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[18F]FDG-PET/CT in Polymyalgia Rheumatica: An Update and Future Aspects

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Polymyalgia rheumatica (PMR) is an inflammatory disorder usually diagnosed in patients older than 50 years of age. It is characterized by sudden onset pain and prolonged morning stiffness in the scapular and/or pelvic girdle, sometimes debilitating and accompanied by constitutional symptoms such as weight loss. In approximately 20% of the cases, it is linked to giant cell arteritis (GCAV) representing a disease continuum. The diagnosis is mainly clinical and noninvasive imaging such as ultrasound of joints may be helpful. In atypical PMR cases, whole body imaging using [18F]FDG-PET/CT may be useful. First, to confirm or rule out the diagnosis of PMR, secondly, to assess the coexistence of a GCA, and thirdly to establish the differential diagnosis with other types of arthritides encountered in this age group, such as elderly-onset rheumatoid arthritis, spondyloarthropathies, crystal-induced arthropathies or the rare remittent seronegative symmetrical synovitis with pitting edema. Relatively typical patterns of [18F]FDG-PET/CT are well known, based on the clinical distribution of the disease (eg, scapular and pelvic girdle, interspinous bursae, sterno-costoclavicular joints, entheses), especially the hypermetabolism at the interspinous lumbar bursae that has shown the best post-test likelihood ratio in a meta-analysis. This article focuses on the differential diagnosis and on the visual and semi-quantitative tools that can be used to guide to the correct diagnosis of PMR as an add-on to the clinical picture. Further, we briefly discuss the options that can improve molecular imaging in the future for inflammatory rheumatisms in elderly.
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Chronic inflammatory rheumatic diseases (CIRDs) affect a non-negligible proportion of elderly subjects and this number will continue to grow as life expectancy increases. Most patients with CIRDs experience pain, reduced workability, and deteriorating quality-of-life because of disability, often leading to adverse impact on their social and mental well-being. In addition, as patients get older, they often have co-morbidities requiring treatment with multiple

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medications; ageing, polymorbidity, and polypharmacy all contribute to an increased risk of developing geriatric syndromes on top of the CIRD that is a predisposing factor.[1] Thus, elderly people affected by CIRD pose considerable challenges for physicians. Consequently, accurate and timely diagnosis is of utmost importance to optimize the management of individual older subjects with CIRDs. In this review, we focus on the role of PET/CT in the evaluation of patients with suspected PMR and its differential diagnoses.

Polymyalgia Rheumatica: Definition

Polymyalgia rheumatica (PMR) is an inflammatory rheumatism of unknown origin, affecting people >50 years, with an onset peak at 75 years.[2,3] It is the second most common inflammatory rheumatic disorder of the elderly after rheumatoid arthritis (RA) with a lifetime risk of around 2%.[4,5] PMR is a complete and complex disease targeting different structures: joints, tendons, tendon sheath, entheses, articular bursae, and muscles.[6-10] The clinical presentation is most usually stereotypic, characterized by sudden onset pain and prolonged morning stiffness in the pelvic and scapular girdle with inflammation of joints and often accompanied by constitutional symptoms. In 15%-20% of the cases, PMR is associated with giant cell arteritis (GCA), a large vessel vasculitis (LVV). There is no specific biological marker for diagnosis, but C-reactive protein (CRP) and erythrocyte sedimentation rate are increased in the majority of cases.[11,12] The diagnosis of PMR is based mainly on clinical features and laboratory work-up, but ultrasound can be helpful. Indeed, according to the 2012 provisional classification criteria for PMR by the collaborative initiative of the EULAR and the American College of Rheumatology, the addition of ultrasound of the hips/shoulders improved the specificity for classification of PMR compared to other disorders (Table 1).[13] Ultrasound of the shoulders and hips show characteristic but nonspecific findings, such as subdeltoid bursitis, biceps or glenohumeral tenosynovitis, hip synovitis, or trochanteric bursitis.

Even though the 2012 EULAR/ACR criteria have been instrumental for research purposes, these do not serve as diagnostic criteria. Nevertheless, there is accumulating evidence that imaging can aid in the differential diagnosis of inflammatory rheumatisms in the elderly, but no single diagnostic test is specific to distinguish one entity from another. Indeed, several disorders can mimic PMR such as elderly onset RA (EORA), late-onset spondyloarthritis (SpA), remitting seronegative symmetrical synovitis with pitting edema (RS3PE), hydroxyapatite deposition disease, inflammatory myositis, or mechanical rheumatic diseases (ie, osteoarthritis) can also exhibit PMR-like symptoms. Furthermore, PMR or RS3PE can be the initial presentation of patients diagnosed at a later stage as EORA, which adds complexity to the diagnostic challenge.

Pathophysiology of PMR remains unknown and may be related to the ageing of the immune system (immunosenescence). Genetic correlations have been observed in patients with concomitant GCA, in whom an association with HLA-DRB1*04 alleles was found. Potential association with previous infection and with neoplastic disorders has also been evoked, without demonstrative proof.[14]

It is often accepted that a low-dose steroids challenge (ie, 12.5-20 mg prednisolone) leading to rapid improvement of symptoms is an empiric and a posteriori proof of the diagnosis, but many other CIRDs may respond as well, hence the nonspecificity of this finding. Conversely, failure to respond to this therapeutic challenge must lead to the search of alternative diagnoses.

PET-CT in PMR: Relevance, Interpretation, and Limitations

PET/CT using [^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG-PET/CT) has become a widely available tool in standard practice in high-income countries and has reached an industrial maturity that favors its use for a wide variety of inflammatory disorders. A recent survey from the EULAR task force documented the current training, implementation, and role of

Table 1 ACR/EULAR Classification for PMR (Reproduced and Adapted From Reference 11) – PMR Classification Criteria Scoring Algorithm- Required Criteria: Age Over 50 Years, Bilateral Shoulder Aching and Abnormal CRP and/or ESR*

	Patients Without US (0-6)	Patients With US† (0-8)
Morning stiffness duration > 45 min	2	2
Hip pain or limited range of motion	1	1
Absence or RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and biceps tenosynovitis and/or glenohumeral tenosynovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders and subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

ACR: American College of Rheumatology; EULAR: European League against Rrhematism; ACPA: anticitrullinuted antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PMR: polymyalgia rheumatica; RF: rheumatoid factor.

*A score of 4 or more is categorized as PMR in the algorithm without US and a score of 5 or more is categorized as PMR in the algorithm with US.

†Optional ultrasound (US) criteria.

modern musculoskeletal imaging techniques, including [18F]FDG-PET, among rheumatologists in Europe.[15] Interestingly, the access to PET/CT varied across EULAR countries, and LVV and fever of unknown origin dominated the requests for PET/CT examinations by rheumatologists.[15,16] Beyond accessibility, a major challenge remains the lack of internationally accepted standards for PET imaging in rheumatologic disorders. Indeed, typical [18F]FDG-PET/CT imaging protocols are usually performed from the vertex to the mid-thighs, with arms raised or down. Of course, total body imaging appears more relevant to leverage the full capabilities of PET/CT imaging and to assess rheumatologic disorders in a unique and standardized 3D-holistic perspective. By defining a general framework, including positioning, topography, and interpretation for example, the grade of uptake, the recent joint procedural recommendations for [18F]FDG-PET/CT in LVV and PMR, endorsed by the international nuclear imaging communities, may be considered a first step towards standardization and harmonization of [18F]FDG-PET/CT imaging applied to rheumatologic disorders.[8] In suspected PMR, the field-of-view must at least be extended to below the knees.

Typical musculoskeletal patterns for PMR include [18F]FDG uptake in the scapular and pelvic girdles, interspinous regions of the cervical and lumbar vertebrae, ischial tuberosity and bursae, and joint capsule of the knees. A recent meta-analysis of 636 patients with some inclusion biases and heterogeneity (due to varying acquisition protocols) comparing PMR to several oncological or various rheumatologic disorders confirmed the high prevalence of [18F]FDG uptake in several targeted sites such as interspinous bursae, ischial tuberosities, hips, sternoclavicular joints and the shoulders (Figs 1-2).[6] The best positive likelihood ratio (LR+) was reached for the interspinous bursae (LR+: 4.00, 95% CI: 1.84-8.71), followed by uptake in the hips, ischial tuberosities and shoulders. Negative likelihood ratio was high for all sites and composite [18F]FDG-PET/CT indices reported in three studies provided a pooled LR+ of 3.91 (95% CI: 2.42-6.32).

Although these results appear relevant at the population level, the controls were not homogeneous and mainly consisted of oncological patients with few challenging PMR-mimicking disorders, hence probably overestimating the performance of [18F]FDG-PET/CT for diagnosing PMR. Furthermore, their relevance at the patient level remains to be elucidated because all PMR-mimicking disorders are characterized by the involvement of the synovio-entheseal complex. The latter is defined by a close spatial and functional relationship between the bursa, the synovium, and the enthesis at multiple sites in the body, in the vicinity of tendon insertions and within the joint capsule. Consequently, various but frequent overlaps in bursitis - tenosynovitis - enthesitis may be observed in rheumatologic disorders, especially in the elderly.

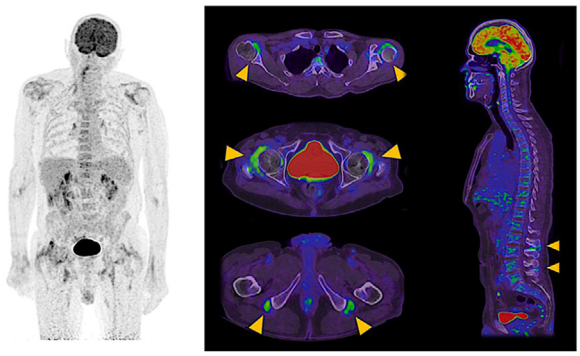

Figure 1 Typical [18F]FDG-PET uptake pattern observed in PMR: typical target sites of [18F]FDG-PET/CT uptake in PMR: shoulder, hips/trochanters, ischial tuberosities, interspinous bursae.

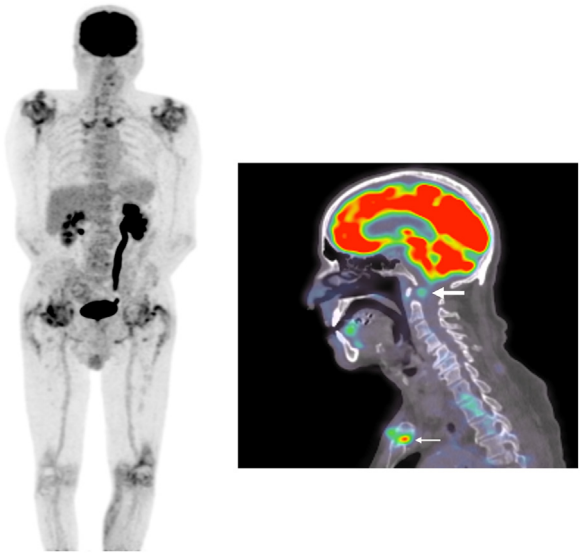

Figure 2 Typical PMR pattern including knee synovitis on the left side (A) and atlantoaxial involvement (B, thick arrow), as well as intense sternoclavicular inflammation (B, thin arrow). Note the serendipitous finding of left ureterohydronephrosis due to a distal ureteral stone.

To improve the diagnostic accuracy of [18F]FDG-PET/CT for PMR and to better differentiate it from PMR-mimicking disorders, several visual or semi-quantitative composite scores/algorithms have been proposed based on the FDG uptake at relevant targeted sites (Table 2). In brief, most scores evaluate [18F]FDG uptake in targeted regions compared to liver uptake as reference, with an uptake equal or higher than liver considered as positive.

The Leuven score (ranging from 0 to 24), includes twelve predefined anatomical sites, each site being scored 0 (no uptake) to 2 (visual uptake ≥ liver uptake).[17] The Besançon score consists of seventeen anatomical sites, each visually graded 0 to 3, a grade 2 or more being considered positive.[18] The algorithm from Saint-Etienne is based on only two anatomical sites (interspinous bursa and trochanteric bursa) and the Heidelberg algorithm is based on five anatomical sites, with a grade two or more being considered positive for both algorithms.[7,19] Van der Geest et al.[20] compared the diagnostic performance of these PET/CT scores and algorithms in PMR. The Leuven score showed the highest diagnostic utility, but the modified Leuven/Groningen score in which the number of predefined targeted sites was reduced to 4 regions (sternoclavicular joints, interspinous lumbar

Table 2 Characteristics of [^{18}F]FDG-PET/CT Scores and Algorithms

Scores/Algorithm	Authors	PMR Patients	Controls Patients	FDG-PET Skeletal Sites	Range of Score	Cut − Off Value	Sensitivity, Specificity, and AUC
Original Leuven score	Henckaerts et al.	Newly - diagnosed Steroid naïve n = 67	Rotator cuff disorders Spontaneous resolution Seronegative RA Adult-onset Still's disease Others * n = 32	12 articular regions. Cervical and lumbar spinous processes, bilateral hips, shoulders, ischiatic tuberosities, great trochanter, sternoclavicular joint	0-24	16	Se 85.1% Spe 87.5% AUC 0.905
Modified Leuven and Groningen score	Van der Geest et al.	Newly - diagnosed Steroid naïve n = 39	Rheumatic diseases Osteoarthritis Undifferentiated arthritis ICI − induced arthritis Others ** n = 19	Sternoclavicular joint Hips Ischial tuberosities Lumbar interspinous bursae	0-14	8	Se 89.7% Spe 84.2% AUC 0.926
Heidelberg algorithm	Owen et al.	Newly - diagnosed Steroid naive n = 33	Age and sex- matched Malignancies Rheumatic diseases Osteoarthritis Inflammatory arthritis n = 132	Ischial tuberosities Peri articular shoulder Interspinous bursa	NA	Positive or negative	Se 90 % Spe 92.4% AUC 0.964
Besançon score	Sondag et al.	Newly - diagnosed and prevalent ± steroids or Methotrexate n = 50	Malignancies n = 53	Presence of 3 or more sites with a significant FDG uptake score $\geq$ 2 FDG uptake score $\geq$ 0.53	0-3	0.53 for FDG uptake score	*Nbr of sites* : Se 74%, Spe 79%, AUC 0.81 *FDG uptake score :* Se 80%, Spe 77%, AUC 0.85
Saint − Etienne Algorithm	Flaus et al.	Newly - diagnosed and prevalent ± steroids n = 55	Rheumatoid arthritis Spondylarthritis Other inflammatory rheumatism *** n = 85	Interspinous bursae Trochanteric bursae	NA	Positive or negative	*Training cohort* Se 73.2% Spe 87.5% *Validation cohort* Se 78.6% Spe 80.1%
Copenhagen scores	Brinth et al.	Newly - diagnosed and prevalent ± steroids n = 78	Malignancies Rheumatoid arthritis Other inflammatory diseases Other or no established diagnoses n = 120	Shoulder joint Ischial tuberosity	0-8	5 for semi quantitative score 4 for the visual score	Se 92% Spe 86%

RS3PE: Remitting seronegative symmetrical synovitis with pitting oedema. SAPHO: Synovitis-acne-pustulosis hyperostosis- osteitis, Se: Sensitivity, Spe: Specificity, NA: Not appropriate.
Others * Fibromyalgia, late onset X - link hypogammaglobulinemia, lupus, polymyositis, osteoporosis, paraneoplastic syndrome, spondyloarthropathy. ICI, immune check-point inhibitor.
Other ** Fibromyalgia, rotator cuff disorders, viral infection.
Other *** unclassified rheumatism, psoriatic rheumatism, paraneoplastic rheumatism, RS3PE, SAPHO

bursa(e), hips, ischial tuberosities), yielded similar diagnostic accuracy with the advantage of a simplified analysis. Recently, Brinth et al.[21] evaluated the performance of existing scoring systems as well as a new simplified scoring system (the Copenhagen score) using either a visual or semi-quantitative analysis of periarticular FDG uptake in the shoulders and at the ischial tuberosities. For semi-quantitative analysis, the SUVpeak at the target site was compared to SUV-mean of superior vena cava and liver and the resulting ratio was converted to a three-point scoring system. All scoring systems, even the simplest ones including few anatomical regions, showed a good performance for diagnosing PMR, in corticoid − free patients. However, systemic steroid treatment up to 4 weeks prior to [18F]FDG-PET/CT, significantly decreases the diagnostic accuracy of all scoring systems. As illustrated above, visual scores are reliable and are currently recommended for clinical routine. Despite interesting results, semiquantification appears less relevant for diagnostic purposes, due to the high dependency of SUV on technical and image processing issues (the well-known "center effect").[22]

Despite the growing availability of [18F]FDG-PET/CT in standard practice and the efforts made by the nuclear imaging community, [18F]FDG-PET/CT currently has no indication in the work-up of isolated typical PMR, neither for diagnosis, risk of relapse nor treatment monitoring. Blockmans et al.[9] showed that [18F]FDG uptake in the shoulders, hips, or processi spinosi did not correlate with the risk of relapse. Regarding the response to treatment, few data are available with inconclusive results, and the gain of [18F]FDG-PET against standard clinical and biological work-up has not been demonstrated yet. Furthermore, it has been shown that site locations and the intensity of [18F]FDG uptake were modified even after ten days of corticosteroid treatments.[23,24] More recently, two French studies by Palard Novello et al.[25] and Devauchelle et al.[26] showed that although the intensity of uptake globally decreased under corticosteroids, correlation with clinical or laboratory findings appeared weak in the long term.

However, [18F]FDG-PET/CT is recommended if concomitant GCA is suspected (Fig. 3).[27] In their recent meta-analysis based on 13 cohorts with 566 newly - diagnosed isolated PMR patients, Hemmig and coworkers reported the presence of subclinical GCA in 23% (0.14-0.36) of PMR patients and up to 29% [0.13-0.53] for those who were screened by [18F]FDG-PET/CT.[28] Previously, Prieto-Peña et al.[29] showed that low back and pelvic pain could be predictive factors for [18F]FDG-PET uptake indicative of LVV in clinically isolated PMR, but in clinical practice, those symptoms are nonspecific and may be also related to isolated PMR. The role of [18F]FDG-PET/CT to rule out neoplasia is more controversial, in the context of PMR. In their study exploiting the UK General Practice research database, Muller et al.[30] reported a significantly increased rate of cancer diagnoses in the first 6 months after PMR diagnosis (adjusted HR of 1.69), which then decreased to reach similar risk compared to controls patients without PMR. In their forty-week prospective monocentric Danish study, Emamifar et al.[31] reported the detection of cancer in only 5% of their PMR patients. These results were corroborated by Moya Alvarado et al.[32] in a cross-sectional study.

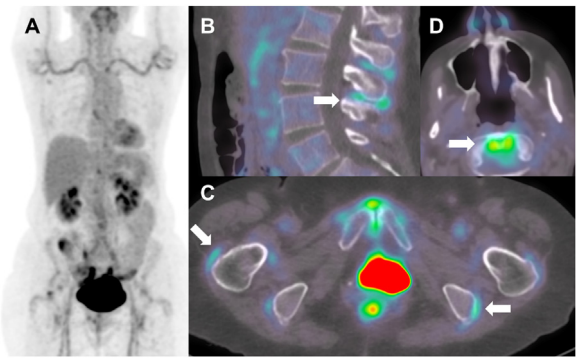

Figure 3 PMR with associated GCA: the pelvic and scapular girdle involvement is limited (A) but associated with uptake at the interspinous bursae (B), trochanteric, pubic and ischiatic enthesitis (C) and atlantoaxial hypermetabolism (D). Vascular uptake is obvious on the MIP image.

Differential Diagnosis

In routine practice, clinical features and laboratory work-up, sometimes with the inclusion of ultrasound should suffice to establish the diagnosis of a typical PMR patient. However, as stated before, the clinical presentation can be atypical and overlap exists with other PMR-mimicking inflammatory rheumatisms, making the diagnosis challenging (Fig. 4).

Elderly Onset Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most frequent chronic inflammatory rheumatism (CIR), affecting 0.3% to 0.5% of the general population.[33,34] Although [18F]FDG-PET/CT is not recommended in RA, several studies assessed the relevance of [18F]FDG-PET/CT to discriminate RA from other CIR.[35-37] Wang et al.[37] built a composite musculoskeletal

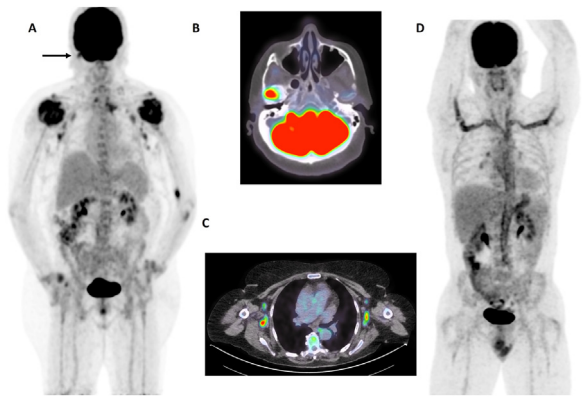

Figure 4 Differential diagnosis. Typical EORA in a 70 year-old seronegative patient: besides extensive shoulder, hips and wrist involvement, there is also intense hypermetabolism of the right temporomandibular joint (arrow) (A-B). Note the presence of reactive axillary lymph nodes, typical of rheumatoid arthritis but not in PMR (C). GCA in a patient referred with complaints suggestive of PMR, without any sign of (peri)articular involvement (D).

score combining FDG uptake of skeletal sites (greater trochanter, interspinous bursae, hips, and curiously sacroiliac joints) and rheumatoid factor to discriminate RA from PMR with a sensitivity and specificity of 90.3% and 82.6 % respectively. Ikuma et al.[38] recently showed that [^{18}F]FDG uptake of at least one ischial tuberosity best differentiates PMR from RA. Similarly, to discriminate early onset RA and PMR, Wakura et al.[39] elaborated a score combining [^{18}F]FDG accumulation at nine anatomic regions and showed that involvement of enthesis and bursa in several areas is more specific for PMR patients. Other sites (scapulohumeral and hip joints, ischial tuberosity) showed also increased FDG uptake but with a lower specificity. Interestingly, Takahashi et al.[40] observed higher median [^{18}F]FDG-PET/CT scores at targeted PMR sites (meaning ischial tuberosity, greater trochanter, and interspinous process) than in RA.

Spondyloarthritis

SpA usually affects young people below 45 years with a multifaceted clinical presentation.[41] Classification criteria integrate radiography, ultrasound, and magnetic resonance imaging, which can show some characteristic findings such as sacroiliitis.[42] Rarely, SpA can affect people over > 45-50 years. In these late-onset SpA patients, the clinical presentation is generally atypical and confusing, leading to misdiagnosis.[43,44] The literature on [^{18}F]FDG-PET/CT in SpA patients is scarce. One study showed a large overlap in [^{18}F]FDG-PET patterns between late-onset SpA patients and PMR, with [^{18}F]FDG uptake of the sacroiliac joints being highly specific but rare in SpA patients (15%).[45] Péan de Ponfilly et al. developed a musculoskeletal score combining [^{18}F]FDG-PET/CT uptake in ischial tuberosity, interspinous process and shoulders to discriminate both groups with a sensitivity of 74.1% and specificity of 77.1%. Although being more frequently observed in PMR patients, the ischial tuberosities, shoulders and interspinous regions were, in fact, involved in the two groups, and none of them were discriminant in multivariate analyses. In addition, it is interesting to note that no differences were observed regarding the other proximal or more distal peripheral joint abnormalities, including trochanters, elbows, knees or wrists. In their study comparing seronegative SpA, PMR, and RA patients, Yamashita et al.[46] showed no difference between PMR and SpA patients for the uptake at the ischial tuberosities, great trochanter, and interspinous bursa. Conversely, sacroiliac joint abnormalities were, of course, highly discriminant for SpA, and were consistent with MRI findings in 57 % of the SpA cases. To note, Wendling and coworkers demonstrated a good concordance between [^{18}F]FDG-PET/CT and MRI to assess spine enthesitis but [^{18}F]FDG-PET/CT failed to detect sacroiliitis in nonradiographic SpA.[47] A recent study by Wanabe et al.[48] in a group encompassing middle-aged patients (mean age: 53 years; range 18-81) showed that [^{18}F]FDG uptake in untreated peripheral spondyloarthritis (pSpA) correlated significantly with serum inflammatory biomarker levels. However, these findings were not confirmed in axial SpA. In the meantime, several studies demonstrated that [^{18}F]-Na-fluoride is superior for this indication, which is more a bony disease than a para-articular disease, as far as the pathophysiology is concerned.[49]

Remitting Seronegative Symmetrical Synovitis With Pitting Edema

RS3PE is a rare disorder affecting elderly people. It is characterized by symmetrical and distal synovitis and pitting edema with negative rheumatoid factor and anti-citrullinated peptide antibodies.[50] This condition has a good response to low − dose steroids. RS3PE can be associated with malignant disease and is classified as a paraneoplastic syndrome. To this purpose, [^{18}F]FDG-PET/CT could be considered as a proper indication. Because of these characteristics, RS3PE can mimic but can also be concomitant to PMR.[51] Several cases reported a multiarticular sometimes tendinous, symmetrical, and diffuse [^{18}F]FDG uptake with periarticular soft tissue uptake in RS3PE patients.[52-54] However, except for the detection of cancers, RS3PE has a reliable clinical and biological diagnosis.

Crystal Arthropathies

In their polyarticular or axial form, crystal arthropathies can mimic PMR or other chronic inflammatory rheumatisms.[55] Chondrocalcinosis is a calcium pyrophosphate disease deposition (CCPD), affecting middle-aged patients and manifesting by acute or chronic episodes.[56] In the axial skeleton, the classical crowned dense syndrome on the C1/C2 spine joint is described but CCPD can touch every spinal ligament or intervertebral disc. To date, there is no study assessing the role of [^{18}F]FDG-PET/CT in crystal arthropathies. Multiple cases report an intense [^{18}F]FDG uptake in the joint and the soft tissue in the presence of calcifications.[57,58] However, CCPD deposition is frequently an incidental finding without clinical manifestation. Joint fluid aspiration and rarely biopsies are often necessary to document the implication of the disease and rule out other diagnoses. Chronic gout can reveal [^{18}F]FDG-PET/CT uptake patterns similar to CCPD patients.[59-61]

Perspectives and Future Work

From this review, it is clear that [^{18}F]FDG-PET/CT can be an add-on to the diagnosis of PMR. However, it has not been accepted yet as a criterion to establish the diagnosis, as stated by international consensus reports such as the EULAR and ACR ones. Large, multicentric, international studies may be needed to determine in which clinical situations the role of [^{18}F]FDG-PET/CT may be essential, to avoid on the one hand overconsumption and on the other hand, missing essential diagnoses that may lead to severe complications (e.g. association with GCA and especially cranial-GCA), or chronic dehabilitation in elderly patients. The role of [^{18}F]FDG-PET/CT in the follow-up of patients and evaluation of

response to treatment also needs to be addressed, especially in patients who have a poor or limited clinical response or a lack of response of the inflammatory markers. In the near future, other tracers may be proposed with better disease-specificity. These may be targeting macrophages, using TSPO or folate-receptors ligands, fibroblast activating protein inhibitors (FAPI), lymphocyte receptors such as CD20 or a number of T-lymphocyte receptors, or various adhesion molecules as recently nicely summarized by van der Geest et al.[62] Importantly, most of the ligands can be labelled with positron emission radionuclides which will enable the best sensitivity and spatial resolution. Again, looking at the ongoing trials, it is essential that future studies aim at providing added value to the currently widely used FDG.

Declaration of Competing Interest

The authors have no conflicts of interest with this paper.

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