

# 18F FDG PET-CT Imaging in Tuberculosis

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## ABSTRACT

Tuberculosis (TB) is the second highest infective cause of death worldwide and the global impact of TB is very important. Among all the TB burden WHO regions, 40% TB cases accounts in the South East Asian region. It has become a medical emergency not only in developing countries but also in some high-income countries. The rising incidence of multidrug resistance (MDR) TB and HIV co-infection has increased the morbidity and mortality of TB despite the availability of cheap and effective treatment. The diagnosis of active TB is almost similar over the world. Conventional radiography and Computed Tomography (CT) imaging play a crucial role in the diagnosis of TB. But these conventional imaging are often nonspecific and unable to provide a definitive diagnosis in cases of atypical and heterogeneous presentation. The signs of TB may mimic other diseases in conventional imaging. The introduction of new imaging tool Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (18F FDG PET-CT) opens the door to evaluate its potential application in TB. The role of this new imaging tool in TB imaging has been well documented. 18F FDG PET-CT may assist in early diagnosis, facilitate differentiation between malignancies and TB, identification of extrapulmonary TB, staging of TB, and in assessment of treatment response. Therefore, familiarity with the spectrum of imaging features and understanding the use of 18F FDG PET-CT in diagnosis and management of TB is important, specially for referring clinicians and the reporting nuclear medicine specialists in TB burden country like Bangladesh. This article reviews the main applications, pattern of imaging spectrum with limitations of 18F FDG PET-CT in TB.

*Key words:* Fluorine-18 fluorodeoxyglucose, PET-CT, tuberculosis.

## INTRODUCTION

Tuberculosis (TB) is the second highest infective cause of death worldwide and most common presentation of active infection (1). According to the World Health Organization (WHO) Global tuberculosis report 2015, estimated 9.6 million people

have developed TB and 1.5 million people have died annually. Among all the WHO regions, 40% TB cases accounts in the South East Asian region (2). Over 95% of TB deaths occur in low and middle income countries. This disease has become a medical emergency not only in developing countries but also in some high-income countries, because of migration of people from TB endemic area to higher-income areas, frequent co-infection with HIV/AIDS, and development of drug-resistant strains of TB (3). Hence the global impact of TB is very important. The rising incidence of multidrug resistance (MDR) TB and HIV co-infection has increased the morbidity and mortality of TB despite the availability of cheap and effective treatment. Globally, 132 120 cases of multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2015, and 124 990 cases were enrolled on treatment (2). The immune-compromised patients are more prone to be infected with MDR-TB, and resistance strains have a greater tendency to involve extrapulmonary sites. Early diagnosis prompts effective treatment and leads to a reduced transmission of TB (4).

The diagnosis of active TB is almost similar over the world. Sputum culture is the gold standard for diagnosis. Traditional Mantoux test is also used to assess immunological response (5). Conventional radiography and Computed Tomography (CT) imaging play a crucial role in the diagnosis of TB. Plain chest radiography is the mainstay in pulmonary TB or lung parenchymal disease, while CT is more sensitive in case of lymphadenopathy and early bronchogenic change.

But these conventional imaging are often nonspecific and unable to provide a definitive diagnosis in cases of atypical and heterogeneous presentation. The signs of TB may mimic other diseases in conventional imaging, such as neoplasms or sarcoidosis. Patients with sputum-negative pulmonary TB (PTB) and extra-pulmonary TB (EPTB) or TB with co-infection of HIV/AIDS are difficult to diagnose due to their atypical presentation and may be missed at all points of patient care. In case of drug resistance TB, the major challenge is treatment failure and treatment monitoring for therapy response is very essential (6). The introduction of new imaging tool Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography, (18F FDG PET-CT) opens the door to evaluate its potentiality in clinical application in TB. The value of this new imaging tool in TB imaging has been well documented through several studies. Hence familiarity with the spectrum of imaging features is required to facilitate timely diagnosis and monitoring of TB treatment (4, 7).

*Mycobacterium tuberculosis* (Mtb) is an aerobic microorganism with complex pathophysiology. It may persist in host cells in variable states; ranging from latent infection to active clinical disease. The complex pathology of the organism provides multiple molecular targets for imaging the infection and targeting therapy. 18F FDG accumulates in inflammatory cells such as neutrophils, activated macrophages, and lymphocytes at the sites of inflammation or infection. TB granulomas consist of macrophages and lymphocytes, which demonstrate high levels of glucose uptake resulting in increased uptake of 18F FDG on PET imaging. In the activated lymphocyte approximately 20 fold increased glucose uptake occurs over 24 hours due to increased glycolysis (8, 9, 10). Hence any active TB infection avidly takes up 18F FDG, like pulmonary TB, tuberculoma, extrapulmonary TB and in other TB related lesions (8, 11, 12, 13). Although characterization of the infection as active or not, extent of the disease always could not be assessed properly with conventional imaging. The 18F FDG PET-CT has reported promising results in

determining active lesion from not active (4).

PET-CT imaging is an integral part in quality management of oncology patients in developed countries and is a growing technology in developing countries. This technology is also increasingly used for evaluation of malignancy in both high and low TB prevalent countries (7). It is an emerging noninvasive imaging tool for diagnosis, staging and assessing therapy response in many infection and inflammations (9). Therefore, understanding of the potential impact of use of 18F FDG PET-CT in diagnosis and management of TB is important, especially for referring clinicians and the reporting nuclear medicine specialists. This article reviews the main applications, pattern of imaging spectrum with limitations of 18F FDG PET-CT in TB.

## PULMONARY TUBERCULOSIS

Pulmonary tuberculosis (PTB) is the most common presentation of TB. Classically, PTB can be divided into primary tuberculosis and post primary tuberculosis. Primary TB is due to first time exposure to the Mtb and post primary TB (also termed as reactivation, secondary or adulthood TB) develops under the influences of acquired immunity (14).

In primary TB the multilobar consolidation may be present in 25% cases. Two third cases are resolves without sequelae. Persistent radiological scar, calcifications or mass like opacities called tuberculomas are seen in 9 % cases (4, 14). In case of children radiologically detectable parenchymal involvement is significantly lower and accounts about 90 -95% cases comparing to adults (43%). The most common abnormality in children is lymph node enlargement TB. Hence CT scan is more sensitive for children than the plain radiography (15, 16). FGD PET-CT may play a potential role in the evaluation of TB in children, but no reported data is available. In case of post primary TB, cavitation is the radiological hallmark and evident in 20 to 45% patients, which is a reliable marker of active TB (17). Bronchial spread of TB is associated with centrilobular nodule and tree in bud lesions in CT. In case of post primary TB hilar or mediastinal lymphadenopathy is uncommon (18).

Depending on the FDG PET scan pattern, Soussan et al. has identified two different patterns of TB, one is lung type pattern and another lymphatic pattern. In lung type the infection is more localized to the lung parenchyma, usually with segmental consolidation with or without cavitations surrounded by micronodules. The infective lesions are mildly hypermetabolic that is mildly FDG avid. In case of lymphatic pattern there will be system involvement with intense infection. Mild FDG avid lymphadenopathy is the characteristic of lung type pattern whereas in case of lymphatic pattern the involved hilar and mediastinal lymph nodes will be more enlarged in size with intense FDG avidity (11, 19, 20).

Tuberculomas are the result of healed primary pulmonary TB and less commonly present in post primary or reactivated TB. Due to increased glucose metabolism tuberculomas accumulate 18F FDG and several studies have reported increased FDG uptake with high maximal standardized uptake value (SUV max) in tuberculoma (7, 21). Study conducted by Goo et al. (22) with histologically proven pulmonary TB in 10 consecutive patients showed increased FDG uptake in 9 tuberculomas out of 10 tuberculomas. The mean  $\pm$  (SD) of SUVmax was  $4.2 \pm 2.2$ . A series study by Sathekge et al. (7) have evaluated the diagnostic accuracy of PET-CT for differentiating benign from malignant pulmonary nodule in the patients with active lung TB by using dual time-point FDG PET-CT (60 minutes and 120 minutes projections). He also found higher SUVmax value in tuberculoma. Similar findings were reported in dual time point PET scan to assess FDG uptake in mediastinal lymph nodes in TB endemic area by Goo et al. and Kim et al. (22, 12). But SUVmax values were not significantly different in benign and malignant lesions. The reported data by Chen et al. (21), who included the patient with mean 18F FDG SUVmax value less than 2.5 and their findings were in agreement with Goo et al. and Kim et al. Another study by Kaneko et al. showed higher

retention indices in both benign and malignant lesions without any significant difference (23).

Through the above studies it is evident that the main limitation of 18F FDG PET-CT scan is the inability to distinguish tubercular from malignant lesion, especially in TB endemic areas. Several studies have investigated the role of dual time point 18F FDG imaging to evaluate pulmonary nodule as benign or malignancy but have shown no promising role.

Pleural effusion is frequently seen in TB patients and accounts in one fourth of the patients with primary pulmonary TB and in 18% cases of post primary pulmonary TB (24). The thickened pleura in TB demonstrates diffusely increased 18F FDG uptake in FDG PET- CT scan, but need to differentiate from FDG avid mesothelioma (25).

#### **DIFFERENTIATION BETWEEN ACTIVE AND INACTIVE TB**

Radiological findings when persist for long time even after complete resolution of TB, questions may arise, whether the infection is active or not. High resolution CT scan is better than chest radiography in predictive active TB with a sensitivity of 96% versus 48% (26). It has been reported that 18F FDG PET-CT scan is able to differentiate active TB from old or inactive disease. The SUVmax of active tuberculoma is significantly higher than the inactive tuberculoma. Kim et al. studied the role of dual time point PET imaging finding in 25 patients to characterize active pulmonary tuberculoma. The SUVmax value of early and delayed images and % Delta SUVmax values were recorded and compared. The active pulmonary tuberculoma showed statistically significantly higher values of SUVmax than inactive tuberculoma. In early images the SUVmax values were in active TB =  $2.3 \pm 0.75$  and inactive TB =  $0.79 \pm 0.15$ . In delayed images values were active =  $2.48 \pm 0.79$  and inactive  $0.79 \pm 0.13$  and in % Delta SUV max values were active =  $8.07 \pm 7.77$  and inactive =  $3.83 \pm 6.59$  respectively. By using the cutoff value of SUVmax

1.05, the sensitivity and specificity were 100% and 100% respectively. Kim et. al concluded that FDG PET can differentiate active TB from old inactive disease by imaging two time points. This procedure would be valuable in the evaluation of treatment response and follow up (12). Another recent study concluded that 18F FDG PET-CT has the potential to become a tool for monitoring the treatment response in extrapulmonary TB or MDRTB (27).

### EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary TB (EPTB) may affect any organ. The most commonly affected sites are lymph nodes, pleura, musculoskeletal, gastrointestinal and genitourinary tract. Immunocompromised individual (AIDS, Leukemia, lymphoma, post organ transplant), diabetics, children, the elderly, person with low socioeconomic status and alcoholics are more affected by EPTB. The AIDS endemic has also increased the incidence of EPTB (4, 28). Patients with extrapulmonary (EPTB) are difficult to diagnose not only due to their atypical presentation but the sample collection (like tissue or fluid) from the affected site for analysis are difficult. Invasive procedures are involved for sample collection. Hence with the recent advancement of the imaging procedure the identification of the disease with correct localization and extent of the disease is a challenge (4, 6).

Studies reported that tubercular lesions can be detected more by 18F-FDG PET compared to CT, especially in EPTB. Sathekge et al. has evaluated the potential impact of dual-phase 18F FDG PET versus routine staging in 16 patients with lymph node TB. In nine patients total 18 lymph node lesions were identified by both early and delayed images of PET scan, but on CT scan 9 lesions out of 18 were missed in five patients, four of them had only extrapulmonary lymph node involvement (7). PET-CT scan may show increased peripheral uptake of FDG with central hypometabolism, depending on the amount of

caseation. All affected lymph node groups can be identified in single setting and allows selection of most suitable group of lymph node for biopsy (29).

Musculoskeletal TB accounts for about 3% of all TB and reported data showed more frequent spinal involvement (around 50% spinal involvement). Diagnosis of spinal involvement is difficult due to lack of specific morphological imaging findings. Failure in timely diagnosis and initiation of treatment leads to serious complication like vertebral collapse, spinal compression or deformity. MRI is the most sensitive modality of early diagnosis (4). Several studies showed the promising role of 18F FDG PET- CT for the diagnosis of spinal TB. In a recent study Skaf et al. reported that FDG scan is highly sensitive and image quality is not affected by metal artifact over other imaging modalities (30). Another recent review by Rivas-Garcia et al. on the image findings in Pott's disease has emphasized the role of advanced imaging such as 18F FDG-PET in the assessment of extent of lesion, to guide for selection of biopsy site, to assist in surgery planning, and to contribute in follow-up evaluation (31). Gartz et al. studied on 16 patients with suspected spondylitis, and differentiate osteodegenerative changes from infective change by measuring the target to background ratio of FDG uptake. The authors concluded that 18F FDG PET-CT was superior to MRI and conventional nuclear medicine imaging (with  $^{67}\text{Ga}$ -citrate and  $^{99\text{m}}\text{Tc}$ -MDP (32).

These findings highlight the potential role of FDG PET-CT in demonstrating lesion extent, in detecting additional lesions missed on morphological imaging, and in serving as a guide for biopsy with aspiration for culture for musculoskeletal TB.

Abdominal Tuberculosis is associated with abdominal lymphadenopathy. Abdominal lymph nodes are best evaluated by CT and for liver involvement MRI plays an added role. Only few reports are available on 18F

FDG PET-CT imaging in abdominal TB and showed that the imaging pattern is nonspecific and varied (33).

In case of central nervous system the MRI is superior to the other morphological imaging and 18F FDG PET-CT imaging may complement the other modalities.

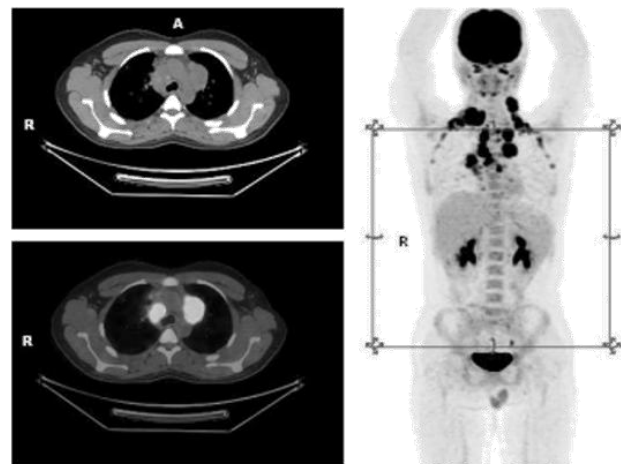
### TB CO-INFECTION WITH HIV

Diagnosis of pulmonary TB in patient who is co-infected with HIV is a challenge. The expected classical findings of pulmonary consolidation, apical involvement, cavitations are less common with presence of lymphadenopathy, pleural effusion, or a miliary pattern (34). Extrapulmonary localizations are frequent in HIV-infected patients and involve brain, pericardium, gastrointestinal tract, peritoneum and genitourinary tract (35). In absence of typical morphologic features, the functional imaging with 18F FDG PET is helpful in the diagnosis TB with co infection HIV. The intensity and pattern of FDG uptake may suggest the diagnosis. Scharko et al. evaluated FDG PET findings in 15 patients infected with HIV-1. They observed distinct lymphoid tissue activation in the head and neck during the acute phase, a generalized pattern of peripheral lymph node activation at the mid-phase and involvement of abdominal lymph nodes during the late stages of HIV infection. This suggests that lymphoid tissue uptake follows a predictable sequence (36). Study by Sathekge et al. has confirmed this observation. In addition authors demonstrated that the FDG signal derived from PET imaging in patients with HIV not only correlates with viral load but is also inversely related to the CD4 cell count. Knowledge of the CD4 cell count and the viral load can therefore be used to predict whether lymph node involvement is likely due to retroviral disease or for other disorder like lymphoma or metastatic disease (37).

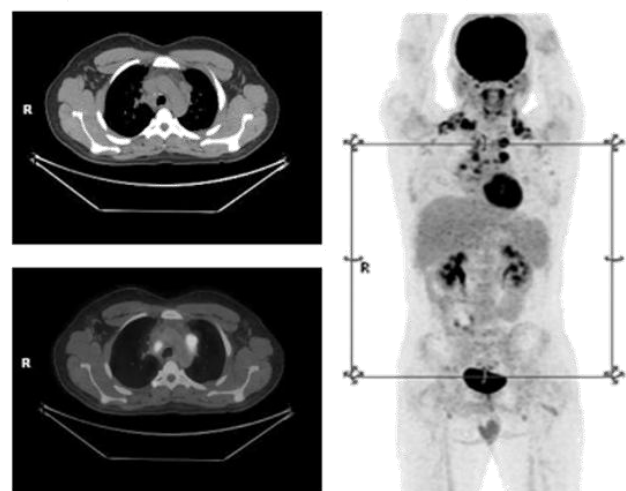
### MONITORING TREATMENT RESPONSE

The most potential and important clinical application of 18F FDG PET-CT in TB is evaluation of treatment

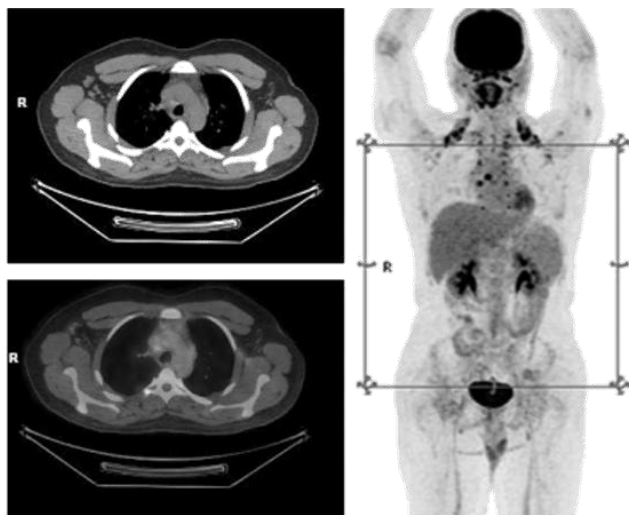
response. The morphological change (decrease in size) of the tubercular lesion often takes longer time comparing to the molecular change. Sometimes after treatment lesions even increases in size leads to a difficult situation for the physicians and they failed to assess the response of treatment or to assess the need of modification of treatment. The 18F FDG PET-CT scan can evaluate the molecular changes related to glycolytic activity within the inflammatory lesion by measuring FDG uptake to evaluate treatment response (38) (Figure 1A-1C).



**Figure 1A:** A 19-year-old male with MDR tubercular lymphadenopathy. Prior to treatment with second line of anti-TB drugs, transaxial 18F-FDG PET-CT showed multiple hypermetabolic mediastinal lymph nodes with a maximum standardized uptake value (SUVmax) of 19.8. Maximum intensity projection image revealed multiple hypermetabolic enlarged cervical, axillary and mediastinal lymph nodes.



**Figure 1 B:** After two months treatment, PET-CT scan showed both morphologic regression and decreased metabolic activity (SUVmax) of 16.2 of mediastinal lymph nodes.



**Figure 1C:** After eight months treatment PET-CT scan showed significant regression of metabolic activities and size of the mediastinal lymph nodes.

Martinez V et al. reported that approximately one-third reduction of SUVmax value after one month anti-TB treatment in pulmonary and extrapulmonary TB suggests good response (39). Another data has shown that SUVmax value (both early and delayed images of dual time point) of involved lymph nodes and the numbers of involved lymph node basins are significantly higher in non-responders than in responders (respective P values of 0.03, 0.04, and 0.002). Using a cutoff of 5 or more involved lymph node basins, responders could be separated from non-responders with sensitivity, specificity, positive and negative predictive value of 88%, 81%, 70%, and 93%, respectively. Using a cutoff value of 8.15 for the early SUVmax of lymph node basins and of 10 for the late SUVmax of lymph node basins, a comparable sensitivity of 88% with lower specificity was 73% and 67%, respectively (40). The accuracy of these findings was slightly lower when FDG PET imaging was performed at 4 months after treatment initiation. Using a cutoff for SUVmax values of involved lymph nodes of 4.5 appeared more accurate. Under these circumstances, Sathekge et al. found that lymph nodes responding to TB treatment could be differentiated

from nonresponsive ones with a sensitivity and specificity of 95% and 85%, respectively. The number of lymph nodes with rim enhancement and low central attenuation was significantly higher in non-responders compared with responders (29).

In developing countries, multidrug-resistant and extensively drug-resistant TB has serious consequences, and monitoring of therapy response is an essential part. The treatment of MDR TB is complex and treatment duration may need to be between 9 and 18 months, and PET might provide an objective measure of treatment response and the required duration. Several studies have confirmed the value of 18F FDG PET-CT in the follow up and evaluation of treatment response, especially in EPTB and MDR TB (29, 33, 39, 41, 42).

## CONCLUSION

Though 18F FDG PET-CT is not specific for TB, it plays a potential role in the evaluation of known or suspected TB, identification of EPTB with disease extension, guide biopsy from active site, staging of TB, and assessment of treatment response.

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