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Review Article

Role of nuclear medicine applications in rheumatological disease

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Abstract

Diagnosing rheumatological diseases is often challenging due to nonspecific clinical presentations. Nuclear medicine offers a sensitive, functional imaging approach to detect inflammatory and non-inflammatory conditions early, aiding in diagnosis, monitoring, and treatment evaluation. Bone scintigraphy using Tc-99m MDP is widely utilized for detecting increased osteoblastic activity in disorders such as rheumatoid arthritis (RA), osteomalacia, and Paget's disease. Hybrid techniques like SPECT/CT and PET/CT, particularly with 18F-FDG, allow for whole-body imaging, improved lesion localization, and assessment of disease activity. These are especially valuable in vasculitis, RA, ankylosing spondylitis, sarcoidosis, and rare conditions like retroperitoneal fibrosis. In addition to diagnostics, nuclear medicine also plays a therapeutic role through radio synovectomy, where beta-emitting isotopes like Yttrium-90 are intra-articularly injected to manage chronic synovitis. PET/CT imaging can also predict treatment response, supporting personalized therapy strategies in autoimmune arthropathies. Nuclear medicine thus provides high sensitivity, comprehensive assessment, and prognostic insight in rheumatologic care, offering both diagnostic and therapeutic advantages over conventional imaging.

Key words: nuclear medicine, rheumatological disease, applications

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Introduction

Diagnosis of Rheumatological diseases is challenging in clinical practice due to their unspecific clinical presentation. Nuclear medicine plays a significant role in diagnosis , assessment and monitoring of wide range of rheumatological diseases. [1]

Nuclear scintigrahic procedures are used for evaluation of inflammatory and non-inflammatory joint diseases. They allow insights into disease activity and extent by visualizing physiological processes at a cellular level. It can detect functional abnormalities at early stages of the disease compared to the conventional imaging. [1]

Traditional bone scintigraphy with Technetium 99m MDP, a bone- targeting radiotracer, and inflammation-targeting radiopharmaceuticals, such as radiolabeled leucocytes was used since decades to detect site of inflammation showing increased uptake at sites of new bone formation, and site of inflammation. They were the most common diagnostic applications for diagnosis and follow up of metabolic and rheumatological bone diseases and for preparation and evaluation of radio synovectomy. [1]

Bone scan was used to confirm a diagnosis of inflammatory Rheumatoid arthritis, osteoarthritis or fracture in osteoporosis, and pseudo fracture in osteomalacia and also used in evaluation of Paget's disease. [1]

Scintigraphical examination is effective in the early diseases stages and plays a complementary role with radiographical examination in more advanced disease stages. [1]

In bone scan, a whole-body imaging is obtained by the gamma camera a few hours after radiotracer intravenous injection to the patient with a dose of 20mci of tc99m MDP and good oral hydration. Bone scan is very sensitive but not specific for inflammation. The most common technique used is triple phase scintigraphy, with early dynamic phase assessing the blood flow of the area affected and the 2nd phase (blood pool phase) being the most useful for identifying inflammation. [2]

Now molecular imaging with [18F]FDG PET/CT, a hybrid imaging method is recently used in rheumatology. It is a functional imaging modality using 18F-fluro-2-deoxy-D-glucose(FDG), a glucose analogue , which show increased utilization and high uptake by malignant and inflammatory cells it can detect increased glucose metabolism at various rheumatological diseases and can used in diagnosis of large vessel vasculitis, fever of unknown origin, sarcoidosis, polymyalgia rheumatica and rheumatoid arthritis and can assess therapy response as well. [3]

The combined use of nuclear medicine techniques together with computerized topography (CT) or magnetic resonance imaging (MRI) provides a combination of functional data of increased cellular metabolism from the PET together with exact localization and description of the affected anatomic structures from the CT or MRI. [3]

Patient is injected with low dose of 18 F- FDG with blood glucose level less than 200 mg/dl. PET scanning start 45–60 min after tracer injection using a standard PET/CT imaging protocol of a whole-body with the patient is lying supine started from the head to the mid-thigh by low dose CT scan Followed by PET emission scan.The degree of FDG uptake can be expressed quantitively by means of the standardized uptake value (SUV). It represents the activity in the lesion in mci/ml.The area of inflammation showing increased uptake and radiotracer concentration reflecting at increased SUV of the lesion. [4]

PET/CT has higher specificity and resolution compared to gamma camera scans, Moreover PET/CT allows evaluation of whole-body articular and extra-articular lesions in one examination, representing an advantage over other conventional imaging technique. [4]

Some radiopharmaceuticals are used for diagnostic scintigraphic procedures using a gamma camera and PET/CT. Other radiopharmaceuticals may be also used as therapeutic options in patients with rheumatic diseases in what is called radio synovectomy for arthritis as the following:

- **Role of nuclear medicine in diagnosis of rheumatic diseases**:

1. Vasculitis:

Vasculitis is an inflammatory condition of blood vessels characterized by vascular infiltration ,if not early detected and managed it results in

destruction of the blood vessel wall and the adjacent structures with significant consequences. Conventional cross-sectional imaging such as (CT) and magnetic resonance imaging (MRI) can demonstrate the anatomical changes once they are established ,but the lack the capability of detection the early inflammatory process which if detected &managed earlier it can improve the outcome & survival rates. [5]

Nuclear imaging studies such as imaging with gallium67 citrate &TC-99 m-HMPAO labelled white cells were used in the evaluation of vasculitis such as Wegner`s granulomatosis and Kawasaki diseases. [5]
However, their low sensitivity resulted in their replacement with molecular imaging such as F-18FDGPET/CT. [5]

It was found that the revolution of PET scanners have the ability to detect lesions around 5mm ,so they are capable of detecting lesions of medium and large blood vessels as Giant cell artetritis & takayassau reather than small vessel vasculitis. [5]

Studies revealed that although F18FDG uptake is non specific for inflammatory lesions,,it can help in the differential diagnosis & demonstrating the disease extent by guiding the sites for biopsy to obtain histological confirmation.
Also it has a role in the assessment treatment response and disease activity monitoring. [5]

2. Rheumatoid arthritis:
It is a chronic autoimmune disease characterized by systemic joint inflammation, nuclear medicine excels in detecting early synovitis and assessing disease activity. Conventional radiography often fails to capture the initial inflammatory processes, whereas nuclear medicine techniques, particularly hybrid imaging such as SPECT/CT and PET/CT, can identify increased metabolic activity and inflammation in joints at nascent stages. [6]

Radiopharmaceuticals like 99mTc-labeled diphosphonates (e.g., 99mTc-MDP) are highly sensitive in identifying increased bone turnover and periarticular uptake indicative of active arthritis, although their specificity is limited when used alone. When combined with clinical data, these agents can effectively highlight inflamed joints. [7]

More significantly, 18F-FDG PET/CT has emerged as a powerful tool, as 18F-FDG accumulates in areas of heightened glucose metabolism, a hallmark of inflammatory cells within the inflamed synovium. This allows for the visualization of active synovitis and the comprehensive assessment of inflammatory extent throughout the body, including subclinical involvement. [8]

Furthermore, radiolabeled leukocytes (99mTc-HMPAO or 111In-labeled WBCs) directly visualize the aggregation of inflammatory cells in affected joints, offering superior specificity for active inflammation compared to traditional bone scans. Emerging tracers, such as 99mTc-nanocolloid and 99mTc-human immunoglobulin, show promise in differentiating arthritis from arthralgia and providing more specific detection of synovitis, while fibroblast activation protein inhibitor (FAPi)-labeled PET tracers are demonstrating remarkable results in visualizing inflammatory changes. [9]

Nuclear medicine also facilitates the comprehensive assessment of disease activity and extent, offering a whole-body view that identifies all actively inflamed joints, even those not clinically apparent. By quantitatively evaluating changes in radiotracer uptake before and after treatment, these techniques enable precise monitoring of therapeutic response, allowing for timely adjustments in treatment strategies. The intensity and distribution of tracer uptake can also correlate with disease severity and potentially predict future joint damage, thus aiding in prognosis. [10]

3. Ankylosing spondylitis:
It is a chronic inflammatory disease primarily affecting the spine and sacroiliac (SI) joints, nuclear medicine plays a vital role in the early diagnosis of sacroiliitis. While MRI is generally preferred for its ability to detect bone marrow edema indicative of early sacroiliitis, bone scintigraphy with 99mTc-MDP can indicate increased osteoblastic activity in the SI joints and spine, though its sensitivity for early sacroiliitis is variable. [11]

In scenarios where MRI is contraindicated, bone scintigraphy remains a viable option. 18F-FDG

PET/CT further contributes by detecting inflammatory activity in the sacroiliac joints and spine, which is beneficial for both early diagnosis and assessing the extent of active inflammation. This metabolic assessment complements anatomical imaging, providing a more complete picture of the disease state. [12]

Nuclear medicine techniques assist in identifying active inflammatory lesions in the spine and peripheral joints that might not be visible on conventional radiographs. They also contribute to monitoring disease progression and treatment response, although MRI remains the primary tool for these aspects in AS. Nuclear medicine provides a valuable whole-body overview of the inflammatory burden. Additionally, in severe AS with significant ankylosis, bone scans can be utilized to detect fractures, which can be challenging to visualize on plain X-rays due to spinal fusion. [13]

Beyond diagnosis and assessment of disease activity, nuclear medicine techniques are increasingly being explored for their potential in predicting response to specific therapeutic agents in RA and AS, particularly with the advent of biologic and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs and tsDMARDs). For RA, baseline 18F-FDG PET/CT metabolic activity in the synovium has shown promise as a predictor of clinical response to anti-TNF- α therapies or rituximab. Patients with higer initial synovial FDG uptake tend to respond better to these treatments, suggesting that the level of inflammatory metabolic activity could serve as a biomarker to guide therapy selection, thereby moving towards a more personalized medicine approach. [14]

In AS, while the evidence is less robust due to the complexity of spinal involvement, preliminary studies suggest that changes in inflammatory activity observed with 18F-FDG PET/CT in the sacroiliac joints and spine could correlate with treatment response to bDMARDs. This predictive capability could minimize delays in achieving remission and avoid the unnecessary exposure of patients to ineffective drugs, leading to improved long-term outcomes and reduced healthcare costs. [15]

4. Sarcoidosis:

Sarcoidosis is a multisystem granulomatosis which may result in a wide variety of clinical and biological presentations. Symptoms are often nonspecific, The diagnosis is based on a pathological hallmark which is the non-necrotizing epithelioid-cell rich granuloma. [16]

FDG-PET is usually not indicated for the assessment of musculoskeletal manifestations, as sonography and other imaging techniques are available. As FDG-PET, however, has a role for functional imaging in sarcoidosis, and positive pulmonary FDG-PET findings were shown to occur in two-thirds of patients with radiographic stage II and III sarcoidosis, occasional findings of arthritis may lead the patient to a rheumatologist. Negative pulmonary FDG-PET findings were common in patients with radiographic stage 0, I, and IV sarcoidosis, but do not exclude inflammatory findings in the musculoskeletal system. [17]

5. Sjögren's syndrome

The 2002 American-European Consensus Group (AECG) criteria defined a positive salivary gland scintigraphy in primary Sjögren's syndrome as showing delayed uptake, reduced concentration, or delayed excretion of Technetium-99m pertechnetate. However, by 2007, the relevance of sialoscintigraphy was already diminishing [18] due to two main reasons:

1. Salivary gland ultrasound (sonography) showed comparable diagnostic accuracy to sialography, with a pooled sensitivity of 80% and specificity of 89%, leading to its proposed use as a replacement in diagnostic criteria. [19]

2.Scintigraphy's limitations, including low specificity and inability to distinguish between uptake and secretion failure, led experts to suggest its use be limited to assessing salivary gland function rather than diagnosis. [20]

In 2016, the ACR-EULAR classification criteria for primary Sjögren's syndrome were introduced, omitting sialography entirely. Though the AECG and 2016 ACR-EULAR criteria are considered equivalent, sialoscintigraphy is no longer recommended for classification purposes and is now rarely used, [21] reserved only for select clinical or research scenarios.

6. Rare diseases:

Paget's disease of bone is a localized disorder of abnormal bone remodeling with an unclear cause. Affected bones become enlarged, weakened, and prone to deformities, fractures, and nerve compression due to bone expansion.[22]

Skeletal scintigraphy plays a major diagnostic role due to its high sensitivity in detecting increased vascularity and osteoblastic activity. A typical scintigraphic finding is intense, uniform radiopharmaceutical uptake across affected areas, with a characteristic "flame-shaped" advancing edge in long bones. [23]

However, scintigraphy is not specific, as similar findings may appear in bone metastases, metabolic bone diseases, or fibrous dysplasia. The preservation or enhancement of normal bone architecture on imaging can help distinguish Paget's disease from these other conditions. [24]

Retroperitoneal Fibrosis is considered a rare disease characterized by a fibroinflammatory mass which surrounds the abdominal aorta and the iliac arteries and may cause obstruction uropathy. [25]

F-18FDGPET/CT has a role in assessment the metabolic activity, predicting the treatment response & relapses in patients with idiopathic retroperitoneal fibrosis,.[25]

Masses appear as pale plaque like mass with ill-defined margins enveloping the adjacent viscera with presence of inflammatory cells as lymphocytes and macrophages. Studies revealed that FDGPET has been successfully applied in the evaluation of disease activity by demonstrating the increased radiotracer uptake at the metabolically active sites. [26]

This facilitate the detection of remote sites of the disease as multifocal fibrosclerosis ,occult neoplasms and infectious process which may occur as secondary to the retroperitoneal fibrosis. [27]

It was reported that FDGPET is a useful tool in confirming the absence of disease activity in patients with low levels of acute phase reactants which can help in the follow up & herald the inflammatory relapses. [28]

❖ Role of nuclear medicine in the treatment of rheumatic diseases:

Radio synovectomy

The main nuclear medicine therapeutic application in rheumatology is Radio synovectomy, that is a well-established noninvasive local therapy in arthritis that involves an intra-articular injection of small radioactive beta emitting particles e.g yttrium-90 colloid, to treat synovitis. [29]

Radio synovectomy is an alternative to surgical synovectomy. It is a useful option for the treatment of persistent arthritis that is refractory to standard treatment.

It requires the application of β-emitting radionuclides to treat the chronic inflammation of the joints. It selectively destroys the hypertrophic synovial membrane using ionizing radiation causing fibrosis and sclerosis of the inflamed synovium and then its restoration and the return of its physiological properties. [30]

Rheumatoid arthritis, spondyloarthropathy, hemarthrosis and osteoarthritis are frequent indications for radio synovectomy. In these cases, synovitis with proliferation of the synovium and hyper perfusion of the joint is observed leading to developing of joint pain and limitation of the movement in chronic cases. The radioisotopes are locally injected in the articular cavity in the depth of synovia in form of radioactive particles in a colloid form with particle size range from 0.05 t0 2 Um and is phagocytized by macrophages and other inflammatory cells causing radiation injury with radiation absorbed dose of 100 Gy to the target cells followed by reducing of effusion and fibrosis of synovia within few months with no destruction of the joint because of the low penetration power of the bet particle of the injected radioisotopes , the surrounding nontarget tissue is spared. [29]

The most commonly used beta emitting radioisotopes are:

Yttrium 90 silicate colloid with half-life of 2.6 days and particle energy of 2.2 Mev and penetration range in the tissue 12mm so it can be used in large joints like knee joint

and Rhenium 186 sulfur colloid with half-life about 3.8 days having particulate energy of 1.07 Mev and 4-7mm penetration range in the tissue,

making it suitable for medium sized joint e.g shoulder and hip joints

Another beta emitting isotope is **Erbium 169 citrate** which is used in small sized joint due to its low penetration range in tissue of 0.2-0.3 mm with 0.34 Mev
Patients who are planned for radio synovectomy are prepared by ultrasonography of the joint evaluating the synovial membrane thickness and triphasic bone scintigraphy evaluating soft tissue inflammation

Injection of the radiotracer needs sterile condition with handling precautions and appropriate shielding this done under local anesthesia with saline and long-acting steroid
Sterile compression and immobilization of the joint for 48 hours is done

Transient increase of the pain due to radiation synovitis is a side effect. However, it has a 40-90 % success rate and its results are comparable to surgery
Being advantageous in being outpatient procedure with low cost and the ability to inject multiple joints [29,31]

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