병변의 ^{18}F-FDG 양전자방출단층촬영/전산화 단층촬영 (Positron emission tomography/ Computed tomography, PET/CT)을 통해 대사 활성도를 평가하고, 그에 영향을 미치는 인자를 분석하였다.

방법: 2010 년 1 월부터 2011 년 1 월까지 서울대학교병원에서 흉부 CT 를 통해 치유된 폐결핵 흔적이 확인된 환자들 중 진료 목적으로 ^{18}F-FDG PET/CT 를 시행했던 63 명을 연구대상으로 하여 단면적 연구를 시행하였다. 해당 병변의 최대 표준화 섭취율 (Maximum Standardized Uptake Value, SUV_{max}) 을 측정하여 연구참여자의 인구학적 및 임상적 특성, 방사선 소견, 그리고 투베르쿨린 피부반응검사 (Tuberculin skin test, TST), 전혈 인터페론 분비검사 (Interferon-γ release assay, IGRA) 결과와 비교하였다.

결과: 치유된 결핵의 흔적에서 SUV_{max} 1.5 이상의 FDG 섭취를 보인 경우는 9 명 (14.3%) 이었다. SUV_{max} 1.5 미만의 FDG 섭취를 보인 군과 비교할 때, 높은 FDG 섭취와 관련있는 인자는 연령 [adjusted odds ratio (aOR), 1.23; 95% CI, 1.03-1.46], 이전 결핵 치료력 (aOR, 60.43; 95% CI, 1.71-2131.65), 그리고 CT 에서 관찰된 병변의 면적 (aOR, 1.34; 95% CI, 1.02-1.75) 으로 나타났다. TST 와 IGRA 양성율은 양 군에서 유의한 차이가 없었다.

결론: 치유된 폐결핵 흔적을 시사하는 방사선 병변의 일부는 ^{18}F-FDG PET/CT 에서 FDG 섭취증가를 보였다. 이의 임상적인 의미에 대해서는 추가적인 연구가 필요하다.

주요어 : 폐결핵; 양전자방출단층촬영; 최대 표준화 섭취율

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