Spinal Tuberculosis Evaluated by Means of 18F-FDG PET/CT: Pilot Study

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Abstract: *Introduction*: Spinal tuberculosis is a serious health care problem and diagnosis is often difficult because many diseases may have similar imaging findings. Hence the need to describe findings of spinal tuberculosis with 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) when compared to CT.

Materials and Methods: Sixteen consecutive patients who underwent 18F-FDG PET/CT and known to have or subsequently were proven to have spinal tuberculosis were analyzed. All patients included underwent whole-body 18F-FDG PET imaging; none of the patients were on tuberculostatics at the time of the PET investigation. We evaluated 18F-FDG uptake visually and semiquantitatively using standardized uptake values (SUVmax) and the ratio of lesion to normal liver (S/L ratio), respectively. The presence of spinal and extraspinal lesions was evaluated histopathologically and by the radiologic findings noted on diagnostic CT. Diagnostic Computed Tomographic (CT) findings were reviewed and compared to 18F-FDG PET/CT.

Results: Only 4 patients had one spinal lesion, while 12 (75%) patients had 2 or more lesions. Those patients that had three or more lesions demonstrated intense FDG uptake with a median of 11.34 (3.8-20.9). Ten (62%) of the patients had both spinal and extraspinal lesions. In most of the cases (75%), the lumbar spine was involved as opposed to the thoracic vertebrae. 18F-FDG PET detected all 39/39 (100%) clinically (sites of disease that resulted in symptoms or signs such as pain, swelling, neurological fallout etc.) and histologically (as reported by the laboratory) observed spinal sites. The median of the SUVmax for spinal lesions was 6.06 (ranging from 2.63 to 16.78). Diagnostic CT reported corresponding morphological changes in only 27 (69%) of the spinal sites identified on 18F-FDG PET/CT. 18F-FDG PET/CT detected 60 of 60 (100%) clinically observed extraspinal sites including pulmonary TB, nodal disease and other musculoskeletal sites versus the 43 of 60 (71%) detected by diagnostic CT only. The median of the SUVmax was 3.61 for nodal sites (ranging from 1.71 to 10.79) and 3.38 for pulmonary sites (ranging from 1.23 to 5.93).

Conclusion: The results suggest that 18F-FDG PET/CT is more effective compared to diagnostic CT only in the identification of sites of active disease and contributes to a better evaluation of extraspinal involvement in TB patients. It also appears to be a very promising imaging modality for the identification of the most appropriate biopsy site, staging disease, predicting multi-drug resistance and monitoring response to therapy.

INTRODUCTION

In Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) and *Mycobacterium tuberculosis* (TB) infection, early identification and diagnosis of active disease is the key to effective control of the disease [1]. Globally, TB continues to be one of the leading infectious causes of morbidity and mortality, accounting for an estimated 9 million cases and 2 million deaths per year [1-4]. The effect of the dual HIV and TB epidemics is felt most acutely in developing countries, with recent estimates of dual infection rising rapidly. HIV-infected patients are at a 20-fold increased risk of contracting TB when compared with HIV-non-infected peers [3, 5-7]. Therefore, there is an increasing clinical need for effective early non-invasive identification and diagnosis of TB. Early identification of possible drug resistant disease is similarly of

great importance since it impacts on management. The vertebral column is the most common site of osseous involvement, comprising in most series about 50% of cases of skeletal TB [8]. The most common location is the vertebral body of L1. If untreated, spinal TB carries the risk of serious complications due to vertebral collapse and spinal cord compression. Diagnosis is often difficult because many diseases such as gram positive, gram negative and fungal infctions as well as malignant disease processes involving the vertebrae may lead to similar imaging findings [9-12]. In addition fluid for diagnostic analysis is often unavailable in extra-pulmonary TB including TB of the spine [13]. Currently Magnetic Resonance Imaging (MRI) and to a lesser extent Computed Tomography (CT) are routine imaging modalities for the evaluation of spinal TB. CT-guided fine needle aspiration is a reasonably accurate means of obtaining material for histopathological evaluation and culture, but is unable to differentiate active disease from old changes. It also has a lower sensitivity for detection of early skeletal disease compared to 2-[fluorine 18]fluoro-2-deoxy-D-glucose (18F-FDG) Positron Emission Tomography

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(PET) [16,17]. Spinal tuberculosis activity is mandatory for the determination of the optimal treatment strategy. As 18F-FDG is known to accumulate in inflammatory cells such as neutrophils and activated macrophages at the site of inflammation [1, 14,15] this enables 18F-FDG-PET/CT to be the preferred modality for real-time assessment of disease activity over CXR, CT, and MRI. Also, preliminary work shows that quantitative 18F-FDG uptake can be used to monitor the effectiveness of treatment [1,16,17]. Therefore, it is required to describe findings of spinal tuberculosis with 18F-FDG PET/CT when compared to diagnostic CT only.

MATERIALS AND METHODS

Approval for this study was granted by the Ethics Committee of the University of Pretoria.

Sixteen consecutive patients who underwent PET/CT and subsequently were proven to have spinal tuberculosis were analyzed. All patients were clinically diagnosed with spinal sespsis based on clinical examination and radiographs. There were 8 men and 8 women. Of the 16 patients 12 were black, 2 were caucasian and 2 were Asian. Three of the 16 patients were known to be HIV positive. The median age of the whole patient group was 36.6 years (range, 33-83 years).

Diagnosis of active tuberculosis was established by histological and culture analysis. Direct microscopy for M. tuberculosis was performed with a Ziehl-Nielsson stain (ZN). Quantification of acid-fast bacilli was performed using parameters specified by the Centers for Disease Control and Prevention (CDC). Mycobacterial cultures were performed with the MGIT system (BD Diagnostics Systems, Sparks, MD) and subsequent sensitivities were determined using the agar proportion method by BACTEC MGIT (BD Diagnostics Systems, Sparks MD). Histological examination of biopsy samples was examined for features of mycobacterial infection including granulomata and Langerhans cells. The ZN stain was examined for acid-fast bacilli. Biopsy samples were submitted for molecular testing using the GeneXpert Diagnostics System (Cepheid, Sunnydale, CA). This platform utilizes real time PCR. The local laboratory at the study site performed microscopy and culture. PCR was performed by a private laboratory [18, 19].

White cell count (WCC), Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels done within 7 days of the PET/CT study was recorded and correlated with the Suv max and number of sites of abnormally increased 18F-FDG accumulation.

All patients included underwent whole-body 18F-FDG PET/CT imaging; none of the patients were on tuberculostatics at the time of the PET investigation. Following 18F-FDG PET/CT-imaging, included patients were put on TB-treatment.

A region of interest was manually drawn over a hypermetabolic area on transaxial attenuation corrected PET images to obtain the SUVmax. The SUV formula: SUV = radiotracer activity × weight of the patient/injected dose, which characterises the relative concentration of the radiotracer in the lesion of interest. We used the SUVmax for the pixel with the greatest uptake in the lesion (maximum pixel SUV). All areas that demonstrated an SUVmax that exceeded the SUV average of a ROI drawn over the liver was considered to be representative of active tuberculosis.

Quantitative 18F-FDG PET/CT imaging results (averaged 18F-FDG SUVmax values derived imaging and the ratio of lesion to normal liver (S/L ratio) and the used of low dose CT for anatomical correlation), were related to diagnostic CT.

18F-FDG PET/CT Imaging

Whole body 18F-FDG PET/CT scans were acquired on a dedicated PET-CT scanner (Biograph, Siemens) from the skull top to the pelvis. Patients were required to be fasting for a minimum of 4 hours prior to 18F-FDG injection. Blood glycaemia was monitored with a portable capillary glucometer. Patients received a dose of 18F-FDG based on their body weight using the following formula ((body weight/10)+1))*37 MBq. PET/CT imaging was performed 60 min after injection of 18F-FDG. Acquisition duration per bed position was 3 min; nine bed positions were acquired.

Images were acquired in a 3-dimensional mode and reconstructed with and without attenuation correction (CT-based) using OSEM (ordered subset expectation maximization) yielding axial, sagittal and coronal slices. 18F-FDG PET/CT images obtained were analyzed for the presence or absence of sites of active tuberculosis (areas demonstrating increased 18F-FDG accumulation with or without corresponding changes noted on CT) by two experienced nuclear medicine specialists, blinded to the clinical data and to the results obtained by diagnostic CT imaging. Disagreements were resolved by consensus. For quantitative analysis, SUVmax values were obtained for all lesions identified by drawing manually defined regions of interest on the attenuation-corrected axial images. The number of sites of spinal involvement was counted and recorded. The number and SUV max values of all extra-spinal sites such as lymph node or pulmonary lesions, were also recorded.

For diagnostic CT scanning, the following parameters were used: collimation of 24 x 1.2 mm; gantry rotation time of 500 ms; tube voltage of 120kV; effective tube current of 100 mAs with online tube current modulation and a table feed of 18mm/rotation. Contrast enhancement was achieved by intravenous administration of 100 ml of non-ionic contrast material (Ultravist) at a rate of 2 ml/sec. Matrix size was 512x512. Diagnostic contrast-enhanced CT images were analyzed in the presence or absence of sites of active or inactive tuberculosis by two experienced radiologists blinded to the clinical diagnosis and 18F-FDG PET findings. Disagreements were resolved by consensus. CT-criteria for the diagnosis of infection included early soft tissue edema, early periosteal reaction and the presence of focal erosions.

Statistical Analysis

Simple descriptive statistics (absolute numbers and percentages) were used to report patient characteristics and sites of involvement. Where data had a normal distribution, values were reported as means with standard deviations. In instances where data was not normally distributed, there were reported as median values with ranges/modes.

RESULTS

Median age of the whole patient group was 36.6 years (range, 33-83 years). There were 8 men and 8 women. Of the 16 patients 12 were black, 2 were caucasian and 2 were Asian.

All 16 patients studied had active spinal disease, 6 of the 16 patients had active spinal and active pulmonary disease. Four of these 6 patients with both active spinal and pulmonary disease had in addition other musculoskeletal sites of active TB (Table **1**). This would suggest that patients with pulmonary as well as spinal TB are likely to have more extensive disease with likely involvement of the musculoskeletal system elsewhere.

Table 1.   Extent and Severity of Involvement

Extent of Involvement (Spinal Sites)	No of Patients	SUV
1 site	4	4.25 (2.92 – 5.07)
2 sites	6	5.74 (2.87 – 10.3)
>3 sites	6	11.34 (3.8 – 20.9)

Only 4 patients had one spinal lesion, while 12 (75%) patients had 2 or more lesions (Figs. **1**, **2**). Those patients that had three or more lesions demonstrated intense FDG uptake with a median of 11.34 (3.8-20.9) (Table **1**). Ten (62%) of the patients had both spinal and extraspinal lesions. In most of the cases (75%), the lumbar spine was involved as opposed to the thoracic vertebrae. 18F-FDG PET/CT detected all 39/39 (100%) clinically observed (resulting in pain, discomfort or neurological fallout or sites that could be detected by physical examination) and histological observed (sites with microscopic or culture evidence of TB) spinal sites. The median of the SUVmax for spinal lesions was 6.06 (ranging from 2.63 to 16.78). CT reported corresponding morphological changes in only 27 (69%) of the spinal sites identified on 18F-FDG PET. 18F-FDG PET/CT detected 60 of 60 (100%) clinically observed extraspinal sites including pulmonary TB, nodal disease and other musculoskeletal sites versus the 43 of 60 (71%) detected by CT (Table **2**). The median of the SUVmax was 3.61 for nodal sites (ranging from 1.71 to 10.79) and 3.38 for pulmonary sites (ranging from 1.23 to 5.93).
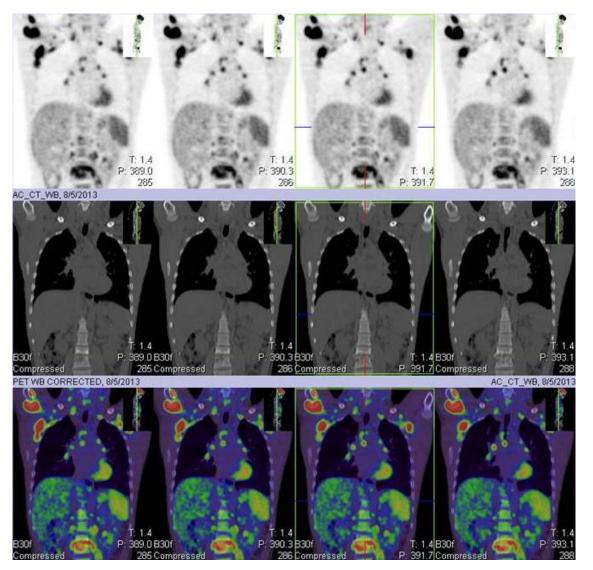

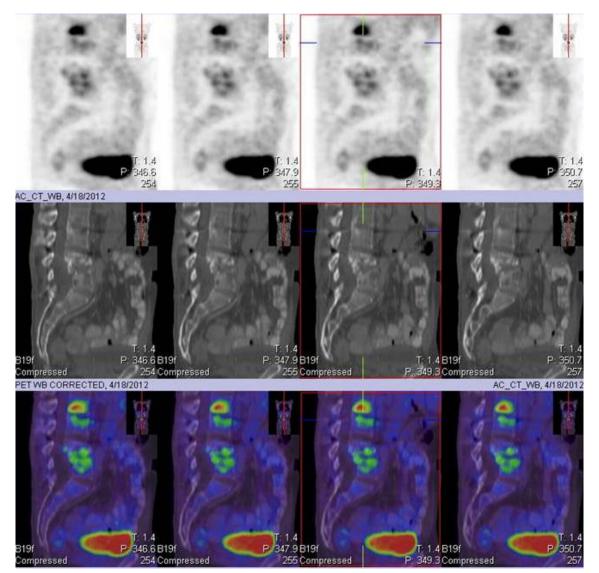**Fig. (1).** 18F-FDG PET/CT demonstrating multiple spinal involvement.

Fig. (2). A 43 year old male patient with 18F-FDG PET/CT showing multiple spinal involvement, and extraspinal involvement (nodal and splenic)

Table 2.   Comparison of 18F-FDG PET and CT

Site of Involvement	18F-FDG PET	CT
Spinal	39 (100%)	27 (69%)
Extraspinal	60 (100%)	43 (71%)

In 75% of cases active spinal disease sites involved the lumbar spine and pelvis (Fig. **3**).

Patients that had both TB and HIV had in most cases the greatest number of nodal groups involved. In all patients the ESR was elevated, in most cases exceeding 50mm/hr (ranging from 18-122). CRP was elevated in all but one patient, ranging from 17.5-287.4 and in most cases exceeding 20. The WCC did not demonstrate any correlation with Suv max or the number of sites of active disease.

DISCUSSION

The early diagnosis and prompt treatment of spinal TB are of fundamental importance in preventing severe spinal deformity (gibbus) resulting from an acute kyphotic angulation. A delay between the initial symptoms and the etiological diagnosis is possibly caused by the low incidence of spinal TB and the slow development of the clinical features [6,7]. Time from symptom onset to diagnosis may range from several days to upto three years, but mostly spans several months [6,7,13]. Typically, multiple vertebral bodies and disc spaces are involved. In our study population the lumbar vertebrae were involved in 75% of cases which is consistent with what has been reported in the literature by other groups [8].

Although the ESR was abnormally elevated in all patients and CRP values were elevated in all but one patient, the absolute ESR and CRP values did not correlate with the
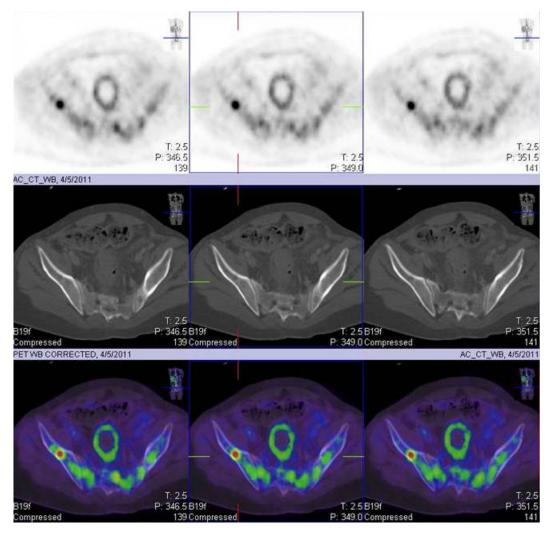
Fig. (3). 18-FDG PET/CT identifies active spinal disease and extraspinal involvement in the pelvis.

SUVmax of spinal lesions or overall disease extent in our study group. It has been reported in the literature that patients may have a normal WBC, and a normal ESR in up to 10% of the cases, which is in agreement with what we have found in our group [4,8,18]. Abnormal WBC, CRP level or complete blood count does not contribute to the diagnosis.

The finding of elevated ESR does not advance the diagnosis, but may be useful for follow-up of treatment response [4,8]. Tuberculin skin testing when positive is not of much help either especially in endemic areas or with recipients of the bacille Calmette-Guérin vaccine. Furthermore, the Mantoux and purified protein skin tests may be negative in as many as 14% of the patients with vertebral TB [18,20,21]. A negative skin test may be caused by anergy, particularly with immuno-suppressed and older patients [18,21]. Finally, the chest radiographs and exposure history may not be positive. Microbiological and/or histological confirmation is required for the final diagnosis of spinal TB and fine-needle aspirate, imaging-guided percutaneous biopsy, or open biopsy may be essential. Determination of spinal tuberculosis activity is mandatory for determination of the optimal treatment strategy. As 18F-FDG is known to accumulate in inflammatory cells such as neutrophils and activated macrophages at the site of inflammation [1,14,15] this enables 18F-FDG-PET/CT to be the preferred modality for real-time assessment of disease activity over CXR, CT, and MRI. 18F-FDG PET/CT was superior in the identification of involved nodal basins compared to CT alone. In our group, the three patients that had both TB and HIV had the greatest number of nodal groups involved (an average of 4 nodal groups per HIV positive patient compared to an average of 1.6 nodal groups in HIV negative patients). Sathekge *et al*. has shown that in cases where 5 or more nodal basins demonstrated active disease, treatment resistance was more likely [8]. This suggests that 18F-FDG PET is a valuable imaging modality for the prediction of possible drug resistance thereby impacting on management [1,8].

The number of involved nodal basins has been linked to an increased likelihood of drug resistant tuberculosis [5,8]. Four of 6 patients who had both active spinal and pulmonary disease had in addition other musculoskeletal sites of active tuberculosis. This would suggest that patients with pulmonary as well as spinal TB are likely to have more extensive disease and may benefit from investigation for involvement of the musculoskeletal system elsewhere.

Although no imaging modality can confidently differentiate benign from malignant disease 18F-FDG PET/CT has proven to be a valuable modality for the identification of the most appropriate biopsy site for histopathological evaluation and diagnosis [16, 17, 22]. Secondly even though definitive diagnosis and exclusion of active TB infection by culture and examination of tissue specimens are always recommended, 18F-FDG-PET/CT may contribute to earlier detection/diagnosis [1,23-25].

This current study suggests that 18F-FDG-PET/CT may be a useful tool in the assessment of the extent of active disease involvement prior to treatment and potentially for the assessment of treatment response [1]. This is in agreement with work done by Schmitz *et al*. [8]. Preliminary work done on animal models as well as humans has demonstrated that quantitative 18F-FDG uptake can be used to monitor the effectiveness of treatment [1, 16,17]. Furthermore, this pilot study shows that extensive involvement of 3 or more vertebral sites appears to have more intense 18F-FDG uptake =11.34 (3.8-20.9). This finding needs to be evaluated further for possible prognostication and to determine the duration and type of therapy.

CONCLUSION

The results suggest that 18F-FDG PET/CT is more efficient in the identification of sites of active disease and contributes to a better overall staging of extraspinal involvement in TB patients. It also appears to be a very promising imaging modality for the identification of the most appropriate biopsy site, evaluating disease extent, predicting multi-drug resistance and monitoring response to therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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