Review Article

The role of PET/CT in the investigation of Fever of Unknown Origin

ABSTRACT

Aims: Fever of unknown origin (FUO) remains a diagnostic challenge for clinicians. The current diagnostic approach includes a detailed medical history, physical examination, laboratory and imaging tests (chest X-ray, ultrasound, CT, MRI). 18F-FDG PET/CT (18fluoro-deoxyglucose PET/CT) is a non-invasive diagnostic imaging technique which is widely used in oncology. The purpose of our review was to summarize the knowledge for the diagnostic role of 18F-FDG PET/CT in the diagnostic approach of patients with FUO, as reported in the literature. **Methodology:** We undertook a systematic review of literature published in PubMed until December 2019.**Results:** Various studies showed that 18F-FDG PET/CT can play an important role as a second-line explorative technique in the diagnosis of patients with FUO. 18F-FDG PET/CT presents high diagnostic accuracy in large vessel vasculitis in orthopedic prosthetic infections, in chronic osteomyelitis and in prosthetic valve endocarditis. However, 18 -FDG/PET has some limitations such as the assessment of urine tract due to the excretion into the urine but also become of the high glucoze metabolism in some organs such as the brain. **Conclusions:** Overall, PET/CT gains increasing interest in the diagnosis of FUO andshould be considered by the clinicians in the exploration of those patients.

Keywords: fever of unknown origin, FUO, PET/CT, endocarditis, soft tissue infections, cancer

1. INTRODUCTION

The definition of fever of unknown origin (FUO) was originally proposed in 1961 by Petersdorf and Beeson [1] they described it as fever of 38.3^{o}C or higher with a duration of two to three weeks, whose cause remains unknown after one week of hospital evaluation. The evolution of diagnostic, laboratory and imaging techniques has led to the elimination of the criterion of “one week of hospital evaluation” from the definition, as it is no longer considered essential for a case with fever to be termed as FUO. The current guidelines stipulate that the cause of the fever must have been investigated for “at least

three days in the hospital, on three outpatient visits, or during one week of logical and intensive outpatient testing, without clarification of the fever's cause" [1-4]

FUO encompasses four distinct subcategories, proposed by Durack and Street [5] based on specific patient characteristics, which call for a distinct diagnostic approach: nosocomial, neutropenic, HIV-related and classical FUO:

(a) **Nosocomial FUO** is defined as fever that develops at least 48 hours following hospital admission. The patient must have no visible signs of infection prior to admission. The most common causes of hospital fever are septic thrombophlebitis, pulmonary embolism, enterocolitis and *Clostridium difficile* infection [4, 6]

(b) **Neutropenic FUO** is a term applied to patients who have a neutrophil count ≤ 500 /mm^3 and exhibit persistent fever whose etiology has yet to be established, despite three days of thorough investigation.

(c) **HIV-associated FUO** entails a febrile condition in an HIV-positive patient, which persists for four weeks (outpatient) or for three days (inpatient), with no obvious cause [4]. This type of FUO poses a diagnostic challenge, primarily due to the unusual pathogens involved in an HIV-related infection (atypical mycobacterial infections, cryptococcosis, histoplasmosis,and CMV infections) [5].

(d) **Classic FUO** which is defined as fever greater than 38ºC with an assessment of at least three days in the hospital or three visits as an outpatient or one week treatment without finding the cause of fever. The most common causes of classical fever are malignancies, infections and diseases of collagen [4]

Durack and Street also suggested a "quality over quantity" definition for fever of unknown origin, given the fact that technical restrictions and time-dependent factors do exist, such as the days needed for a blood culture to detect a pathogen or other factors that may delay diagnosis. Thus, they proposed that a fever should be termed as FUO after an "appropriate intelligent standard inpatient or outpatient workup" has failed to illustrate the cause of the fever [7]

Concerning the wider causative categories of FUO, these have remained surprisingly unchanged in terms of average frequency, since the initial studies conducted in the 1960's [8]. Infections account for the majority of FUO cases (30%-40%), followed by neoplastic (20%-30%) and miscellaneous conditions (alcoholic hepatitis, pulmonary emboli, vascular disorders) (15%-20%), rheumatologic diseases (10%-20%) whereas a small amount of patients remain undiagnosed (5%-15%). It is noteworthy that infective causes of FUO are more frequently observed in tropical and subtropical regions, in contradistinction to the western world [8].

Table 1. Major causes of FUO

FUO cause	Frequency (avg.)
Infections	30%-40%
Neoplasms	20%-30%
Miscellaneous	15%-20%
Rheumatologic conditions	10%-20%
Undiagnosed	5%-15%.

A thorough search until February 2019 was conducted in PubMed using the following keywords "FUO", "Fever of unknown origin", "PET", "Positron electron tomography", "Fever".

2. DIAGNOSTIC IMAGING MODALITIES

Given the wide variety of FUO causes, a thorough assessment of laboratory results is necessary, accompanied by a targeted approach, concerning the imaging modalities employed. A relatively new imaging modality, the positron emission tomography-computed tomography (PET/CT), has, since its advent in the early 2000's, gained considerable attention, with reference to unveiling the cause of FUO. The reason is that the 18FDG-PET, especially when conducted in combination with a CT (18FDG-PET/CT), can provide high spatial resolution and detect cancerous or infective regions that are metabolically active [5, 9]. Some of the disadvantages of the 18FDG-PET/CT include radiation and a cost that still remains high; unfortunately, the specific imaging modality is not being used as part of a routine FUO diagnostic workup [10]

3. PRINCIPLES OF 18F-FDG PET IMAGING

18F-FDG PET/CT scan is carried out following an intravenous injection of 18F-labeled FDG, a 2-deoxyglucose analog. Imaging can commence 30 to 60 minutes after the injection, and allows for a whole-body depiction of regions that exhibit increased uptake of the substance, namely regions that overmetabolize glucose. 18F-FDG has a half-life of approximately 110 minutes [1]. Body sites that exhibit an augmented glucose metabolism usually encompass malignancies and various types of infections, something that has been attributed to an overexpression of glucose transporters (GLUTs) isotypes [11]

GLUTs constitute transmembrane transporters that are specific for glucose and facilitate the cellular entrance of glucose entrance so that glycolysis can take place. 18F-FDG is subjected to the so-called "metabolic trapping" in the cells, in cases where glucose metabolism is high, as in inflammatory, malignant and infectious sites [12-14] PET or PET/CT cameras can detect the radioactive emission of the molecule and can accurately map the sites of glucose over metabolism. [12-14]. It is noteworthy that hyperglycemia in patients that are about to undergo a PET/CT scan can interfere with 18F-FDG uptake, therefore lowering the quality of the diagnostic image [12-14], especially in diabetic patients.

4. THE USE OF PET/CT IN CLINICAL PRACTICE

PET/CT was initially used in the staging of oncology patients. It is an important means of imaging due to its high diagnostic accuracy, and plays an important role in diagnosing and assessment of the therapeutic effect in this patient group.

The radiopharmaceutical substance used is 18F-FDG PET/CT which, upon administration, is absorbed by cells with high glucose consumption, such as neoplastic and activated inflammatory cells such as neutrophils, macrophages and lymphocytes. FDG accumulates in malignant tissues and at tissues of infection and inflammation. 18F-FDG PET/CT is increasingly being used in the investigation of fever of unknown aetiology (FUO).It is used as a second-line diagnostic tool after the failure of the first-line strategy such as chest X-ray, ultrasound, and CT scan [82-85]. There are accumulating data which point out the use of PET/CT in the diagnosis of the following causes of FUO:

4.1 Endocarditis and prosthetic heart valve infections

Infective endocarditis is a difficult-to-diagnose severe infection that primarily affects prosthetic heart valves, but can also be observed on native heart valves. With mortality rates often exceeding 40%, early diagnosis and an appropriate therapeutic plan are mandatory. Diagnosis is achieved mainly through positive blood cultures, cardiac echocardiogram and a comprehensive assessment via the Duke criteria; however, for patients with prosthetic valves (PVs) and implantable cardiac electronic devices (ICEDs) a conclusive diagnosis is often challenging [15, 16]. Before the advent of 18F-FDG-PET/CT, CT with iv contrast material was used to depict possible infection foci on prosthetic heart valves. 18F-FDG-PET/CT has been documented, by preliminary studies, to exhibit better accuracy in comparison to a contrast-mediated CT scan, despite its having limitations as well [15] However, various studies, including one by *Wasselius et al.,* concluded that the use of 18F-

FDG can lead to false-positive results in a considerable number of non-infected individuals [17-19].

Furthermore, Bartoletti *et al* [9] described some patients with suspected of prosthetic valve infection (PVE), which were initially investigated via transthoracic echocardiogram yielding negative results. Further testing was performed with 18F-FDG PET/CT; all six patients were found to have infectious endocarditis and in four of them the valve had to be replaced [9] .The significance of 18F-FDG-PET/CT in the challenging diagnosis of prosthetic valves endocarditis (PVE) was also shown in a study by *Saby et al*; their study included 72 patients and they reached to the final inclusion of 18F-FDG-PET/CT scan in the latest revision of the Duke criteria [20] . *Pizzi et al* [21] analyzed 92 patients with suspected PVE or cardiac device infectious endocarditis (IE) all submitted to echocardiography and 18F-FDG PET/CT. Echocardiography was positive in 42 cases, negative in 33 and doubtful in 17. PET/CT significantly increased the sensitivity from 52 to 90.7% However, these authors included initially rejected patients by modified Duke criteria, probably making less cost-effective the indication of 18F-FDG PET/CT in suspected IE.[22]

As far as patients with native valve endocarditis (NVE) are concered, there have been insufficient studies concerning the specificity and sensitivity of 18F-FDG-PET/CT. In a retrospective study in 88 patients ,*Kouijzer et. al* showed that the sensitivity of 18F-FDG-PET/CT in diagnosing infective endocarditis in native heart valves is low [15]. However, it is an imaging modality that, if co-evaluated with the Duke criteria, other radiologic imaging techniques and laboratory findings, can certainly contribute to the diagnosis of infective endocarditis of the native heart valves, as well [15, 23, 24]. Another advantage of using 18F-FDG-PET/CT as part of the diagnostic approach in these patients is its ability to illustrate the original source of infection, even though it may fail to depict the valvular damage itself.[16].

It should also be noted that 18F-FDG PET/CT can play a paramount role in illustrating infected cardiac devices, a diagnosis that is otherwise very challenging to achieve. When the levels of glucose is high in the bloodstream, lead to increased FDG uptake by the myocardium, thus rendering the interpretation of the 18FFDG-PET/CT results impossible, in this case patients who are to be submitted a 18FFDG-PET/CT scan should follow certain dietary restrictions, starting from 24 hours prior to taking the exam: a low-carbohydrate diet should be combined with foods rich in free fatty acids (FFA) the day prior to the exam, and total fasting is mandatory for at least 12 hours before the procedure [25, 26]. This is explained via the glucose/FFA cardiac metabolism. When glucose is abundant in the bloodstream, insulin excretion directs cardiac metabolism to rely principally on glucose; insulin also leads to an excessive expression of GLUTs. Both effects that insulin has on cardiac metabolism leads to an increased glucose and subsequently FDG uptake by the myocardium, thus rendering the interpretation of the 18FFDG-PET/CT results impossible [22, 24, 27]. On the other hand, fasting redirects the myocardial metabolism primarily to FFA, which allows for an accurate assessment of the scan results [83-85], restriction of carbohydrates prior to the 18F-FDG PET/CT scan can greatly eliminate false positive or inconclusive results and is always stipulated when the test is to be carried out [28].

18FFDG-PET/CT can not only accurately diagnose IE in cases where diagnosis is difficult to achieve with more conventional modalities, but has also proven to be a valuable tool in the detection of endocarditis-related peripheral septic emboli [16]. One study by Van Riet *et al.* showed that 40% of 25 patients with a definitive diagnosis of IE, had suffered septic emboli, whereas two other reports by Bonfiglioli *et al.* and Asmar *et al.* diagnosed the same complication in 24% of their patients with IE [29-31]. Another study by Kestler *et al*, also confirmed the diagnostic superiority of the 18F-FDG-PET/CT in detecting septic emboli caused by IE; the imaging modalities specificity and sensitivity were reported as being 80% and 100% respectively and the septic emboli were detected sooner in the clinical course of the patients than it would have been possible with conventional imaging techniques [32].

Asymptomatic infective foci that cause distant dissemination has also been studied by Vos *et al*; such infection sites prove challenging to detect via conventional methods and the specificity, sensitivity, positive and negative predictive value (PPV & NPV) of the 18F-FDG-FDG PET/CT scan was proven to exceed 87% comprehensively. In this study, 115 patients with diagnosed gram-positive bacteremia were compared to 230 patients who had not undergone investigation with a 18F-FDG-FDG PET/CT scan; this imaging technique was found to be considerably more sensitive in detecting distant sites of infection , when compared to scintigraphy (67.8 vs 35.7%) [33, 34].

4.2. The use of PET/CT in orthopedic infections

PET/CT can contribute to the diagnosis of other infections that are challenging to diagnose via CT/MRI due to the anatomical location of the infected site, such as osteomyelitis, spondylodiscitis and orthopedic implant infections [28].

Osteomyelitis in diabetic patients suffering from foot ulcers has also been a subject of debate concerning the optimal diagnostic imaging modality. Several studies report that the PET/CT is diagnostically superior to the MRI scan in terms of a definitive osteomyelitis diagnosis in patients with foot ulcers and low clinical suspicion of the infection [35, 36]. However, a study by Schwegler *et al.* presented a different opinion concerning the sensitivity of the PET/CT, concluding that the MRI scan produced more accurate results in the diagnosis of osteomyelitis in the subgroup of diabetic patients with foot ulcers [21] .

Spondylitis and spondylodiscitis are two infections that can be accurately diagnosed via a FDG-PET/CT scan, with extensive evidence provided by three separate studies published between 2000-2002 [37-39]. Diagnostic accuracy of FDG-PET/CT was compared with 67Ga-citrate SPECT, MRI and 99mTc-MDP in patients with spondylitis and spondylodiscitis. The imaging of FDG-PET/CT was superior to MRI, 67Ga-citrate, and 99mTc-MDP.

Concerning the diagnosis of infections of metallic prosthetics used in arthroplasty, although the PET scan has proven useful in differentiating between a septic and aseptic intervention, the presence of metallic implants causes the procedure to yield unreliable results; this is attributed to a nonspecific inflammatory response of the tissue surrounding the operated joint, that results to granulomatous inflammation [40-43].

4.3 The use of PET/CT in vasculitis and thyroid disease

Large vessel vasculitis is a probable cause of FUO and can be diagnosed with the use of 18F-FDG PET/CT; its sensitivity has been shown to be 77%-92% and specificity 89%-100% in untreated patients according to two separate studies [44, 45]. Due to its restricted spatial resolution, this imaging modality is generally not employed to detect small- and medium vessel vasculitides [46]. Still's disease, periarteritis nodosa and various multisystemic granulomatous diseases (Churg-Strauss syndrome or Wegener's granulomatosis) have also been diagnosed in the context of FUO via a 18F-FDG PET/CT scan [47-50].

Another unusual cause of FUO, subacute thyroidis, has been diagnosed via 18F-FDG PET/CT. Neoplasm of the thyroid is another cause of FUO with frequency 3%-20% [26, 51, 52].

4.4 The use of PET/CT in diagnosis of FUO in HIV positive patients

Two studies by Martin *et al*. and Castaigne *et al.* focused on the contribution of 18F-FDG PET/CT in diagnosing the cause of FUO in HIV-positive patients. Castaigne *et al.* were successful in diagnosing 90% of the patients with malignancies or tuberculosis, whereas Martin *et al.,* reported abnormal findings in all 20 patients who were positive asymptomatic but viraemic for HIV and experienced prolonged fever [53, 54]. A retrospective study

investigated the value of FDG-PET/CT in 20 patients positive for HIV on dialysis with prolonged fever FDGPET/CT was helpful in 75% of patients. [55].

Furthermore, one of the largerst studies for the use of 18F-FDG PET in discovering the cause of FUO, in HIV positive patients reported that out of 112 patients that met the criteria, approximately 46% were successfully diagnosed with the aid of 18F-FDG PET [56].

4.5 The use of PET/CT in tuberculosis and sarcoidosis

The PET scan can prove valuable in diagnosing other non-orthopedic infections, such as sarcoidosis, tuberculosis and intracellular infections [57-59]. 18F-FDG PET/CT can greatly contribute to the detection of septic dissemination from deep infectious foci, in the presence of bacteremia. According to a meta-analysis conducted by Besson *et al*., the sensitivity of the specific imaging modality in FUO/ bacteremia, proved to reach up to 96.7% [26].

Tuberculosis (TBC), one of the major causes of FUO that should not be disregarded, has been successfully diagnosed via 18F-FDG PET/CT on multiple occasions and its activity and extent can be evaluated with this modality [60, 61]. Due to the potential complications of a biopsy and the unobtainability of certain tissues due to their location, 18F-FDG PET/CT can greatly contribute to the diagnosis of extra pulmonary TB as well. A fact that should not be overlooked, however, is that the augmented uptake of the radiopharmaceutical may not always be indicative of an active TB lesion in a patient with a positive interferon gamma release assay (IGRA) or Mantoux tuberculin test; on the contrary, it may represent a host immune system response that will eventually prevail [62, 63].

FDG-PET/CT has, beyond any doubt, contributed greatly to the diagnosis of extra pulmonary manifestations of tuberculosis (TB), especially when combined with serum interferon-gamma release assay (IGRA). Tuberculous lymphadenitis and TB of the lumbar spine, rare causes of FUO, have been detected via FDG-PET/CT in two patients affected by end-stage renal disease [64].

The main challenge associated with the interpretation of 18F-FDG PET/CT scan is related to successfully distinguishing malignant from inflammatory lesions [65-67]. 18F-FDG PET/CT solely illustrates hypermetabolic regions, something to be considered, as both cancer and inflammation matching the hypermetabolic disease profile. There are rare cases of misinterpretation such as the one documented by Park *et al*., of a patient with secondary syphilis and generalized lymphadenopathy being misdiagnosed as lymphoma based on abnormal 18F-FDG PET/CT findings [68]. 18F-FDG PET/CT is also unable to differentiate between TB from its atypical type, sarcoidosis or lymphadenopathy linked to HIV [67, 68].

Another distinct pathology that can be diagnosed with a FDG-PET/CT scan is sarcoidosis; the imaging modality in question can detect both pulmonary and extrapulmonary sarcoidosis and is particularly valuable in detecting lesions of the mediastinum, posterior lungs, lymph nodes of the hila, as well as lesions not located in the thoracic region, even when compared to 67Ga-citrate SPECT [69]. Heart and brain sarcoidosis can also be evaluated using FDG-PET/CT. [69].

4.6 PET/CT in the diagnosis of tumor associated FUO

Concerning the contribution of FDG-PET/CT in the detection of malignancies involved in FUO cases, overexpression of GLUT-1, -3 and -5 isotypes and the excessive production of enzymes catalyzing glycolysis both account for the augmented uptake of the radiopharmaceutical substance [11, 70, 71]. Although the FDG-PET/CT scan is an indispensable tool in diagnosing neoplasms, its use remains limited in several cancers of the urinary tract [72]. The reason is its low sensitivity, which has been found to amount to 8% for renal cell carcinoma and 88% for solid renal neoplasms [73]. Various studies have shown that, despite its specificity being almost 100%, the FDG-PET/CT evinces considerably lower sensitivity compared to a CT scan, concerning the diagnosis of primary renal cell carcinoma, retroperitoneal lymph node metastases, pulmonary parenchyma

metastases and bone metastases [74]. A study by Ramdave *et al*., however, reported a similar accuracy between PET/CT and conventional CT, with reference to primary renal tumor diagnosis [75] . The reason underlying the low sensitivity of the FDG-PET/CT in the detection of renal malignancies is the physiologic uptake and excretion of the radiopharmaceutical in the urinary tract; IV diuretics have been proposed as a way to overcome this particular drawback [72, 76]. Lastly, in cases that the inflammation associated with FUO is found in the brain, myocardium, bowel and bladder, the results of FDG-PET/CT have also been found to be ambiguous.[72, 76] .

18F-FDG PET/CT has a sensitivity of 60% and specificity of 100% for primary renal cell cancer (RCC) vs abdominal CT which demonstrated 91.7% sensitivity and 100% specificity. PET/CT was proven to be 100% specific for primary tumors, retroperitoneal lymph node metastases/renal bed recurrences, liver metastases and bony lesions compared to abdominal CT [77].

18F-FDG PET/CT in the diagnosis of osteosarcoma showed a sensitivity of 95 %, a specificity of 96 % and an accuracy of 95 % to diagnose distant metastases [17]. The sensitivities for the initial diagnosis were 100% and for the recurrence were 88.1% for soft tissue and 91.7% for osseous sarcomas [78].

On the other hand 18F-FDG PET in diagnosing Hodgkin lymphoma (HL) and non-Hodgkin lymphoma has a very high sensitivity [79].

5. CONCLUSIONS

18F-FDG PET / CT is a useful non-invasive imaging method in the diagnosis of fever of unknown origin (FUO). It has the advantages of higher resolution, and higher sensitivity in chronic infections compared to other conventional imaging techniques, and exposes the patients to less radiation in comparison with other imaging techniques. 18F-FDG PET allows the diagnosis of a wider range of diseases but it is not yet a routine procedure in the work-up of FUO because of the high cost In practice, FDG PET / CT is a second-line exploration in the diagnosis of fever and it is used after failure of the first-line diagnostic strategy.

18F-FDG PET / CT can be very helpfulness in infectious diseases because of its diagnostic effectiveness, especially if the underlying disease lacks characteristic symptoms. Finally. as far as the cost-effectiveness of the method, although it seems to have a high cost, the use of PET/CT in FUO could avoid unnecessary investigations and reduce, thus, the duration of hospitalization and of the pointless administration of antibiotics.

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