REVIEW ARTICLE

MINI-REVIEW: ROLE OF ^{18}FDG PET/CT IMAGING IN VASCULITIS AND POLYMYALGIA RHEUMATICA

Maseeh uz Zaman,[1] Nosheen Fatima,[1] Sidra Zaman,[2] Areeba Zaman,[3] Unaiza Zaman,[4] Anwar Ahmed[1]

[1] Department of Radiology, Aga Khan University Hospital (AKUH), Karachi, Pakistan.
[2] Dr. Ruth K. M. Pfau Civil Hospital, Karachi, Pakistan.
[3] Department of Medicine, Sunny Downstate Hospital, NY, USA.
[4] Department of Hem-Oncology, Oklahoma University, Oklahoma, USA.

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ABSTRACT

Autoimmune vasculitis has two major variants Takayasu arteritis (TA) and giant cell arteritis (GCA) which often coexists with polymyalgia rheumatica (PMR). In recent days, the role of ^{18}FDG-PET/CT imaging has been evaluated in diagnosis, disease monitoring and metabolic response assessment in these patients. This mini-review would focus on various diagnostic strategies, guidelines for standardized ^{18}FDG PET/CT acquisition and interpretation, pitfalls and challenges in its use in current clinical practice.

Key Words: Vasculitis; Giant Cel Arteritis; Takayasu Arteritis; ^{18}FDG PET/CT; diagnosis; response assessment; standardized

Term vasculitis encompass various inflammatory conditions affecting large and medium size vessels (LVV).[1] These are broadly categorized as Giant Cell Arteritis (GCA) and Takayasu Arteritis (TKA). In more than 50% cases, GCA overlaps with polymyalgia rheumatica (PMR) which is another inflammatory condition affecting bursae, joints, tendons and sheaths.[2] Both GCA and TKA predominantly involve female gender. However, there are certain salient differences between these two entities. GCA predominantly involves European population, almost always >50 years of age (peak incidence 70 75 years). GCA may involve cranial arteries (C-GCA) like temporal, maxillary or vertebral arteries but more commonly involves aorta and its main branches (LV-GCA).[3] C-GCA most commonly involves temporal arteries and may result in visual loss due to optic nerve infarction caused by involvement of ocular arteries. LV-GCA is more common than C-GCA and predominantly involves aorta and its main branches. TKA predominantly affects Asian population and commonly involves aorta, carotid, renal and mesenteric arteries and less commonly cranial and rarely involve ocular arteries.[4] As PMR overlaps with GCA, it has a peak incidence of 70-75 years involving the bursae and periarticular soft tissues.

Clinical Presentation: GCA and TKA have non-specific signs and symptoms. Patients usually present with fever of unknown region, headache, jaw or arm claudication and more than 90% have raised erythrocyte sedimentation rate (ESR >50 mm 1st hour) and C-reactive protein (CRP).[5]

Diagnosis: For diagnosis of C-GCA, temporal artery biopsy is considered as gold standard although with a reported higher false-negative rate

Correspondence : Prof. Maseeh uz Zaman
Section of PET/CT and NM Imaging,
Department of Radiology, Aga Khan University Hospital (AKUH), Karachi, Pakistan.
Email: maseeh.uzzaman@aku.edu

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(about 40%).[6] Imaging is predominantly used for diagnosis of vasculitis. In this regard, color doppler ultrasound (CDUS) is considered as modality of choice followed by magnetic resonance angiogram (MRA) and computerized tomography angiogram (CTA) while US and MRI are used for PMR.[7] Since we have been living in era of hybrid imaging being dominated by 18-Fluorodeoxyglucose (^{18}FDG) positron emission tomography and computerized tomography (PET/CT), we will review briefly its role in management of TKA, GCA and PMR.

^{18}FDG PET/CT Imaging

Clinical Background: It was introduced in 1998 and it has essentially revolutionized clinical oncology and fields of neurology and cardiology. Being a hybrid imaging equipped with anatomical and functional details, its diagnostic accuracy is significantly higher. Over the last two decades,^{18}FDG is the most popular substrate in clinical use due to longer half-life of F-18 (110 min) and dependence of most tumors upon glucose as primary energy source. However, glucose dependence is also seen in infective and inflammatory conditions which reduces specificity of ^{18}FDG. Interestingly this limitation of ^{18}FDG PET/CT has been exploited to explore its role in diagnosis and management of GCA, TKA and PMR. Limited specificity caused by metabolic agent (^{18}FDG PET) is addressed by using morphological details from low-dose CT or contrast enhanced CT.

Acquisition: After an overnight fasting (>6 hours) when fasting blood glucose (FBS) is less than 200 mg%, ^{18}FDG is injected intravenously and after at least 60-minute uptake time, whole body CT followed by PET images are acquired. In PET/CT scanner having angiography capability, intravenous contrast may be used for better morphological details [^{18}FDG PET/CTA].

Clinical applications in Vasculitis and PMR: In a normal ^{18}FDG PET/CT study, uptake of 18FDG in aorta and its major branches should be less than hepatic uptake (Fig.1a,b). In GCA and TKA, vascular uptake of ^{18}FDG will be higher than hepatic depending on the extent and severity of vascular inflammation (Fig.2a,b). In PMR, ^{18}FDG uptake in periarticular tissue and bursae will be higher than hepatic uptake along with higher vascular uptake as it overlaps with GCA (Fig.3). Since metabolic changes precede morphological alteration in early phase of disease, various researchers have explored ^{18}FDG PET/CT for early diagnosis and therapeutic response assessment in LVV and PMR. As morphological changes usually appear late, these are helpful in diagnosis of in late phase and evaluation of complications associated with LVV like development of stenosis and aneurysm. Appreciable change in ^{18}FDG uptake has also been observed on PET/CT at least 10 days after start of glucocorticoid and immunosuppressive therapy. This has also attracted treating physicians to use ^{18}FDG PET/CT for metabolic response assessment.[8]

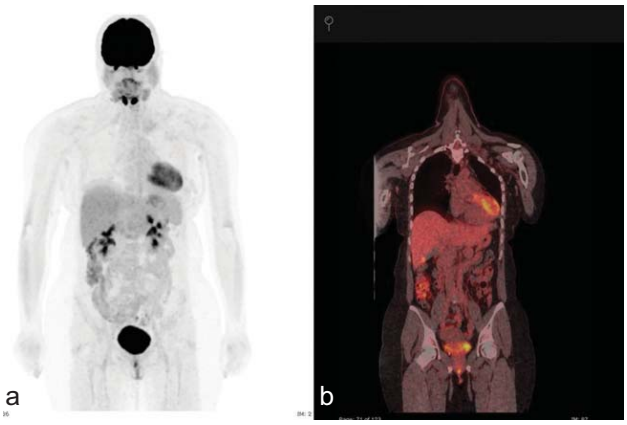

Figure 1: ^{18}FDG PET/CT (**A:** Maximum Intensity Projection MIP; **B:** Fused Coronal Image) in a normal individual. Vascular uptake is lesser than hepatic uptake.

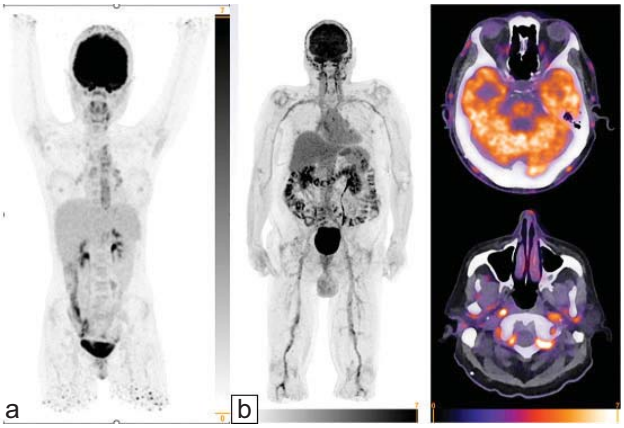

Figure 2: (A) 18FDG PET/CT (MIP image) in 16 year old girl showing enhanced tracer uptake over thoracic and proximal abdominal aorta [Grade III -higher than liver]. **(B)** ^{18}FDG PET/CT in 80 year old male with LV-GCA (MIP image) and C-GCA (fused axial slices).

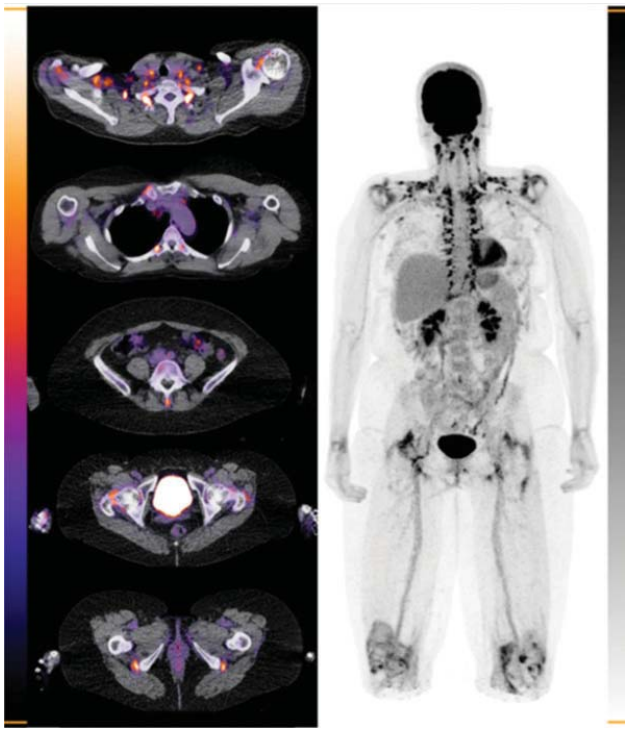

Figure 3: ^{18}FDG PET/CT imaging in 59 year female with PMR associated with GCA (Left: fused axial slices at different body levels; Right: MIP image) showing enhanced ^{18}FDG uptake (greater than liver) over periarticular soft tissue along with enhanced vascular uptake in thighs and neck (concomitant GCA). Benign brown fat uptake in neck and paravertebral at thoracic spine.

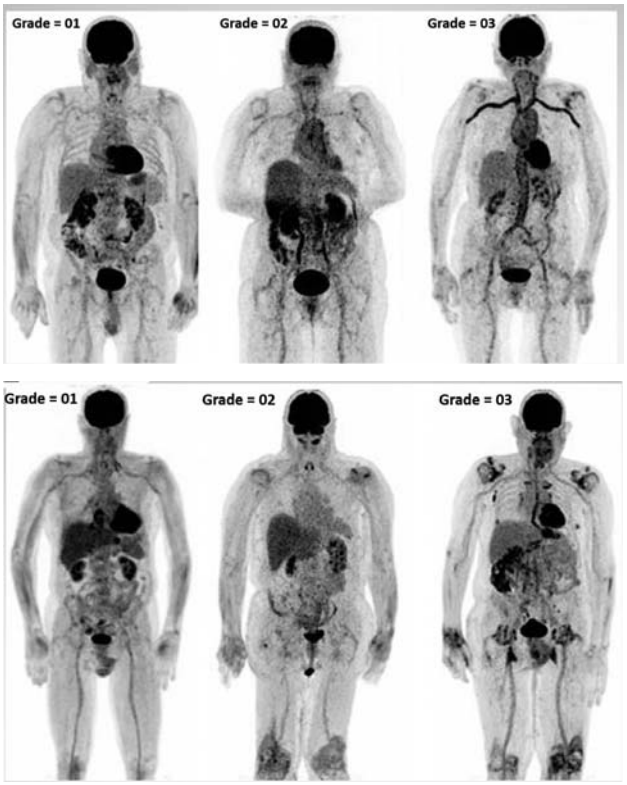

Figure 4: A: ^{18}FDG PET/CT MIP images in 03 different patients with GCA showing Grade 1-3 uptake. **B:** ^{18}FDG PET/CT MIP images in 03 different patients with PMR showing Grade 1-3 uptake in periarticular soft tissue (also variable grade vascular uptake due to associated GCA in these patiengts).

Guidelines for Standardized Acquisition and Interpretation: As most of studies for LVV and PMR used non-standardized ^{18}FDG PET/CT imaging and interpretation protocols, in 2018 various nuclear medicine societies issued first position statement to implement a standardized acquisition and interpretation protocol worldwide. This position statement recommended (a) minimal fasting of 6 hours; (b) FBS < 126 mg%, (c) withdraw or discontinue steroid until PET is doneand (d) minimal 60 min interval between ^{18}FDG injection and acquisition of images. A standardized interpretation criteria comprised of a 4-point grading system comparing ^{18}FDG vascular uptake with liver has been introduced (Grade 0: No uptake; Grade 1: vascular < liver; Grade 2: vascular = liver; Grade 03: vascular > liver). Grade 0 and 1 are considered negative, grade 2 as suggestive and grade 3 as positive for vasculitis (Fig.4a,b). Similar grading system comparing periarticular soft tissue ^{18}FDG uptake with liver has been recommended for PMR as well (Fig.3).[9]

Recently European Alliance of Association in Rheumatology (EULAR) has issued an updated imaging guidelines in LVV.[10] This document comprised of 03 overarching principles (1) early imaging must be considered in suspected GCA; (2) imaging must done by trained specialist following standardized acquisition and reporting criteria; (3) in cases of high clinical suspicion of GCA with positive imaging findings, vascular biopsy is not recommended.[10] The updated guidelines also recommend CDUS as first imaging in suspected GCA and MRI in suspected TKA. In suspected relapse where inflammatory markers are unreliable, CDUS, ^{18}FDG PET/CT and MRI are recommended. However, recent guidelines endorsed to follow the 4-point visual grading scale issued in 2018 position statement.[10] On literature review, one of the earliest studies was published in 2009 by Blockmans et al., revealing enhanced ^{18}FDG vascular uptake in 83% patients with LVV (predominantly subclavian artery

74%).[11] A meta-analysis of six studies upon GCA patients published in 2011, revealed a pooled sensitivity of 80%, specificity 89% and negative predictive value of 88%.[12] Another meta-analysis of 57 studies of TKA cases published in 2018 revealed a pooled sensitivity and specificity of 81% and 74% respectively.

Pitfalls of ^{18}FDG PET/CT Imaging: It is important to understand pitfalls associated with ^{18}FDG PET/CT imaging. The most important confounding factor is blood glucose level which has a negative correlation with vascular uptake and could result in falsely low sensitivity.[8] Similarly, oral glucocorticoids more than 3 days at time of imaging, would also lower sensitivity as it increases blood glucose level and hepatic uptake of ^{18}FDG which reduces sensitivity of visual grading scores. However, most challenging is ^{18}FDG uptake in atherosclerotic plaque but it is usually non-homogenous and focal with or without calcification while in LVV metabolic activity is diffuse and circumferential over vascular wall.[8]

Treatment Response Assessment: Response assessment is challenging in LVV and PMR as sign and symptoms are non-specific.[8] During relapse lower titers of inflammatory markers are not uncommon.[14] Therefore, role of imaging has been explored. It is generally considered that functional information (metabolic imaging) precedesmorpho-logical details. Various published studies have shown appreciable reduction in ^{18}FDG uptake in vascular wall and PMR at least 10 days after the start of steroid, methotrexate and anti-interleukin-6 receptor therapy (Ant-IL6).[15] However, few studies have shown failure of ^{18}FDG uptake to get normalized in vascular wall and periarticular soft tissue despite of attaining clinical remission (Fig.5).[8] A meta-analysis of 08 studies of GCA and TKA revealed a pooled sensitivity of 78% and specificity of 71% due to failure of ^{18}FDG to Grade-0/1despite of achieving clinical remission.[16] Another prospective study upon 100 consecutive patients of GCA and TKA who were followed for 98 months also revealed a lower sensitivity (60%) and specificity (80%).[17] Recently published study has found lower sensitivity and specificity of ^{18}FDG PET/CT in response assessment in patients with PMR for same reason as observed in LVV.[18] Due to this limitation, ^{18}FDG is not routinely recommended for treatment response assessment in patients with LVV and PMR. However, with introduction of more specific immuno-PET tracers (like F-18 labelled IL-2 receptor) for vasculitis would allow more thorough insight into pathogenesis.[8] Binding of PET tracers to specific immune cell subsets, could potentially be more accurate than ^{18}F-FDG for treatment monitoring in LVV.

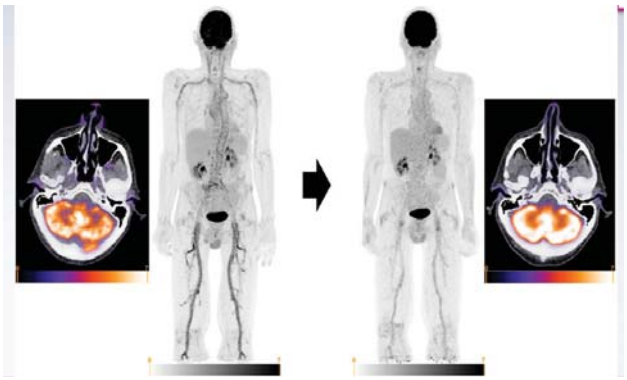

Figure 5: ^{18}FDG PET/CT imaging in 67-y-old male with GCA showing Garde-III vascular uptake at time of diagnosis (pre-treatment) and after 1 year of steroid and methotrexate treatment; significant interval reduction in vascular uptake is seen.

In current clinical scenario, 18FDG PET/CT imaging is considered a robust modality in diagnosis, monitoring and treatment response assessment in patients with GCA, TKA and PMR. It is pertinent to adopt standardized imaging protocol and interpretation criteria to mitigate challenges to enhance its diagnostic strength in these clinical conditions.

Conflict of Interest: None.

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