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Towards more accurate ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging in active and latent tuberculosis

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ABSTRACT

Tuberculosis (TB) is one of the leading causes of death worldwide. Although the disease is curable and preventable, it is underdiagnosed in many parts of the world. Positron emission tomography (PET) imaging using ^{18} F-FDG in TB can localise disease sites and the extent of disease. ^{18}F-FDG accumulates in the immune cells that participate in inflammation and granuloma formation, such as activated macrophages and lymphocytes. Therefore, FDG PET/CT scanning is now being evaluated for its usefulness in the diagnosis of extrapulmonary TB and in monitoring the response to treatment. FDG PET/CT imaging is positive and has high sensitivity in active TB, complementing conventional radiological imaging (X-ray, computed tomography, magnetic resonance imaging) in the diagnosis of primary pulmonary, extrapulmonary, and post-primary or miliary TB. FDG PET/CT has low specificity when it is used for solitary pulmonary nodule characterization, and its ability to differentiate TB from malignancy is limited in this setting. Dual point imaging has been proposed as a way to overcome this limitation. FDG PET/CT can reliably differentiate active from inactive disease, and there is promising evidence that it can contribute to the assessment of the response to treatment with an impact on patient management. FDG PET/CT has been found positive in cases of latent TB infection and its ability to identify activation early is currently being explored. More studies are needed to establish the utility of this method in recognizing multidrug-resistant TB cases. Furthermore, other PET radiotracers might prove useful in the functional imaging of TB infection in the future.

Introduction

Tuberculosis (TB) is a contagious infectious disease, which, despite advancements in diagnosis and treatment, remains one of the top 10 causes of death and the leading cause of death from an infectious agent (WHO, 2019). It is caused by *Mycobacterium tuberculosis*, a highly aerobic bacterium that primarily affects the lungs. Extrapulmonary TB can also occur, mainly in immunosuppressed patients (e.g., HIV patients), and represents approximately 15% of new and relapsed cases of active TB (WHO, 2019; Kiazyk and Ball, 2017).

TB is transmitted through airborne droplets from coughs and sneezes. Persons who are infected with *M. tuberculosis* can either develop active symptomatic disease, which needs immediate treatment, or can remain asymptomatic with latent TB, carrying the risk of disease reactivation in the future. It is estimated that almost one quarter of the world population (approximately 1.7 billion people) have already been latently infected and 10% of them will show reactivation of the disease (WHO, 2019; Cohen et al., 2019).

Although the disease is curable and preventable when there is timely diagnosis and treatment, the World Health Organization (WHO) Global Tuberculosis Report 2019 reported 10 million new cases of TB with 1.5 million deaths from the disease worldwide in 2018, while a multidrug-resistant form of the disease is on the rise and represents an additional challenge (WHO, 2019).

The WHO has developed a strategy to end TB by 2030, with 5-year targets for reductions of TB cases and deaths, among others. However, despite efforts made, the targets for the 2020 milestone

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are far from having been reached, with the exception of the European Region (WHO, 2019). One of the main reasons for this is the underdiagnosis of disease.

In this context, imaging is expected to play an even greater role in the battle against TB in the future. Currently, conventional chest X-ray remains the primary imaging modality for screening purposes, while computed tomography (CT) and magnetic resonance imaging (MRI) are modalities of choice for the evaluation of specific body parts (Skoura et al., 2015). Positron emission tomography (PET)/CT with ^{18}F-fluorodeoxyglucose (FDG) has shown promise not only in the early detection of TB, but also in the assessment of the response to treatment. The aim of this review article is to present up-to-date data on the role of PET/CT in active and latent TB and to evaluate the contribution of this modality to the achievement of the goal to end the TB epidemic in the coming decades.

Pathophysiology of TB infection and mechanisms of ^{18}F-FDG uptake

^{18}F-FDG is a radiolabelled glucose analogue that has been used successfully in tumour imaging, due to the high metabolism that cancer cells exhibit. The observation that ^{18}F-FDG also accumulated in inflammatory processes during routine scans in cancer patients led to the exploration of the clinical utility of this radiotracer to image infection and inflammation, including TB (Jamar et al., 2013). ^{18}F-FDG uptake in TB is thought to be associated with the increased metabolic needs of activated macrophages and lymphocytes, which have a prominent role in TB and other granulomatous diseases (Heysell et al., 2013). On the basis of this simple rationale, FDG PET/CT is an accepted imaging modality that can contribute to the diagnosis, staging, and localization of TB, as well as the assessment of the response to treatment (Skoura et al., 2015; Jamar et al., 2013; Heysell et al., 2013; Ankrah et al., 2016).

The latest evidence may provide a more detailed view of the accumulation of ^{18}F-FDG in immune cells that participate in the different phases of TB infection. Upon infection with *M. tuberculosis*, macrophages are polarized towards the M1 profile. The M1 polarization is associated with metabolic reprogramming of the macrophage in which the glycolytic flux is increased and the oxidative phosphorylation downregulated, a phenomenon similar to the Warburg effect in cancer cells. This process involves the upregulation of genes encoding enzymes that are also important for ^{18}F-FDG uptake in the cells, such as glucose transporters and hexokinases (Shi et al., 2019). This state of early macrophage activation is necessary for the production of antimicrobial and proinflammatory molecules, which will attempt to clear the infection and promote granuloma formation in order to prevent dissemination of the mycobacteria (Ankrah et al., 2016; Shi et al., 2019). Granulomas consist of macrophages, lymphocytes, neutrophils, and fibroblasts, which may demonstrate some degree of ^{18}F-FDG uptake as well (Borchert et al., 2019).

The mycobacteria do not suffer the host's immune response passively, but are armed with mechanisms to interfere with the macrophage response. Therefore, after the early defending phase, a late adaptation/resolution phase may be observed, during which there is dampening of glucose uptake and glycolysis and improved survival and/or growth of *M. tuberculosis* (Shi et al., 2019). The persistence of the *M. tuberculosis* in a state of dormancy within the infected macrophages may lead to latent TB infection (LTBI), which is defined clinically as an asymptomatic state with reactive tuberculin skin test (Shi et al., 2019; Dutta and Karakousis, 2014).

PET/CT in active tuberculosis

In primary pulmonary TB, FDG PET/CT is able to localize the granulomas in the lung parenchyma, which are typically FDG-avid. Therefore, FDG PET/CT is useful in the assessment of the activity and extent of pulmonary disease.

Two patterns of FDG-avid active pulmonary TB have been described: the lung pattern and the lymphatic pattern. The lung pattern is present in patients with predominantly pulmonary symptoms and disease restricted to the pulmonary parenchyma (Figure 1), consisting of areas of lung consolidation with or without cavitation and satellite micronodules. The ^{18}F-FDG uptake in these lesions is usually low-to-moderate, reflecting a milder form of disease. In the lymphatic pattern, the main finding is enlarged mediastinal and hilar lymph nodes with high FDG uptake, representing an intense infection that can also have extra-thoracic involvement with systemic symptoms (Skoura et al., 2015; Soussan et al., 2012).

Another form in the clinical spectrum of TB is miliary TB, which is more prevalent in the elderly, children, and immunocompromised patients (e.g., HIV patients), and can manifest either as primary or post-primary TB (i.e., under acquired immunity) (Burrill et al., 2007). Miliary TB is characterized by multiple millet seed-sized (1–2 mm) granulomas in the lung and other organs, resulting from massive lympho-haematogenous dissemination of *M. tuberculosis* (Sharma et al., 2012). The typical radiographic pattern in the chest on X-ray and high-resolution CT is bilateral diffuse reticulonodular lung lesions, which show increased FDG activity on PET/CT. This miliary pattern can be accompanied by the 'tree-in-bud' sign, describing well-defined, linear, branching opacities that represent endobronchial spreading of infection, and are usually seen in post-primary disease (Skoura et al., 2015; Sharma et al., 2012; Lee and Im, 1995; Curvo-Semedo et al., 2005). Pleural effusion can be present in up to 25% of the patients, which is usually unilateral on the same side as the primary pulmonary focus. Enlarged FDG-avid hilar and mediastinal lymph nodes are seen in patients with primary disease and less commonly in the post-primary setting (5–10%) (Jeong and Lee, 2008). Complications such as pericardial effusion, empyema, and bronchopleural fistula are rare (Burrill et al., 2007). ^{18}F-FDG PET/CT, as a whole-body imaging method, has the advantage of localizing and monitoring the response to therapy in extrapulmonary TB when there is no pulmonary involvement and in identifying additional extrapulmonary sites of disease in TB. ^{18}F-FDG uptake can occur in sites such as the liver, abdominal lymph nodes, and bones (Figures 2 and 3), or diffusely in the spleen as a sign of active infection (Vorster et al., 2014; Rodriguez-Takeuchi et al., 2019; Bomanji et al., 2019). FDG PET/CT might also be useful to identify extrapulmonary involvement of the central nervous system, but MRI is considered superior in this setting (Vorster et al., 2014; Rodriguez-Takeuchi et al., 2019; Bomanji et al., 2019; Gupta et al., 2009; Chaudhary et al., 2017).

A known limitation of FDG PET/CT, when it is used for the assessment of a solitary pulmonary nodule, is the lack of ability to differentiate a tuberculoma from a malignant lesion. This results in false-positive results in patients with a suspicion for malignancy (Li et al., 2011). The maximum standardized uptake value (SUVmax) has not been proven as a reliable marker in the differential diagnosis of TB from malignancy, as there is significant overlap and no cut-off threshold can be identified (Ankrah et al., 2016). Dual time point imaging has been suggested as a method that can increase the specificity of FDG PET/CT, but more studies are needed to establish the efficacy of this approach (Yen et al., 2008; Cheng et al., 2013).

Despite the low specificity and positive predictive value (PPV), the high sensitivity and negative predictive value (NPV) of FDG PET/CT imaging in TB has led to the use of the method for

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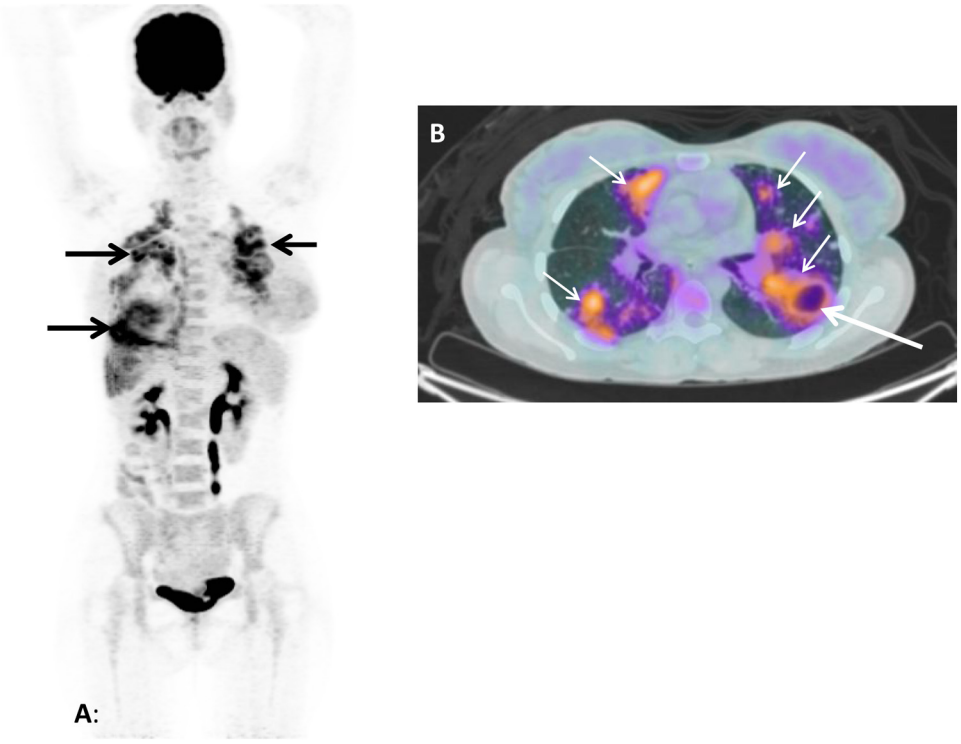

Figure 1. ^{18}F-FDG PET/CT scan showing pulmonary tuberculosis in a 32-year-old female patient. (A) Whole-body projection is shown. The black arrows indicate, from top to bottom, F-FDG uptake in lung parenchyma and a small right avid pleural effusion. (B) Transaxial fused images at the level below carina showing left and right lung parenchymal activity (small white arrows) and cavitation on the left (large white arrow).

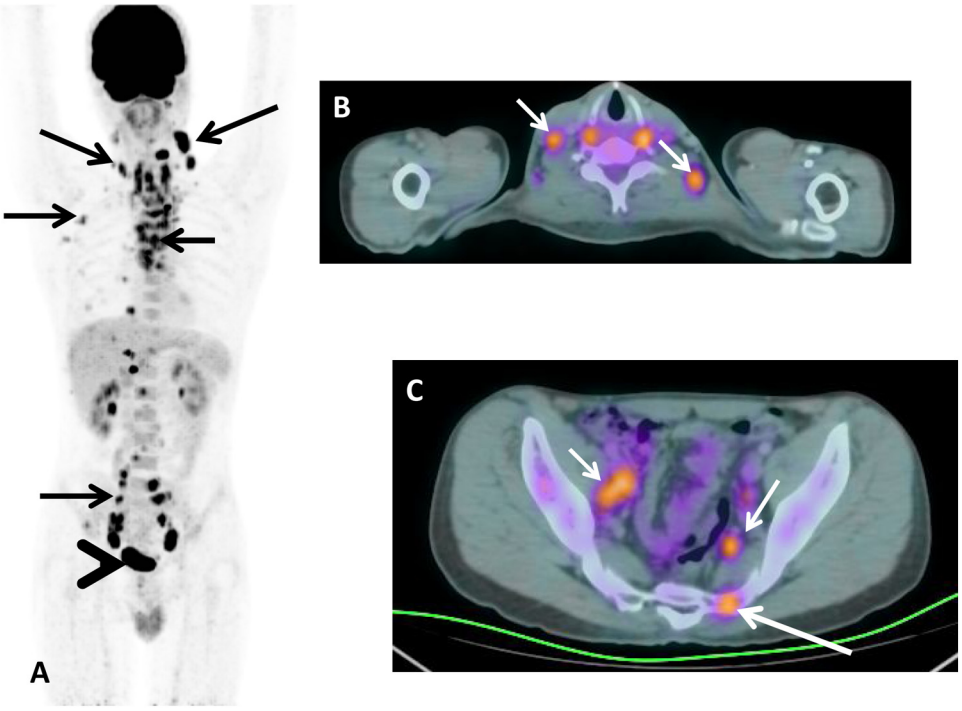

Figure 2. ^{18}F-FDG PET/CT scan showing nodal extrapulmonary tuberculosis in a 28-year-old male patient. Biopsy of the left cervical node confirmed tuberculosis. (A) Whole-body projection is shown. The black arrows indicate, from top to bottom, F-FDG uptake in bilateral cervical nodes, right axillary node, mediastinal nodes, and right pelvic nodes. The arrow head at the bottom shows excreted activity in the urinary bladder. (B) Transaxial fused images at the level of the cervical region showing the left and right cervical nodes (small white arrows). (C) Transaxial fused images at the level of the pelvis region showing left and right pelvic side wall nodes (small white arrows) and a lesion in the left sacral region (long white arrow).

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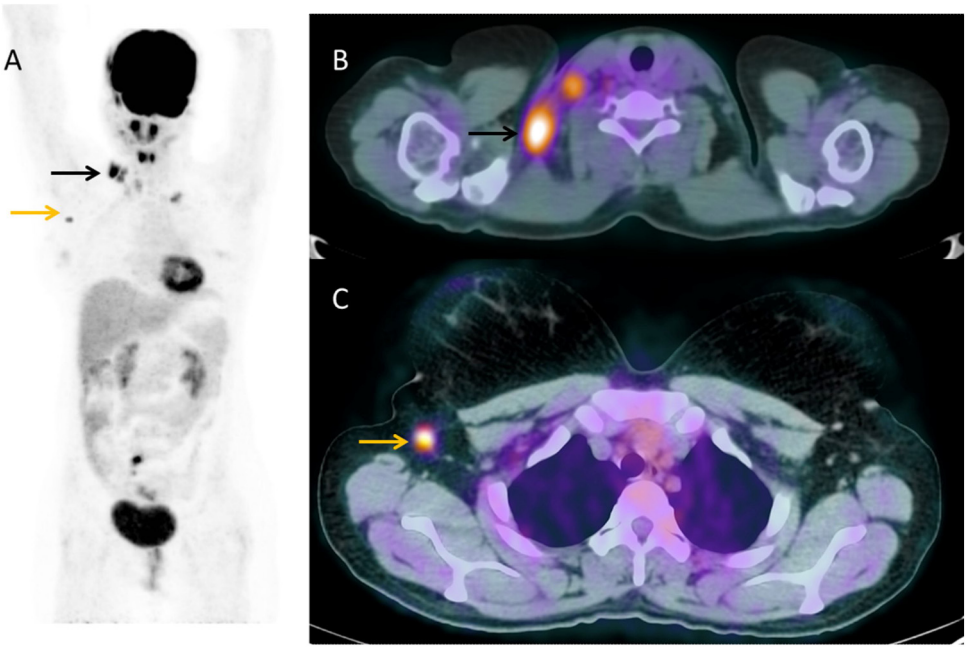

Figure 3. ^{18}F-FDG PET/CT scan showing nodal extrapulmonary tuberculosis in a 35-year-old female patient. (A) Whole-body projection is shown. The black arrow indicates F-FDG uptake in the right supraclavicular lymph nodes, which were palpable on clinical examination. The yellow arrow shows additional F-FDG uptake in a small right axillary lymph node that was not palpable. (B) Transaxial fused images at the level of the supraclavicular region showing the palpable lymphadenopathy (black arrow). (C) Transaxial fused images at the level of the axillae showing an additional site of disease in a small right axillary node (yellow arrow).

distinguishing between active and inactive disease before the resolution of radiographic features. This is particularly useful in the post-treatment setting to assess the response, as the rise of multidrug-resistant forms of TB, along with high rates of poor adherence to therapy leading to persistent TB, represent major challenges. Specifically, in a study exploring the utility of dual time point imaging, a cut-off SUVmax of 1.05 at 60 min after injection was suggested to be optimal in distinguishing active from inactive tuberculomas, with 100% sensitivity and specificity (Kim et al., 2008). A study by Malherbe et al. showed that persistent FDG uptake in pulmonary lesions that did not resolve after treatment was correlated with ongoing *M. tuberculosis* mRNA transcription and a high risk of recurrence (Malherbe and Shenai, 2016). Timely identification of TB persistence could lead to individualized management strategies, including shortening of the first-line regimen and earlier initiation of second-line drugs. The potential of FDG PET/CT to be used as a reliable marker for the evaluation of the response to second-line or alternative therapeutic regimens has also been demonstrated in animals and humans (Coleman et al., 2014). However, further studies are needed to confirm the value of FDG PET/CT in the assessment of the treatment response and to standardize criteria of response, as a recent attempt at meta-analysis could only identify four studies with high heterogeneity, which had measured SUVmax changes in TB lesions before and after treatment (Sjölander et al., 2018).

PET/CT in latent TB

As mentioned above, latent TB refers to a disease state in which the *M. tuberculosis* adopts a dormant state within the infected macrophages in order to evade complete obliteration by the successful host's immune response. In this quiescent state of minimal activity, no ^{18}F-FDG uptake is anticipated and therefore FDG PET/CT imaging is not expected to be clinically valuable. However, there has been a description of patients with FDG-positive lung lesions and lymphadenopathy, who were asymptomatic with negative sputum cultures (Malherbe and Shenai, 2016). Studies in non-human primates have shown that the dichotomization of TB into latent and active is not accurate, and that these are rather the extremes of a spectrum of states, in which latent disease is gradually activated, passing through a stage of subclinical infection with increased bacterial burden. In this state of subclinical infection, there might be intermittent ^{18}F-FDG avidity, which, if properly appreciated, might lead to early treatment before the appearance of symptoms (Kim et al., 2008; Heysell et al., 2013; Treglia et al., 2011). A study of a cohort of asymptomatic HIV-positive patients living in South Africa, diagnosed with latent TB by positive QuantiFERON Gold In-Tube test, was able to identify patients with evidence of subclinical disease who had a higher risk of progression, based on FDG PET/CT findings. Specifically, it was shown that there is heterogeneity within what is currently diagnosed as latent TB, with findings of pulmonary fibrotic scars and FDG-avid infiltrates or active nodules being consistent with subclinical disease (Esmail et al., 2016). A published case series by Ghesani et al. showed that asymptomatic subjects with close contact to TB patients had positive findings in baseline ^{18}F-FDG PET/CT studies, which resolved after treatment for latent TB (Ghesani et al., 2014). Further studies are needed in patient series in order to evaluate to what degree the use of FDG PET/CT imaging is able to identify these patients and if this early identification of TB activation has a significant impact on the treatment outcome.

Future directions

As clinical data on the utility of imaging in active and latent TB accumulate, the following areas of particular interest for imaging with FDG PET/CT are emerging.

First, there seems to be promising potential for FDG PET/CT to be a reliable marker for the assessment of the response to treatment, which remains an unmet need in view of multidrug-resistant forms of disease being on the rise.

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Second, as latent TB is being redefined with new clinical states identified in the spectrum from asymptomatic infection to overt disease (Ghesani et al., 2014; Achkar and Jenny-Avital, 2011), imaging with FDG PET/CT might contribute to the differentiation of these states and the early identification of disease activation, with implications for the management of patients.

Third, the lack of specificity of ^{18}F-FDG uptake has limited the utility of this method in the initial diagnosis of TB and differentiation from malignancy, and further studies are needed to address this limitation. The results from dual time point imaging have not been encouraging (Ankrah et al., 2016), but there is evidence that the evolution of radiomics and machine learning will improve lung nodule characterization (Drain et al., 2018).

Apart from ^{18}F-FDG, other PET radiotracers may be appropriate for TB imaging, such as radiolabelled choline, ^{18}F-fluorothymidine (FLT), and ^{68}Ga-citrate, but few clinical studies exist (Ankrah et al., 2016). Moreover, radiolabelled chemotherapeutics such as ^{11}C-rifampicin, ^{11}C-isoniazid, and ^{11}C-pyrazinamide have been tested preclinically in animals to determine the adequacy of accumulation of the drugs in the infection site, providing a first glimpse of a theranostics potential in TB (Chen et al., 2017).

Conclusions

It is known that the majority of deaths from TB occur in low-income countries where there is no adequate infrastructure for nuclear imaging (Ankrah et al., 2019; Perini et al., 2019). Therefore, the expected impact of ^{18}F-FDG PET/CT in the diagnosis of TB and in the improvement of patient outcomes will not be significant if the current shortage of worldwide availability of PET imaging is not improved.

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Ethical approval

Ethical approval was not required.

Conflict of interest

All authors declare no conflicts of interest.

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