^{18}F FDG PET-CT Imaging in the Evaluation of Diagnosed Extra Pulmonary Tuberculosis

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ABSTRACT

***Objective*: Extra Pulmonary Tuberculosis (EPTB) presents with atypical symptoms and heterogeneous clinical features. Management of EPTB including diagnosis, localization, extension and monitoring treatment response of active disease is quite challenging. Moreover, localization of active disease, differentiation between active and latent disease by conventional methods is troublesome. So this study was done to evaluate the metabolic activity of active disease by ^{18}F Flurodeoxyglucose (FDG) PET-CT in diagnosed cases of EPTB patients.**

***Patients and methods:* A total of 17 patients with EPTB were included in this study. FDG PET-CT scan was performed to evaluate the metabolic activity of tubercular lesions before anti-TB treatment. Clinical features, biochemical changes including ESR, WBC count, CRP, MT test and maximum standardized uptake value (SUVmax) of most intense FDG avid lesions and sizes were recorded in ^{18}F FDG PET-CT scan.**

***Results:* All 17 patients (09 female, 08 male) had lymph node involvement, two had bone TB and two had abdominal TB. Active TB lesions showed increased FDG uptake in extra-pulmonary tubercular lesions in 16 patients. The mean SUVmax value of the involved lymph nodes were 9.4 ± 6.0 and the mean size (maximum diameter) 19.8 ± 10.4 mm (mean ± SD). One histologically proven EPTB patient had non avid lesions in FDG PET-CT scan.**

***Conclusion:* ^{18}F FDG PET-CT scan plays an important role in the localization, extension and differentiation between active and latent TB. In this study, the metabolic activity and size of the involved tubercular lymph nodes were increased in active lesions. Increased FDG uptake in active tubercular lesions may help in treatment monitoring of EPTB. Non avid lesions in EPTB patients suggested latent TB which can change further management plan. Although PET-CT is an expensive technology, application of this sophisticated imaging technique in atypical or doubtful cases of EPTB might modify the treatment plan significantly after proper evaluation of the disease status.**

***Key Words:* FDG PET-CT, Extra pulmonary TB, Active TB.**

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INTRODUCTION

Tuberculosis (TB) is a major clinical burden in the world as well as in Bangladesh. According to the Global TB Report 2016, more than two billion people in the world are suffering from TB which is approximately one third of the global population. Bangladesh is one of the world's high TB burden countries; positioning sixth in the world (1).

A National Tuberculosis Control Program (NTP) report states that the total number of TB patients increased from 57% to 61% between 2015 and 2016. It is also estimated that 25.51% of TB infections occur extrapulmonarily in Bangladesh (2). Worldwide, TB is the second highest infective cause of death after HIV (3). Newly adopted Sustainable Development Goals (SDGs) target for elimination of the TB epidemic by 2030 (4).

Diagnosis of Pulmonary TB (PTB) is done by medical history, Mantoux Test (MT), appropriate laboratory tests which include acid fast staining, microscopic analysis, and mycobacterial culture of fluid and tissue samples. Sputum culture is the gold standard method for diagnosis of PTB. Conventional imaging like chest radiograph, Computed Tomography (CT) is also used for diagnosis of PTB. CT is more sensitive in case of lymphadenopathy and early bronchogenic changes. Generally, TB has an excellent outcome with the standard treatment. However, there are subsets of patients who develop multidrug resistance TB (MDR TB) and EPTB, who have serious consequences. EPTB occurs in immunocompromised patients with HIV infection or in malignancy. Detection of EPTB is challenging as it presents with atypical symptoms and heterogeneous presentation. Sample collection is difficult in EPTB and needs invasive procedures (5).

MT test can be used to test for TB infection which has been used to and assess the immunological response. The test has limitations of being falsely negative in

immunocompromised patients, while it gives false-positive results are seen in patients with other types of mycobacteriosis or history of previous vaccinations against TB (3). TB blood tests are also called interferon-gamma release assays or IGRAs that uses a blood sample to find out if someone is infected with TB bacteria, but it cannot differentiate between active and latent TB (5,7).

Conventional methods including MT, biopsy tissue, fine needle aspiration cytology (FNAC), CT scan, magnetic resonance imaging (MRI) etc. are usually used to diagnose EPTB, but they are not specific and sometimes access to the lesion sites become difficult. These conventional methods sometimes cannot differentiate between latent and active disease. Hence definitive diagnosis of active TB in atypical and heterogenous presentations is difficult. In this regard, ^{18}F FDG PET-CT scan may be helpful (3, 14).

Although ^{18}F FDG PET-CT scan is well known for the evaluation of the management of carcinoma, moreover; it can also be used in the assessment of infectious disease TB. The principle mechanism for the high accumulation of FDG in the infectious lesions is primarily due to high glycolytic activity of the activated inflammatory cells such as macrophages and neutrophils. These two cell types utilize large amount of glucose as the main source of energy for phagocytosis and chemotaxis. Hence, ^{18}F FDG PET-CT imaging may play a potential role in the localization and extension of the disease (3, 6,7,8). It is also reported the efficacy of using FDG PET-CT scan for determining active and latent TB as well as treatment follow up of EPTB (9).

In PET-CT scan, intense FDG uptake by tuberculous lesion is a significant sign of active TB. Hence, present study was undertaken to explore the role of non-invasive ^{18}F FDG PET-CT scan in EPTB patients to localize and assess the extent of active disease.

PATIENTS AND METHODS

It was an observational study. A total of diagnosed 17 EPTB patients were enrolled in National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka during the period of July 2017 to June 2018. Study was conducted with the approval of Medical Research Ethics Committee (MREC) and under International Atomic Energy Agency (IAEA), Coordinated Research Project (CRP)-15021. Patients with age < 18 years, pregnancy and other co-morbid conditions were excluded from the study. Baseline ^{18}F FDG PET-CT scan in diagnosed cases of EPTB was performed before anti-TB treatment. Clinical features like evening rise of fever, weight loss, malaise, coughing, biochemical changes including ESR, WBC count, CRP, MT test were recorded. The maximum standardized uptake value (SUVmax) of most intense FDG avid lesions and sizes were recorded in whole body ^{18}F FDG PET-CT scan. Statistical analyses were carried out by using SPSS version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical data were expressed in number and percentages. Parametric data were expressed in mean + SD.

RESULTS

The age distribution of the study patients is shown in Table 1. It was observed that majority 11 (64.7 %) patients belonged to age 21 to 30 years. Sex distribution of study population is shown in Figure 1.

The site of involvement was depicted in Figure-2. It was observed that all 17 patients had lymph node involvement, two had bone involvement and two had abdominal involvement including terminal ileum and adrenal gland.

Table 1: Distribution of the study patients according to age (n=16)

Age (in years)	Number of patients	Percentage (%)
18-20	4	23.5
21-30	11	64.7
31-40	1	5.8
>40	1	5.8
Mean ± SD		27.2 ± 11.2
Range (min-max)		(18 - 65) Years

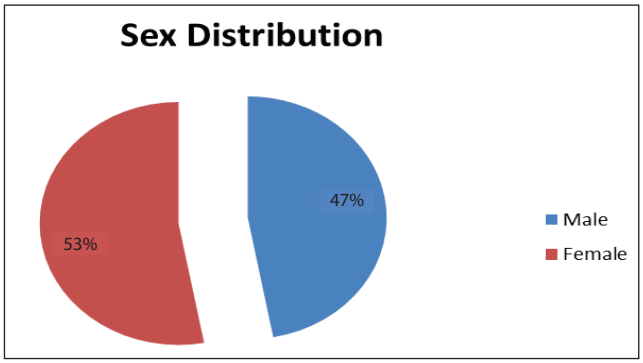

Figure 1: Pie chart showing sex distribution of the study patients.

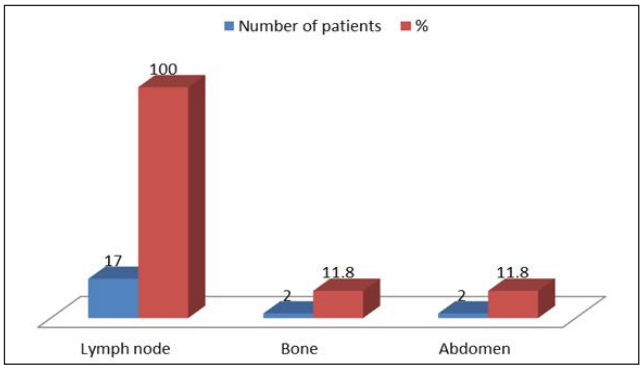

Figure 2: Column showing distribution of the study patients according to site of involvement.

The distribution of the study patients according to method of diagnosis of EPTB was out of total 17 patients 70.6% (12) was diagnosed by biopsy and 29.4% (05) by clinical features and radiology (Table 2)

Table 2: Distribution of the study patients according to method of diagnosis (n=17)

Diagnosed by	Number of patients	Percentage (%)
Biopsy	12	70.6
Clinical features plus Radiology	5	29.4
Total		100

Table 3 shows distribution of the study patients according to previous history of TB. It was observed that 47.1% patients (8) had positive history of previous TB.

Table 3: Distribution of the study patients according to previous history of TB (n=17)

History of TB	Patients (n=17)	Percentage (%)
Yes	08	47.1
No	09	52.9
Total	17	100

Table 4 shows distribution of the study patients by tuberculin skin test (MT test). It was observed that majority 13 (76.5 %) patients had positive MT test and 4(23.5%) patients had negative MT test.

Table 4: Distribution of the study patients by MT test (n=17)

MT test	Patients (n=17)	Percentage %
Positive	13	76.5
Negative	4	23.5
Total	17	100

The mean SUVmax value and size of the involved lymph nodes were shown in Table 5. It was observed that mean SUVmax value of the involved lymph node, bone TB and abdominal TB were 9.4 + 6.0, 10.1 ± 4.5and 5.7 ± 1.1 (mean + SD) respectively. Mean size of the involved lymph nodes was 19.8 ± 10.4 mm (mean + SD).

Table 5: Mean SUVmax value and size of the involved lymph nodes among the study patients

	Lymph node TB	Bone TB	Abdominal TB
Mean SUVmax ± SD Range	9.4 ± 6.0 (2.9-20.8)	10.1 ± 4.5 (6.9-13.3)	5.7 ± 1.1 (4.9-6.5)
Size (cm) Range	19.8 ± 10.4 (6.8-45.0)		

The patient's characteristics of clinical, biochemical and FDG PET-CT features including sex, WBC, ESR, CRP (C reactive protein), MT, histopathology, SUV max and size of the lymph nodes (LN). It is observed that 16 patients had raised ESR, 14 had raised CRP, 13 had positive MT test and 12 had granulomatous infection on histopathology out of total 17 patients. It is also observed that one patient had positive MT test, positive histopathology and non-avid lesions in 18F FDG PET-CT scan.

Figure-3 shows the FDG PET-CT scan of EPTB patient showing intense FDG uptake (SUVmax: 20.8, measures about 19.0 mm) in mediastinal lymph nodes in Maximum Intensity Projection (MIP) view, axial PET-CT view and axial CT view.

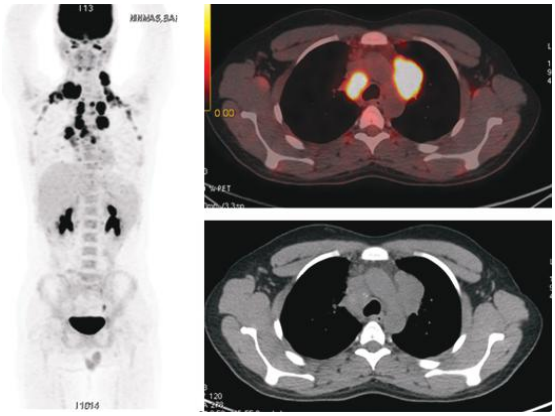

Figure 3: ^{18}F FDG PET-CT scan of EPTB patient in mediastinal lymph nodes.

In the ^{18}F FDG PET-CT scan of EPTB patient showed non avid lesions in Maximum Intensity Projection (MIP) view, axial PET-CT view and axial CT view (Figure 4).

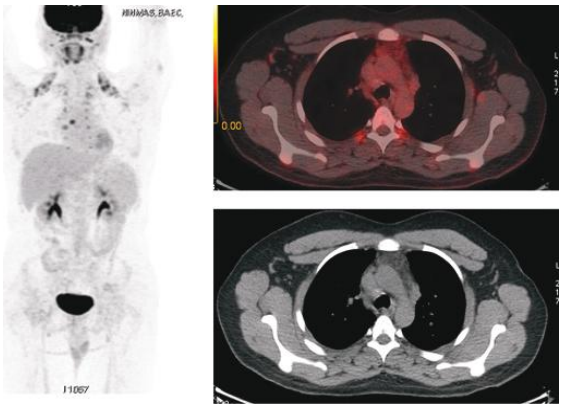

Figure 4: ^{18}F FDG PET-CT scan of EPTB patient in mediastinal lymph nodes.

Figure 5 shows the 18F FDG PET-CT scan of EPTB patient showing FDG avid bony lesions in Maximum Intensity Projection (MIP) view, axial PET-CT view and axial CT view.

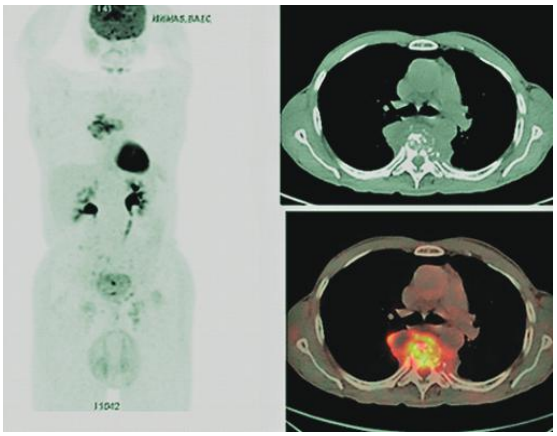

Figure 5: ^{18}F FDG PET-CT scan of EPTB patient in bone TB.

DISCUSSION

In this study, it was observed that majority 64.75% patients belonged to age between 21-30 years and the mean age was 27.2 ± 11.2 years (mean ± SD) with age ranged from 18 years to 65 years (Table 1). The highest prevalence of age group was 20-24 years in a study (2). However, other studies found higher mean age comparing to the current study which may be due to geographical variations, ethnic differences, socio-economic factors and genetic causes (9, 12).

In this current study, it was observed that majority patients 9 (53%) were female out of total 17 patients (Figure 1) which were closely resembled with other several recent studies (9,10,11).

In the current study, it was observed that the commonest site of involvement of EPTB was lymph nodes (Figure 2). Sathekge reported in his study the predominant site of involvement of EPTB was lymph nodes and he showed 23 cases of lymph node involvement among 24 cases (12). Regarding the sites of TB involvement, Martinez also observed the most common site of EPTB was lymph nodes (9), which resembles with the current study.

In this present study, EPTB was diagnosed by histopathology in 12 cases (70.6%) and rest of the 5 cases was diagnosed by clinical features and radiology (Table 2). In a study by Sathekge, TB was diagnosed in 12 patients by histopathology and 8 TB patients were diagnosed by sputum microscopy and culture (13). In another study, Demura found TB in 25 patients and 22 in mycobacterium aviumintracellulare complex by bacteriological examinations (14). Sathekge also showed HIV associated TB cases were diagnosed histopathologically in 12 patients, sputum smear were diagnostic in 8 patients and 4 patients were diagnosed clinically, which were closely resembled with the present study (12). In another study, Martinez showed 09 out of total 21 patients were diagnosed by histopathology, 8 by microscopy and culture and 4 by clinical presentations (9).

In this study 8(47.1%) patients had past history of TB and 52.9% were newly diagnosed EPTB (Table 3). Martinez reported that out of 21 patients 5 cases had past history of TB (9). Martinez also found that 11 patients of EPTB had positive MT test out of 21 patients (9). Similarly in current study, majority 13(76.5%) of the cases had positive MT test (Table 4).

In this study, Table 6 showed the patient's characteristics of clinical, biochemical and FDG PET-CT features including sex, WBC, ESR, CRP, MT, histopathology, SUV max and size of the lymph node (LN) and FDG PET- CT findings. It is observed that 16 patients had raised ESR, 14 had raised CRP, 13 had positive MT test, and 12 had granulomatous infection on histopathology out of total 17 patients. These findings are compatible with other study (9).

In this study out of 17 patients' 16 patients showed FDG avid extra-pulmonary lesions. It was observed that mean SUVmax value of the involved lymph node, bone TB and abdominal TB were 9.4 + 6.0, 10.1 ± 4.5 and 5.7 ± 1.1 (mean ± SD) respectively. The mean size of the involved lymph nodes was 19.8 ± 10.4 mm (mean ± SD). The high accumulation of FDG in the infectious lesions is might be due to high glycolytic activity of the activated inflammatory cells such as macrophages and neutrophils, which utilize large amount of glucose as the main source of energy for phagocytosis and chemotaxis. Similar increased FDG accumulation in tubercular lesions was also observed in several studies. Martinez in his study found the median SUVmax value: 8.6 in tubercular lesion; range of SUVmax value from 3.1 to 15.5 (9). Sathekge found higher metabolic activity in in 8 TB patients (SUVmax 11.2 ± 4.0, mean ± SD) in FDG PET scan (13). Lefebvre also found mean SUVmax: 8.7 in generalized lymph node TB (LNTB) and SUVmax: 8.5 in localized LNTB. (11). All studies showed significant uptake of FDG or increased SUVmax value in active TB; which resembles with this present study. Hence, ^{18}F FDG PET-CT imaging may play a potential role in the localization lesions and extension of the EPTB (3,6,7,8).

In this study only one patient had no FDG uptake in the involved lymph node in PET-CT scan despite of having positive MT test, raised WBC count and presence of granulomatous infection in lymph node on histopathology (Table 6 and Figure 4). Studies suggested that latent TB may not have FDG uptake (3, 15). This patient might had latent TB infection and for confirmation further follow-up was recommended.

CONCLUSION

^{18}F FDG PET-CT scan plays an important role in the localization, extension and differentiation between active and latent TB. In this study, the metabolic activity and size of the involved tubercular lymph node were increased in active lesions. Increased FDG uptake in active tubercular lesions may help in treatment monitoring of EPTB. Non avid lesions in EPTB patient revealed latent TB which can change further management plan. Although PET-CT is an expensive technology, but in atypical or doubtful cases of EPTB, ^{18}F FDG PET-CT scan will be helpful to evaluate the disease status and modification of treatment regime in non-responders cost-effectively. A nationwide large-scale study would be the better way for clinical validation.

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