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EDITORIAL COMMENTARY

FDG-PET imaging to detect and characterize underlying causes of fever of unknown origin: an unavoidable path for the foreseeable future

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Introduction

Fever of unknown origin (FUO) remains one of the most difficult diagnostic challenges frequently encountered by clinicians. It is defined as fever of 38.3 °C (101 °F) or higher for at least 3 weeks in immunocompetent, otherwise healthy patients with no identified cause of fever after undergoing a set of obligatory investigations [1].

FUO can be caused by a wide range of underlying disorders, including infections, occult malignancies, and non-infectious inflammatory diseases. These diseases are highly heterogeneous in nature, and are managed by several different medical specialties, which further complicates early diagnosis.

Medical imaging plays an essential role in the diagnostic process and in determining the underlying cause of FUO, which requires highly sensitive methods to detect the earliest evidence of the disease. Structural imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) can be used to detect focal pathological abnormalities. However, by virtue of their structural nature, these modalities are best suited for illustrating late-stage changes, and lack the sensitivity and specificity for early and accurate diagnosis.

In contrast, molecular imaging modalities are capable of detecting disease activity at the molecular and cellular levels, and therefore at their earliest manifestations. Molecular changes precede structural alterations which occur in the advanced stages of most human disorders. Based on experience gained over the past four decades, positron emission tomography (PET) imaging of the biodistribution of ^{18}F-fluorodeoxyglucose (FDG) stands out in many settings as the most sensitive methodology for detecting the earliest evidence of an active disorder throughout the body. FDG-PET is an excellent test for the detection and localization of ongoing disease sites that were clinically unknown or could not be detected by conventional imaging techniques.

In this editorial, we describe the critical role of combined FDG-PET-CT imaging in the challenging clinical setting of FUO and emphasize its cost effectiveness in managing this relatively common and potentially fatal disorder.

Non-specificity of FDG-PET imaging: a curse but also a blessing in the appropriate setting

FDG as a tracer for measuring regional glucose metabolism by PET imaging was introduced in 1976 by investigators at the University of Pennsylvania, primarily for determining regional brain function [2]. Soon thereafter, this PET tracer was employed to assess brain tumors because of the high glycolytic activity of malignant cells, as was described by Warburg in 1930 [3, 4]. By the late 1980s and early 1990s, when PET instruments were introduced for examination of other organs in the body, it was noted that sites of inflammation due to either an underlying infectious disorder or other pathologic state were also visualized by this novel technology [5, 6]. Over the past three decades, FDG-PET imaging has been employed as an investigational tool for the detection of active inflammatory disorders and their response to therapeutic interventions [7, 8]. Obviously, this approach has been employed in clinical scenarios where infection/inflammation was the main focus of patient clinical assessment. Therefore, based on the experience gained over the years, we have realized that the non-specificity of FDG is an asset, and as such, can play a major role in the management of a variety of common disorders.

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The introduction of PET-CT over the past two decades [9] and PET-MRI [10] in recent years has further enhanced the role of FDG-based imaging in this perplexing human malady. Combined PET-CT imaging has been proven an effective modality, resulting in effective therapeutic interventions in this population.

Infectious disorders

FDG-PET has shown a great deal of promise in detecting infectious disorders, due to the high expression of glucose transporters (GLUT) in inflammatory cells (Fig. 1) [11, 12]. In developing countries, infections account for the majority of FUO cases, while in developed countries, infectious diseases are the second most common cause of FUO, after non-infectious inflammatory diseases (NIID) [13]. Tuberculosis (TB) is the most common infection causing FUO in developing countries [14–16], and FDG-PET has been shown to be very sensitive for the early detection of TB [17], which indicates the suitability of PET in FUO. According to a recent Chinese multi-center study, abnormal PET findings leading to final diagnosis were observed in approximately two-thirds of the FUO cases, and infection appeared to be the most frequent diagnosis (42%) [18] (this editorial is drafted based on the data generated from this prospective research to emphasize the importance of FDG-PET in this disorder). In another study in patients with FUO and suspicion of infection or inflammation foci, FDG-PET demonstrated sensitivity, specificity, and positive and negative predictive values of 93, 90, 87, and 95%, respectively [19]. These observations imply that FDG-PET is a superior diagnostic tool for detecting the major underlying infectious causes of FUO.

Fig. 1 FDG-PET image was acquired in a patient who was hospitalized twice, and an extensive workup was conducted over several days to determine the cause of FUO. Finally, FDG-PET was performed as a last resort for further assessment of this desperate clinical scenario. The image clearly shows a focus of abnormal uptake in the mediastinum (arrow), which proved to be a focal site of infection that was drained, resulting in complete recovery from continuous fever. The site of infection was overlooked on contrast-enhanced CT scan which was performed prior to FDG-PET images. This clearly demonstrates the importance of intense FDG uptake as a focal abnormality, allowing visualization of lesions in certain locations which are missed by conventional structural imaging modalities

FUO in immunocompromised patients is another domain in which FDG-PET can play a role in disease management. The primary cause of FUO in HIV-positive patients worldwide is infectious diseases, among which mycobacterial infection is the leading cause [20]. In one study conducted by Castaigne et al., FDG-PET was considered “helpful for diagnosis” in nine out of ten HIV-positive subjects, among which six were diagnosed as infection (TB) and three were diagnosed as neoplasms (two lymphomas, one Kaposi’s sarcoma) [21]. The only patient without abnormal FDG-PET findings suffered from drug-induced fever. In a prospective study, Martin and colleagues established the usefulness of FDG-PET in the investigation of FUO in HIV-positive patients, even those with viremia, which had previously been a matter of debate [22]. The authors confirmed that the presence of hypermetabolic central lymph nodes had 100% specificity for focal etiology of fever, even in viremic patients, and lack of increased FDG uptake in the central lymph nodes in FUO patients had 100% negative predictive value for focal disease. A few studies have demonstrated the potential for FDG-PET in neutropenic patients with FUO, revealing a high negative predictive value for ruling out foci of inflammation [23, 24].

Systemic vasculitis

Activated inflammatory cells demonstrate enhanced glycolysis and therefore an increase in FDG accumulation (Fig. 2). The mechanism of FDG uptake in these activated cells is due to the use of glucose as the primary energy source only upon activation during the metabolic burst of these cells. Today, examining patients with suspected large vessel vasculitis (LVV) by FDG-PET is the most well-established indication among the inflammatory disorders, with overall sensitivity and specificity of 77 to 92% and 89 to 100%, respectively [26].

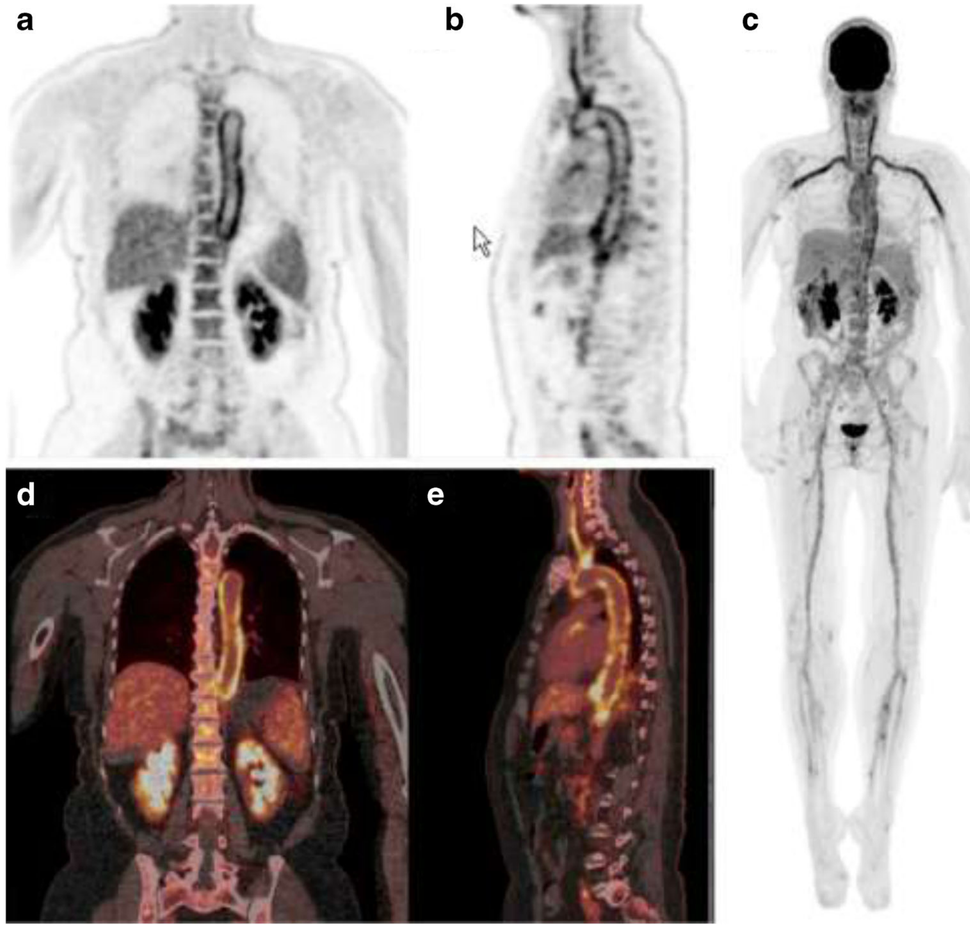

Fig. 2 A 60-year-old woman presented with fever, night sweats, and arthralgia. Physical examination was normal. Erythrocyte sedimentation rate (ESR) was 125 mm/h and leukocyte count was 12.4 × 109/L, with normal creatinine level and liver function tests. FDG-PET/CT showed highly increased FDG uptake in the aorta, subclavian arteries, and femoral arteries. The patient was diagnosed with LVV. Her symptoms resolved and ESR normalized upon treatment with corticosteroids. Reproduced with permission [25]

A large meta-analysis by Lee et al., which reviewed a total of 439 PET images to evaluate the value of FDG-PET in detecting LVV, reported pooled sensitivity and specificity of 88 and 81%, respectively [27].

Vaidyanathan et al. retrospectively compared the effectiveness of FDG-PET and contrast-enhanced CT (CECT) to diagnose suspected LVV in 36 patients. They reported excellent accuracy for FDG-PET, while CECT had only good accuracy, in the diagnosis of LVV [28].

A recent meta-analysis conducted by Soussan et al. included 413 patients and 299 controls pooled from 21 studies. Based on their results, FDG-PET demonstrated sensitivity and specificity of 90 and 98%, respectively, for the diagnosis of giant cell arteritis, while for Takayasu arteritis, pooled sensitivity and specificity was 84% [29].

In a retrospective study by Takahashi et al., the authors reported sensitivity of 92.6% and specificity of 90% for FDG-PET in detecting and identifying polymyalgia rheumatica (PMR) [30]. Wakura et al. further emphasized the role of FDG-PET in diagnosing PMR and differentiating it from late-onset rheumatoid arthritis, with sensitivity and specificity of 86.7% [31]. FDG-PET has the potential to become the most accurate diagnostic modality for PMR [32].

Malignancy

The critical role of FDG-PET in assessing malignancies is now well established. Malignant cells show significantly enhanced FDG uptake due to the Warburg effect, allowing for disease localization, lesion delineation, staging, and monitoring the course of subsequent interventions. In 1992, it was reported that neoplastic disease was becoming a common etiology of FUO in developing countries [33]. However, more recent studies indicate that the percentage of FUO caused by malignancy has decreased relative to that caused by non-infectious inflammatory diseases [34].

Lymphoma is the most common neoplastic cause of FUO [35]. Several investigators have pointed out that rare sites of involvement by intravascular large B-cell lymphoma can be clinically asymptomatic early in the process. Therefore, FDG-PET imaging may prove to be superior in detecting disease sites compared to pelvic CT and MRI, which often appear negative [36, 37]. In addition to primary splenic lymphoma, rare sites of involvement such as colonic lymphoma and pituitary lymphoma have been found to cause FUO and have been effectively detected by FDG-PET [38, 39]. In rare cases, FDG-PET will yield false-negative results in carcinoid tumor and mucosa-associated lymphoid tissue (MALT) lymphoma [40]. Low uptake in tumor cells also results in lower sensitivity of FDG-PET for detecting pulmonary adenocarcinoma [41]. In general, differentiated tumor cells have low glycolytic activity and therefore are not detectable by FDG-PET imaging. Delayed imaging at 2–3 h may allow visualization of such malignancies [42].

In a meta-analysis by Bharucha et al., the authors reviewed the efficacy of FDG-PET imaging in 749 patients with FUO. Based on follow-up studies, 112 patients received a final diagnosis of a malignant disease (15%) [43]. In this population, FDG-PET was diagnostic in 107 (96%) cases. Additionally, among the malignancies causing FUO, lymphomas were the most common (62%), followed by lung cancer (6%), leukemia (5%), and hemophagocytic disease (5%). Malignancies of unknown primary were diagnosed in 5% of patients.

Many studies have shown FDG-PET to be a powerful modality for assessing hematological malignancies and other neoplastic diseases [44–47]. In a retrospective study evaluating the utility of FDG-PET in diagnosing, staging, and restaging primary splenic lymphoma, 96.2% sensitivity, 91.7% specificity, and 94% accuracy were reported [48]. Therefore, FDG-PET imaging can play a role in managing patients with FUO and suspected hematological malignancies.

New technical approaches such as dual-time-point imaging are set to further improve the specificity of FDG-PET by discriminating between inflammatory and malignant disorders based on the pattern of FDG uptake over time [42]. While most inflammatory processes show a constant and gradual loss of FDG uptake over the course of several hours after tracer administration, malignant cells continue to accumulate the tracer for several hours. Therefore, the patterns and trends in FDG uptake may provide useful information about a malignant process as the underlying cause of FUO.

Although FDG has been the most useful tracer for assessing patients with FUO, efforts are being made to use other PET-based radiotracers for the detection of inflammatory disorders. In particular, radiolabeled nanoparticles may play a role in organs with high FDG uptake, which may prevent the detection of sites of inflammation [49]. We wish to emphasize that the role of imaging radiolabeled white blood cells with single gamma-emitting radionuclides is very limited in patients with FUO.

Overall efficacy of FDG-PET imaging in assessing FUO

Wang et al. conducted a retrospective multi-center study that included 376 patients with FUO and inflammation of unknown origin (IUO). Based on this review, 33% of patients had underlying infectious process, 32.4% had rheumatologic diseases, 19.1% had malignancies, and 15.4% had other miscellaneous and unknown etiologies. The authors concluded that 89.6% of patients benefited from FDG-PET, and it provided additional diagnostic information for 77.4% of patients [50].

Another prospective study by Keidar et al., which included 48 subjects with FUO, reported that FDG-PET identified the underlying pathology in 46% of the patients and contributed to the diagnosis or exclusion of a focal pathologic etiology of the febrile state in 90% of patients. They also reported a negative predictive value (100%) for assessment of FUO [51].

Conclusion

Based on substantial amounts of data that have been generated over the past few decades, FDG-PET is the most effective method for whole-body examination to determine the underlying cause in patients with clinical diagnosis of FUO. We believe FDG-PET should be considered as the study of choice in patients with this diagnosis. Arguments about the accessibility of PET and its related costs for a serious and potentially fatal disease may not be relevant in this setting. When we are dealing with a common and treatable disorder such as FUO, these arguments may not be valid because of the high cost effectiveness of this modality. Therefore, we would encourage our colleagues to embrace PET as the future imaging modality of choice for assessing FUO. Efforts should be made to secure reimbursement for FDG-PET imaging for the workup of FUO on a routine basis so that we can minimize human suffering and avoid unnecessary and costly procedures and interventions.

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