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EDITORIAL

An update on the unparalleled impact of FDG-PET imaging on the day-to-day practice of medicine with emphasis on management of infectious/inflammatory disorders

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The concept of FDG-PET imaging was discussed for the first time among three investigators from the University of Pennsylvania, Abass Alavi, David Kuhl, and Martin Reivich, in the early 1970s [1]. These investigators had realized the potential for this novel radiolabeled compound in human research and clinical practice based on autoradiographic imaging studies using 14C-deoxyglucose in animals [1]. This initial discussion led to contacting chemists at the Brookhaven National Laboratory (BNL), which soon led to a joint effort to label deoxyglucose with 18F and determine its role by examining brain function in human beings. This investigation was led by Alfred Wolf and his colleagues at BNL and eventually, the compound was successfully synthesized and tested for toxicity before plans were made to image its distribution in human beings [2]. By mid-1976, an investigational new drug (IND) application was secured from the FDA for administering this radiotracer to normal human volunteers. Finally, in August 1976, the compound was shipped by a private plane to Philadelphia and successful images of the whole body by a conventional rectilinear scanner and tomographic images by a SPECT instrument were acquired by Abass Alavi at the University of Pennsylvania [3]. Soon thereafter, research protocols were drafted to determine the patterns of cerebral glucose metabolism with this compound in central nervous system disorders by Penn/BNL and UCLA investigators [4, 5]. The results from these early research studies conducted initially at these institutions and then later by a few other centers in the USA and Europe in the 1980s clearly demonstrated the great promise of FDG for both research and clinical applications.

In spite of the complexity and technical challenges that were faced by this demanding technology, over the past 4 decades, the role of this powerful imaging modality has been validated and well-established for assessing numerous disorders [6, 7]. Soon after its introduction, this approach was proven to be of great value in diagnosing Alzheimer's disease with very high sensitivity and specificity which has remained unmatched by any other technique to date [8–10]. Other applications in the 1980s and 1990s included detection of seizure focus in temporal lobe epilepsy [11–13], vascular disorders [14], and a variety of neuropsychiatric diseases such as schizophrenia and manic depression [15–18]. However, the major observation that was made from the early research studies in animal [19] and in human brain images with FDG was its critical role in detecting and characterizing malignant cells, particularly, brain tumors [20, 21]. These early research projects were carried out by investigators at BNL, Penn, and NIH. For the first time, the observation that was described by Warburg in the in vitro setting, where he was able to demonstrate high glycolytic activity of cancer cells compared with normal tissues, was verified by in vivo imaging with FDG [22, 23]. The latter further enhanced the potential for employing FDG-PET imaging to expand the horizons of this powerful methodology beyond central nervous system disorders.

In parallel with synthesis of FDG and testing its novel application in human diseases and disorders, efforts by Michael TerPogossian and colleagues at Washington University had resulted in designing and testing early PET

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instruments for imaging positron-based radiotracers [24]. The initial instruments provided images in a limited axial field of view and therefore were employed for assessing small organs such as the brain and the heart. By the early 1980s, efforts were made to assemble advanced instruments that could image the entire body with extended fields of view, which have been improved substantially over the past 3 decades [25].

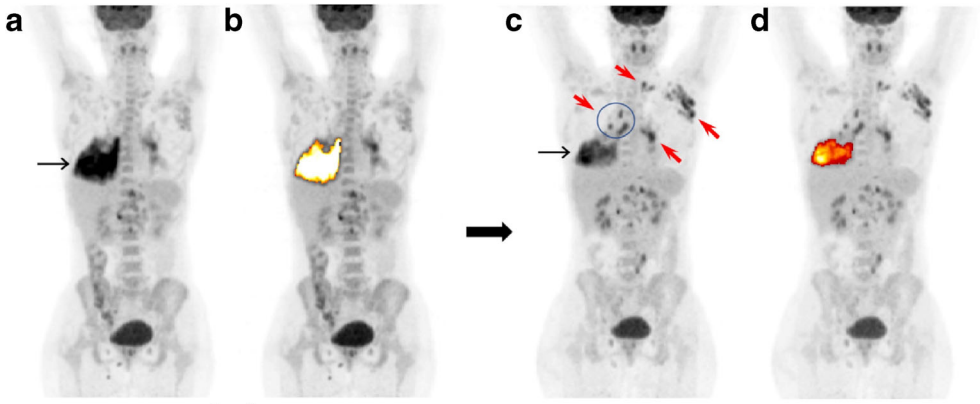
Major advances that have been made in designing and building sophisticated PET instruments have further enhanced the impact of FDG-PET in many settings where imaging larger segments of the body along with structural data are essential for accurate diagnosis. In particular, the introductions of PET/CT in 2000 [26] and PET/MRI in 2008 [27] have substantially improved the performance of PET in disciplines such as radiation therapy and surgery. These instruments have allowed precise localization of FDG-positive targeted lesions.

The introduction of total-body PET imaging during the past year by investigators at UC Davis and Penn is expected to substantially enhance the role of this powerful modality even further [28]. This instrument allows imaging of the entire body within minutes and by administering substantially lower doses of FDG than the amounts currently being administered with limited field of view PET/CT scanners. Furthermore, total body imaging is going to allow for global disease assessment in serious diseases and disorders such as atherosclerosis, osteoporosis, vascular complications of many malignancies, and systemic inflammation including rheumatoid arthritis and psoriasis.

The synthesis of FDG, which was somewhat cumbersome and limited to academic institutions, was significantly simplified over the ensuing years and this has allowed rapid expansion of this technology to most advanced centers around the world. Since the 1990s, applications of FDG-PET have expanded to include imaging various malignancies and this has resulted in the acceptance of this technology by the oncologists for the diagnosis and treatment response following various therapeutic interventions [25]. By the mid-1990s, it was noted that FDG-PET imaging could potentially play a role in the detection of infection and aseptic inflammation due to a variety of disorders [29]. In the early 2000s, studies were reported describing FDG uptake in the atherosclerotic plaques in the aorta and other major arteries [30, 31]. Similarly, it was shown that clots in the venous system have substantial glycolytic activity and can be visualized by this technique [32–34]. In addition, detecting FDG uptake in the myocardium has been adopted for assessing myocardial viability before coronary artery bypass surgery [35, 36]. Therefore, over the past 2 decades, the domain for FDG-PET applications has expanded substantially and, in fact, the rate of expansion of this technology has exceeded that of any other modern imaging techniques in recent years [7]. Moreover, the molecular dimension and the ability to overlook major parts of the body in a single examination séance are going to change and improve our understanding of many diseases as exemplified by FDG-PET findings of significant vasculitis inside the body in what until now was considered a serious skin disease, namely psoriasis [37]. In addition, the superior sensitivity of PET and targeting at the molecular level opens for much earlier disease detection than with conventional structural imaging. A striking example of that is the detection of bone *marrow* instead of bone metastases by means of FDG-PET probably months or years before changes in the skeletal bone matrix become apparent by CT imaging, where they may persist even after active cancer cells are no longer present [38].

In contrast to CT and MRI, which were adopted without any hesitation, the medical community was reluctant to accept the validity of exploring PET as a viable modality for assessing any of the diseases and disorders enumerated above. In fact, early applications of PET were primarily supported by grants from the NIH, other government agencies, foundations, and institutional funding. It was not until 1998 when Medicare (US Government Insurance Agent) approved the use of this technology for characterizing lung nodules and for initial staging of non-small cell lung cancer (NSCLC). Fortunately, over the past decade, Medicare has expanded its coverage of PET for most malignancies and this has allowed rapid expansion of this technology particularly in the USA [39, 40]. In fact, without the latter initiative, PET would have never survived as a viable imaging technique. Unfortunately, clinical acceptance of FDG-PET as a very powerful method for assessing infection and inflammation has been somewhat slow and limited to centers where research funding has been secured from various agencies [41–47]. This is very disappointing since, based on reports that have appeared in the literature, FDG-PET imaging appears to be the most successful imaging approach for detection and characterization of many infectious and inflammatory disorders [7]. Efforts are being made to educate both the scientific and clinical communities about the unparalleled role of this technique in such domains.

Finally, FDG-PET is the most quantitative imaging technique for assessing disease activity in medicine, and as such, it contributes enormously to determine the course of disease and the effectiveness of various interventions [48]. Particularly, its ability to provide a single value as evidence for global disease activity is essential for overall assessment of multiple benign and malignant disorders [49]. Previously, the mentioned limited fields of view was a hindrance to such overall assessments, but with the extended fields of modern scanners, their higher sensitivity and correspondingly shorter image acquisition times, not to mention the advent of the total-body PET scanner [28], the concept of providing a global disease score (GDS) representing the extension and severity of disease in part of (D) or in the total body has come into reach as illustrated in Fig. 1 in a HIV/TB-positive patient. Until recently, to provide such scores have often been too time-consuming for application in the daily routine since it requires careful



	MTV	SUVmean	pvcSUVmean	SUVmax	TLG	pvcTLG
Baseline	184.4	9.3	12.1	14.9	1727.2	2238.6
Follow up	87.4	6.8	9.4	11.4	597.6	830.5

Fig. 1 Baseline (**a**, **b**) and follow-up (**c**, **d**) maximum intensity projection (MIP) PET images of an HIV/TB-positive patient. The lung lesion decreased in size and disease activity following 2 months of antiretroviral therapy (black arrows). Coincident with response to treatment in the lung lesion, an increased lymph node reaction was observed on FDG-PET scan (red arrows). The FDG-avid lung inflammatory site was segmented semi-automatically using an adaptive contrast-oriented thresholding system (ROVER; ABBX, Radeberg, Germany). The values for metabolic tumor volume (MTV), SUVmean, partial volume corrected SUVmean (pvcSUVmean), SUVmax, total lesion glycolysis (TLG), and partial volume corrected total lesion glycolysis (pvcTLG) at the baseline and the follow-up are noted in the table. (These images are courtesy of Professor Mboyo-Di-Tamba Vangu, University of the Witwatersrand, Johannesburg)

segmentation of all disease areas and lesions in the body, which implies great observer experience and, in particular, when it comes to small lesions, correction for partial volume effect. However, with the rapid introduction of artificial intelligence-based systems for quantitative, observer-independent processing of PET images in seconds or a few minutes, overall disease assessment will become a major target for future clinical research and implementation [49].

In this review, we will describe in great detail the role of FDG in a variety of infectious and inflammatory disorders.

Early in the history of FDG-PET imaging, occasional reports of false-positive findings due to infection or inflammation in patients with malignant tumors were a nuisance to oncologists who had to realize that FDG was not a cancer-specific tracer [50]. It has now been established that this is because cells involved in the inflammatory response (e.g., neutrophils, macrophages, and activated leukocytes) similar to malignant cells often express high levels of glucose transporters. In addition, circulating cytokines seem to increase the affinity of these glucose transporters for FDG [51, 52]. Tahara et al. reported on the first cases using FDG directly for imaging infection with increased accumulation in abdominal abscesses in humans [53], and since then, there has been a growing interest in using PET and PET/CT for the study of infectious and inflammatory diseases [29, 54, 55]. Generally speaking, the use of FDG and PET in infectious and inflammatory diseases can be divided into systemic whole-body diseases and focused, organ- or symptom-specific diagnostics.

In the former category falls one of the most well-established indications, namely fever of unknown origin (FUO), a heterogeneous group of diseases with a multitude of differential diagnoses, i.e., infectious, malignant, or inflammatory diseases all with an element of hypermetabolism. Patients often present with unspecific symptoms and few diagnostic clues, and it may be challenging to reach an etiologic diagnosis [56, 57]. Whole-body FDG-PET/CT is sensitive in guiding the clinician towards more specific investigations and provides clinically helpful and important information towards reaching a diagnosis in overall 50–60% of patients (i.e., 42–92% of cases depending on how the authors define "helpful"), substantially better than any other diagnostic procedure [58, 59]. Also, one must remember that the underlying studies usually include patients without a firm diagnosis after a multitude of other diagnostic procedures, i.e., often the most difficult patients.

Another challenging whole-body ailment is bacteremia of unknown origin; early studies found clinically relevant findings in up to half of patients with bacteremia of unknown origin or suspected metastatic spread with high positive and negative predictive values [60, 61] and established FDG-PET/CT to be cost-effective due to significantly lower relapse rates and mortality [62, 63]. More recent studies have corroborated these initial findings in heterogeneous settings of bacteremia of unknown origin with PET leading to change in clinical management in half of the patients, also after prolonged febrile periods in patients heavily pretreated with antibiotics [64]. FDG-PET/CT has also been shown to have a direct therapeutic consequence in one-third of critically ill septicemic patients with unknown etiology [65], and high sensitivity and significant clinical impact in 53–75% of

immunocompromised patients with febrile neutropenia [66, 67]. Another entity with potential metastatic infection is infective endocarditis (IE), especially prosthetic valve endocarditis; focal FDG uptake in the valve area may be indicative of endocarditis, often an incidental finding in FUO or equivocal cases, but imaging the heart is difficult without prolonged fasting due to the physiologic myocardial uptake of FDG; thus, FDG-PET may better contribute in infective endocarditis by detecting clinically occult metastatic infectious foci, as an adjunct to echocardiography in equivocal cases, or in suspected cardiac device infection [68–71].

Looking at more specific indications, FDG-PET/CT is second to none in chronic osteomyelitis; a meta-analysis pooling data from 23 studies found FDG-PET had the highest accuracy in diagnosing and excluding chronic osteomyelitis, with a sensitivity of 96% and a specificity of 91%, compared with 78% and 84% with combined bone and leucocyte scintigraphy, and 84% and 60% with MRI [72]. Similarly, with spondylodiscitis, a meta-analysis found sensitivity and specificity of 97% and 88%, respectively [73], and a recent study established that FDG-PET/CT is especially adept in the early phase with sensitivity of 96% compared with 50% with MRI within the first 2 weeks after symptom debut [74]. Although it only represents 2–4% of osteomyelitis cases, structural imaging may be insufficient in spondylodiscitis, because morphologic changes are often nonspecific and discrimination between infection and degenerative changes is challenging. Although the specificity of FDG-PET may be lower in the initial postoperative period due to unspecific inflammation [75], excellent results are achievable in patients with suspected spinal infection related to metallic implants, i.e., overall sensitivity, specificity, and accuracy in the range of 94–100%, 87–93%, and 91–97%, respectively, with corresponding results for patients with metallic implants: 91%, 71%, and 83%, respectively—in one study, FDG-PET was found to increase the physician's confidence, which added significantly to the clinical decision-making process and treatment strategy in two-thirds of patients [76, 77].

FDG-PET has also been employed in the diagnosis of prosthetic joint infections. Although still controversial, several meta-analyses as well as prospective comparisons have demonstrated more robust results with FDG-PET (i.e., pooled sensitivity and specificity of 70–95% and 84–93%, respectively) compared with combinations of white blood cell scintigraphy and bone marrow scintigraphy (i.e., pooled sensitivity and specificity of 33–80% and 93–96%, respectively) [47, 78–81].

Finally, several studies have pointed to FDG-PET as a useful modality in the diagnostic challenging diabetic foot. One study reported lower sensitivity but higher specificity and accuracy with FDG-PET than with MRI [82], while another found both higher sensitivity and accuracy with FDG-PET, concluding that this method was able to reliably differentiate Charcot's neuroarthropathy from osteomyelitis [45]. A recent prospective study found that FDG-PET/CT imaging of the diabetic foot had a sensitivity, specificity, and accuracy of 100%, 92%, and 95%, respectively, in the diagnosis of osteomyelitis [83].

Vascular graft infection is a rare but serious complication carrying high mortality and morbidity with a substantial risk of limb loss or death [84, 85]. It is often difficult to distinguish morphologically between graft infection, non-infected hematoma, and lymphocele. While CT has low sensitivity in low-grade infections, FDG-PET may lack specificity. In the first hybrid PET/CT study, Keidar et al. found excellent sensitivity and specificity of 93% and 91%, respectively [86]. Whereas subsequent studies generally confirmed the high sensitivity, specificities varied considerably, i.e., two recent meta-analyses found pooled sensitivities and specificities of 95–97% and 80–89%, respectively, with confidence intervals for specificities ranging from 69–96%. Even so, FDG-PET/CT generally performs much better than CT with several studies finding both sensitivities and specificities in the 55–65% range only [85, 87]. However, several caveats pertain to the available FDG-PET literature, e.g., patient populations are generally a heterogeneous mix of acute and chronic, low-grade infections, various graft types, and most are heavily pretreated with antibiotics. Also, methodologies are generally suboptimal with regard to a reference standard and a lack of consensus on interpretation strategy.

Due to the nonspecific nature of FDG, more infection-specific tracers are desirable. A multitude of alternative candidates has been assessed preclinically, including several different isotopes (e.g., ^{64}Cu, ^{68}Ga, and ^{124}I). Although results have been promising and scientifically interesting, a recent systematic review established a significant lack of standardization in the preclinical settings and that only few have been translated into humans and with disappointing results [88].

Besides mere diagnosis, the use of FDG-PET/CT for response evaluations of treatments for infectious diseases has also been explored, albeit to a much lesser extent than in malignant diseases, e.g., spondylodiscitis [89], vascular graft infections [90, 91], and tuberculosis [92]; results have been promising, but further and larger prospective studies are warranted in this setting.

Non-infectious inflammation is also FDG-avid by mechanisms similar to those of infectious diseases, i.e., higher glucose transporter expression in inflammatory cells and increased affinity of the glucose transporters for FDG under the influence of circulating cytokines [46, 93]. Most validated clinically is vasculitis characterized by inflammation and necrosis of the vessel wall, most commonly affects large- and medium-sized arteries, e.g., giant cell arteritis (GCA) and Takayasu's arteritis [94]. In GCA, biopsy of the temporal artery remains the reference standard, but false-negative results are seen in as many as 40% of patients [93]. Furthermore, a significant proportion of patients have extra-cranial disease

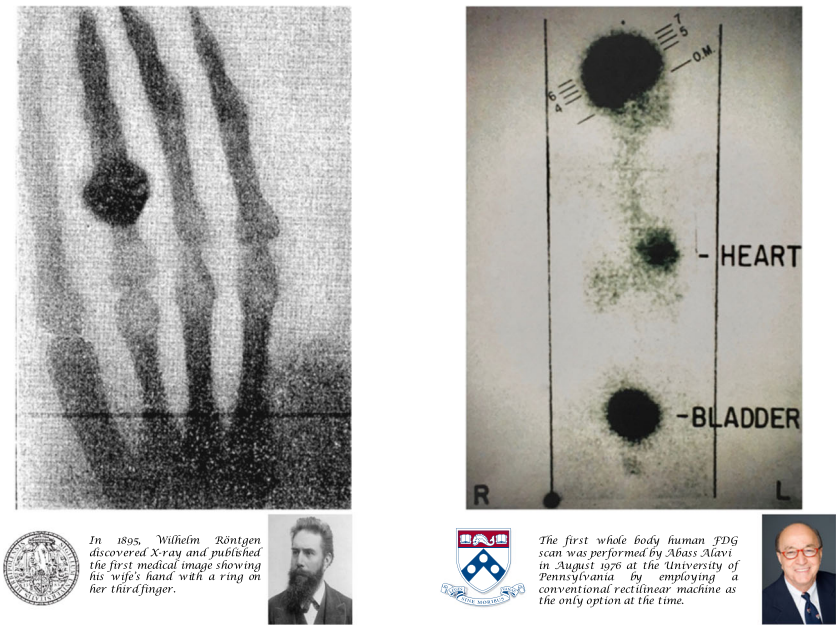


Fig. 2 Introduction of X-ray to medicine by Röntgen in 1895 (left) has had a substantial impact on the day-to-day practice of medicine. Similarly, imaging with FDG (right) has been another major step forward by enhancing the role of medical imaging and this has led to an unparalleled impact on both research and patient care

manifestations, and thus, imaging remains important to help locate suitable biopsy sites and assess disease extent and response to treatment. Evidence on FDG-PET in GCA is mounting, and recent systematic reviews have found sensitivities and specificities of 80–90% and 89–98% [95, 96], respectively, in GCA, and 70–87% and 73–84%, respectively, in Takayasu's arteritis [96–98]. Earlier studies underlined problems with visualizing the smaller arteries in the head-and-neck including the temporal artery because of its small caliber and proximity to physiologic uptake in the adjacent brain, but a recent study found high diagnostic accuracy for GCA using a dichotomous assessment of FDG uptake in cranial arteries [99]. A well-known pitfall is glucocorticoid treatment known to hamper FDG uptake and leading to false-negative scans, but another recent study found remaining high sensitivity within the first 3 days of high-dose glucocorticoids, whereas sensitivity was significantly reduced after 10-day treatment [100]. Polymyalgia rheumatica is a systemic disease entity characterized by soft tissue inflammation, synovitis, and bursitis, and is often associated with large-vessel vasculitis. As with GCA, available imaging has been sparse, but in recent years, several reports have proposed several well-defined anatomical areas related to bursae and axial joints where increased FDG uptake is associated with polymyalgia rheumatica [101–103].

Reports on FDG uptake in sarcoidosis emerged in the early 1990s, and whole-body FDG-PET is a sensitive marker of sarcoidosis activity [104, 105]. Although not the modality of choice in the initial diagnostic workup due to its inability to differentiate benign granulomatous disease from lymphoma, a systematic review identified nine studies with a total of 379 patients and reported great potential in several areas, e.g., assessing disease activity and thus aiding the monitoring of treatment response as early as 6 weeks following initiation of therapy, and for staging and detection of sites that are clinically occult [106]. Also, FDG may have a role in cardiac sarcoidosis, but the same caveats as with infective endocarditis apply, i.e., patient preparation is pivotal to suppress physiologic uptake in the myocardium [107, 108].

Several other inflammatory diseases have been suggested and investigated using FDG-PET with potential, but evidence is still equivocal. These include inflammatory bowel disease where physiologic FDG uptake may complicate matters, but two meta-analyses found overall sensitivity and specificity of 84–85% and 86–87%, respectively [109, 110]. A possible application is a differentiation between inflammatory and fibrostenotic strictures with obvious advantages for treatment planning and avoiding invasive surgical procedures [111]. All of this could be of special significance in pediatric inflammatory bowel disease [112]. Also, FDG has been suggested to detect and assess inflammatory joint disorders [113], also for monitoring treatment response because morphologic assessment of synovial thickening is difficult [114], but important with the effective but expensive new biological drugs that may present serious side effects [115]. Finally, FDG has been proposed in venous thromboembolism (VTE) as commonly used diagnostic imaging techniques do not address some of the important aspects of this disease [32]: VTE may present in the entire venous vasculature, but routine imaging only assesses lower extremity veins and pulmonary arteries; an underlying disease like cancer is often a key factor in the development of VTE, but patients are not examined routinely to

disclose this; and differentiating acute from chronic VTE is impossible by routine imaging, but has profound influence on treatment strategy. A recent systematic review has summarized the potential within all of the mentioned domains, but the literature is still too sparse for firm conclusions [116].

The enormous impact of FDG-PET imaging on many disciplines of medicine competes with any other major development to date. The increasing number of newer applications of FDG for assessing diseases beyond cancer has significantly improved patient care far beyond any other imaging technique over the past decades. As it becomes more and more evident that contrast agents designed for CT and MRI are associated with serious side effects, it is conceivable that FDG will be used in place of these radiologic contrast agents in the future. In addition, the introduction of FDG has resulted in the survival of PET as an imaging modality and made PET as the most powerful imaging technique to assess disease processes at the molecular level. Furthermore, the survival of PET as such a powerful modality has resulted in the development of new radiotracers that are revolutionizing our ability to assess many diseases and disorders at the molecular level. These advances are going to be essential for characterizing the underlying causes of numerous maladies and developing potential approaches for therapeutic interventions. As such, it may be appropriate to portray the introduction of FDG-PET to medicine as compared with that of X-ray by Roentgen in 1895 (Fig. 2).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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