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REVIEW

Metabolic and molecular imaging in inflammatory arthritis

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ABSTRACT

It is known that metabolic shifts and tissue remodelling precede the development of visible inflammation and structural organ damage in inflammatory rheumatic diseases such as the inflammatory arthritides. As such, visualising and measuring metabolic tissue activity could be useful to identify biomarkers of disease activity already in a very early phase. Recent advances in imaging have led to the development of so-called 'metabolic imaging' tools that can detect these changes in metabolism in an increasingly accurate manner and non-invasively.

Nuclear imaging techniques such as ^{18}F-D-glucose and fibroblast activation protein inhibitor-labelled positron emission tomography are increasingly used and have yielded impressing results in the visualisation (including whole-body staging) of inflammatory changes in both early and established arthritis. Furthermore, optical imaging-based bedside techniques such as multispectral optoacoustic tomography and fluorescence optical imaging are advancing our understanding of arthritis by identifying intra-articular metabolic changes that correlate with the onset of inflammation with high precision and without the need of ionising radiation.

Metabolic imaging holds great potential for improving the management of patients with inflammatory arthritis by contributing to early disease interception and improving diagnostic accuracy, thereby paving the way for a more personalised approach to therapy strategies including preventive strategies. In this narrative review, we discuss state-of-the-art metabolic imaging methods used in the assessment of arthritis and inflammation, and we advocate for more extensive research endeavours to elucidate their full field of application in rheumatology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic and molecular imaging techniques have the potential of improving our understanding and the management of arthritis by offering a multimodal assessment of the molecular, functional and structural aspects of inflammation.

WHAT THIS STUDY ADDS

⇒ Fibroblast-targeted and macrophage-targeted positron emission tomography/CT offers a whole-body assessment of inflammation by targeting pathologically activated cell compartments that sustain arthritis.

⇒ Fluorescence optical imaging and multispectral optoacoustic tomography are emerging techniques that have shown potential in detecting vascular and metabolic tissue changes that may precede the onset of clinical inflammation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research is needed to validate these novel imaging techniques in arthritis and to explore their exact field of application in clinical practice.

INTRODUCTION

Inflammatory arthritis (IA) represents a diverse group of chronic immune-mediated inflammatory disorders characterised by recurring joint inflammation and by the progressive destruction of articular structures. Rheumatoid arthritis (RA) and spondyloarthritis (SpA) including psoriatic arthritis (PsA) and crystal-related arthritides (eg, gout, calcium pyrophosphate deposition disease) are the most common conditions of this group, with an estimated cumulative worldwide incidence ranging from 115 to 149 per 100 000 adults.[1] The management of IA poses significant challenges, as early diagnosis and treatment initiation are crucial for preventing irreversible joint damage and the development of disability. Alongside the clinical assessment, musculoskeletal imaging has become an integral part of the assessment of arthritis and has led to major improvements in diagnostics and disease outcomes. Imaging techniques such as X-ray, musculoskeletal ultrasound (MSUS), CT and MRI have become indispensable tools for rheumatologists and are recognised as the standard of care for the diagnostic work-up and follow-up of patients with IA in international guidelines and classification criteria.[2 3] However, accurately depicting inflammation of the musculoskeletal system on imaging,

especially in the early phases or when overlapping degenerative conditions are present, still poses a very significant challenge for which improvements to our diagnostic armamentarium might be needed.

Limitations and new developments in arthritis imaging

Conventional imaging methods have inherent limitations, primarily due to their focus on anatomic and functional aspects, which can result in a reduced ability to identify inflammation before it becomes macroscopically visible. Techniques like X-ray and CT may not effectively capture early signs of inflammation and soft tissue abnormalities, leading to delayed diagnosis and intervention.[4] MSUS and MRI, on the other hand, offer a more comprehensive assessment of soft tissues and a more accurate identification of subtle inflammatory changes associated with early as well as established disease phases.[5] MSUS changes have been associated with an increased risk of erosion and osteoproliferation,[6] as well as with the development of arthritis in at-risk populations. However, operator-dependence and limited penetration for deep structures such as the axial skeleton are major drawbacks affecting reproducibility and that frequently lead to requiring additional imaging. Similar to MSUS, MRI alterations such as synovitis, tenosynovitis and osteitis have been strongly associated with an increased risk of developing radiological structural damage[7] and of progression to arthritis[8 9] while also offering better reproducibility. In the field of MRI, novel sequences are emerging to overcome the limitations of conventional imaging by providing a more in-depth assessment of joint tissues. The novel ultra-short echo-time (UTE) MRI sequences, for instance, allow the assessment of tendon and entheses in high resolution even in the absence of T2 signal prolongation related to inflammatory processes, which would otherwise not always be feasible using conventional T1-weighted and T2-weighted MRIs.[10] This allows an in-depth assessment of the structural characteristics of tendons and entheses and enables quantitative measurements that could be used as biomarkers of biomechanical degradation.[10] These advancements, however, still do not provide any additional multimodal information about cellular metabolism and molecular changes at the tissue level. Unlike UTE sequences, a recent example of molecular imaging applied to this technique is the use of chemical exchange saturation transfer MRI (CEST MRI) in osteoarthritis. CEST MRI provides an in vivo, non-invasive assessment of various metabolites involved in cartilage damage through the chemical exchange between bulk water protons and protons bound to exogenous or endogenous solutes.[10] Glycosaminoglycans (GAGs) such as hyaluronic acid and chondroitin sulfate constitute a crucial component of the extracellular matrix in joint tissues and have a pivotal role in maintaining the structural integrity and lubrication of cartilage.[11] As such, their depletion serves as one of the earliest indicators of cartilage degeneration. By exploiting the chemical exchange between protons in GAGs and water, GAG-CEST MRI allows for high-resolution mapping of molecular concentrations in tissues, even preceding morphological alterations.[10 12] GAG-based imaging with GAG-CEST MRI holds significant potential for improving the diagnosis and management of osteoarthritis. However, little to no data is available on its use on inflammatory joint diseases, and the use of MRI in general is still limited by relatively low accessibility, long scanning times, the limitation to a single scanning region and the necessity of using contrast agent. As such, accurate and time-effective imaging techniques that allow retrieval of multimodal molecular and metabolic information from the joints of patients with arthritis are still missing.

To address these needs, recent advancements in medical imaging techniques have focused on developing novel non-invasive and sensitive methods to assess joint inflammation by measuring cellular-level and tissue-level changes in metabolism and function rather than on the mere structural assessment of the joint.[10 13] These include whole-body nuclear imaging methods such as positron emission tomography (PET)/CT as well as optical-imaging based bedside techniques such as the multispectral optoacoustic tomography (MSOT) and the fluorescence optical imaging (FOI). These so-called 'metabolic imaging' methods aim to offer advanced capabilities in detecting cellular activity and vascularity, enabling the identification of subclinical inflammation at an earlier stage compared with conventional imaging instruments. So far, these metabolic imaging techniques have shown promising results in evaluating treatment efficacy, disease remission and prognosis within and outside of the field of rheumatology, such as in the non-invasive assessment of intestinal inflammation in inflammatory bowel disease and in the early detection of metastatic disease in patients with cancer, enabling clinicians to tailor therapy and improve patient outcomes.[10 13] An overview of the functioning principles of PET/CT, MSOT and FOI can be found in figure 1, while figure 2 shows a schematic representation of the molecules and structures that can be targeted in the metabolic imaging of arthritis.

With the advances in precision medicine, metabolic imaging represents a paradigm shift towards early disease interception, the development of preventive strategies for arthritis and ultimately personalised and targeted therapies.[10 13]

Therefore, in this review we cover current applications of the established metabolic imaging techniques in the diagnosis and management of patients with IA. Moreover, we review the major challenges and opportunities of novel and upcoming diagnostic modalities in this field.

Metabolism in the pathophysiology of synovitis and enthesitis

The pathophysiology of synovitis and enthesitis involves a complex interplay of immunological, genetic and environmental factors that widely differ between them. At the immunological level, while adaptive immune system activation and autoimmunity play a major role in the development and chronification of synovitis,[14 15] enthesitis

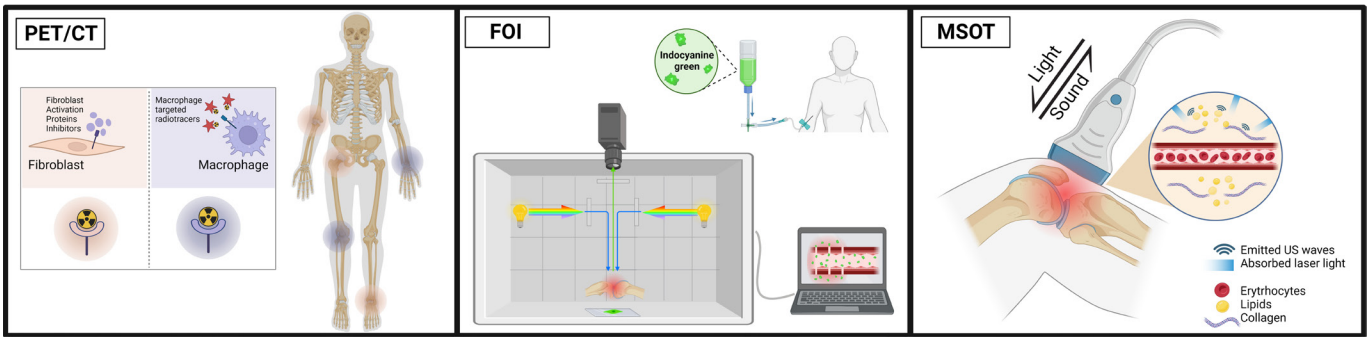

Figure 1 Overview of the functioning principles of the metabolic and molecular imaging of arthritis with PET/CT, MSOT and FOI. In PET/CT (left panel), fibroblast-targeted and macrophage-targeted radionuclide are administered intravenously to trace the activity of the mesenchymal and monocyte cell compartments in the joints throughout the whole body. In FOI (middle panel), joints are exposed to light at specific wavelengths after the intravenous administration of indocyanine green contrast agent, allowing the visualisation of microvascular changes with high resolution through the use of a near-infrared thermal camera and a computer system. In MSOT (right panel), target tissues are exposed to near-infrared laser light, which exploits the photoacoustic effect by inducing chromophore substances inside the joint to emit low-energy sound waves. These optoacoustic profiles are specific for each molecule and can be captured and quantified by a specific receiver. FOI, fluorescence optical imaging; MSOT, multispectral optoacoustic tomography; PET, positron emission tomography.

seems to be triggered predominantly by an innate immune response sustained and triggered by biomechanical stressors.[16] At a tissue level, synovitis appears as a highly energy demanding process manifesting with hypertrophy, massive infiltration of activated lipid-laden macrophages in the inflamed joint, collagen fibre degradation through matrix metalloproteinases and osteoclast activation leading to bone reabsorption.[17] Enthesitis is a

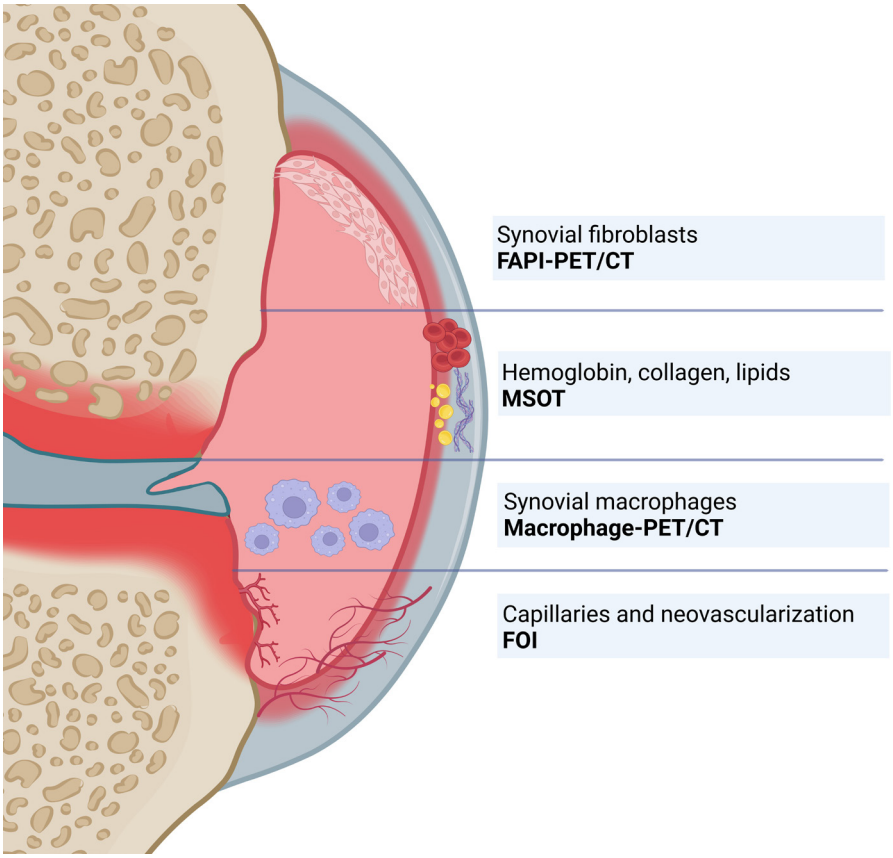

Figure 2 Schematic representation of the molecules and structures that can be assessed by molecular and molecular imaging. The cellular metabolism of synovial fibroblast and macrophages can be detected by FAPI-targeted and macrophage-targeted PET/CT, respectively; fluorescent optical imaging (FOI) visualises neovascularisation and microcirculation; multispectral optoacoustic tomography can be used to measure the relative concentration of metabolites related to inflammation such as haemoglobin, collagen fibres and lipids. FAPI, fibroblast activation protein inhibitor; ; MSOT, multispectral optoacoustic tomography; PET, positron emission tomography.

more bradytrophic phenomenon, with less cellular infiltration and hypertrophy.[16] However, local prostaglandin E2 and production in response to mechanical forces triggers vasodilation, neovascularisation and mesenchymal cells activation in the neighbouring bone marrow that stimulates new collagen and bone deposition by osteoblasts.[16] Moreover, altered lipid metabolism has been implicated in the pathogenesis of synovitis and enthesitis, with changes in the levels of lipids and lipid-derived mediators influencing inflammation and immune responses.[18]

As such, cellular metabolism undergoes alterations in both synovitis and enthesitis, leading to increased energy demands and altered nutrient utilisation within the affected tissues and these changes have been shown to take place already in the early phases of inflammation. Indeed, one of the most prominent metabolic changes at this stage is the increased metabolic demand with higher glucose and oxygen consumption as well as the upregulation of glycolysis in inflammatory cells.[16] As these metabolic shifts precede the development of visible inflammation, they could have a utility as very early biomarkers of disease activity. As such, the development of tools that can detect these subtle metabolic changes could prove of high relevance in improving the management of patients with IA.

Understanding arthritis-related metabolic changes sheds light on the disease's pathophysiology and opens new possibilities for targeted interventions. So far, metabolic assessments had to rely on invasive biopsies and were thus limited by the acquisition of tissue samples from patients. The development of innovative non-invasive imaging techniques such as PET/CT, FOI and MSOT can overcome this obstacle and have the potential of addressing some unmet clinical needs such as distinguishing primary articular inflammation from degenerative conditions like osteoarthritis or identifying subclinical inflammation before the onset of damage. This comprehensive multimodal imaging approach has broad implications for our understanding of the complex biological phenomena underlying arthritis and offers a chance of improving arthritis care and advancing personalised medicine in rheumatology.

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PET-CT IMAGING

PET-CT molecular imaging is a valuable tool for evaluating oncologic and inflammatory conditions that allows the visualisation of tissue metabolic activity by using radiolabelled tracers. It offers precise detection and distribution of metabolically active lesions throughout the body in a single examination, surpassing conventional imaging, usually limited to a single region of interest. PET scans are highly sensitive for identifying active inflammation, which makes them highly valuable for diseases such as polymyalgia rheumatica and large vessel vasculitis,[19] for which it represents a mainstay for diagnosis. By pinpointing areas of increased metabolic activity, PET-CT provides insights into disease activity, treatment response and differentiation between inflammation and structural changes without inflammatory activity. While its use in IA is more common in research settings and when conventional methods yield inconclusive results, it is gaining importance due to new tracers targeting specific cell compartments, such as activated fibroblasts and macrophages which have increased the clinical and scientific relevance of this technique.

FLUORO-D-GLUCOSE-PET/CT

PET/CT with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG PET/CT) is a functional imaging modality that allows a quantification of glucose uptake in soft tissues throughout the body, therefore measuring their overall metabolic activity. Whole-body joint evaluation in IA has been proved feasible with a PET/CT system using an ultra-low-dose protocol and has been studied extensively in the context of RA, PsA and immune checkpoint inhibitor-related arthritis.[20] Several studies so far have demonstrated that ^{18}F-FDG-PET can be a sensitive imaging technique for detecting and assessing synovitis specifically. Palmer *et al* were the first to describe that ^{18}F-FDG-PET demonstrates high sensitivity and specificity in detecting synovitis in patients with RA.[21] Later on, these findings were reproduced in both RA and PsA, where substantial ^{18}F-FDG uptake was shown along the inflamed tendons, at the entheses, in synovial joints and in the nail bed.[22] Accumulating evidence has shown that ^{18}F-FDG uptake in affected joints correlates strongly with the presence of clinical arthritis, and that ^{18}F-FDG-PET can be useful in monitoring disease activity and response to treatment.[22 23] Raynor *et al* have been developed an overall quantitative score of ^{18}F-FDG-PET measurements that correlates strongly with both clinical (swollen joint count, modified Disease Activity Score) as well as laboratory (C reactive protein, erythrocyte sedimentation rate, interleukin (IL)-6, IL-1) parameters of inflammation.[24] Interestingly, there is also evidence that ^{18}F-FDG-PET detects subclinical synovitis in patients with early RA[25] and psoriasis (without known PsA),[26] potentially enabling an early diagnosis and intervention in these at-risk populations.

Overall, the available evidence suggests that ^{18}F-FDG-PET holds promise as a valuable imaging technique for assessing synovitis, monitoring disease activity and evaluating treatment response in various forms of arthritis. However, on a trial with the aim to assess reliability and predictive value of ^{18}F-FDG-PET to successfully tapering Tumor Necrosis Factor α (TNF)-inhibitors on RA, ^{18}F-FDG-PET scores were not found predictive suggesting caution and the need of further studies to investigate the role of ^{18}F-FDG-PET as a risk stratification tool.[27] At last, a recent study has brought to attention the potential lack of specificity of ^{18}F-FDG-PET, as a substantial number of incidental falsely positive or not joint-specific signal alterations[28] were detected that may lead to unnecessary further investigations. As such, using whole-body FDG-PET scanning for musculoskeletal purposes, whether in a research or clinical context, implies a comprehensive explanation of the potential risks and benefits of this imaging modality.

Fibroblast activation protein inhibitor PET/CT

There has been growing interest in the application of ^{68}Ga-fibroblast activation protein inhibitor-04-PET/CT (FAPI-PET/CT) in the context of immune-mediated inflammatory diseases.[29] ^{68}Ga-FAPI-PET/CT is a novel molecular imaging technique that targets fibroblast activation protein (FAP), which is expressed by mesenchymal stromal cells and fibroblast during tissue remodelling in the context of malignancy or in response to chronic inflammatory stimuli.[30] Indeed, several highly prevalent cancers have displayed robust signals on this novel imaging technique, offering potential for improved diagnosis and treatment planning.[31] Preclinical studies using PET with a radiolabelled anti-FAP antibody on murine experimental models of RA could demonstrate a high tracer accumulation in arthritic joints.[32] Also, another recent murine study found that the depletion of FAP-expressing fibroblasts could suppress inflammation and stop the development of bone erosions.[33]

The first successful applications of ^{68}Ga-FAPI-PET/CT in rheumatology spawn from studies on systemic sclerosis-associated interstitial lung disease (SSc-ILD) and IgG_4-related disease. Bergmann *et al* could demonstrate that the magnitude of pulmonary ^{68}Ga-FAPI uptake in SSc-ILD correlates with progression of disease, independently of the extent of involvement on CT scans and lung function at baseline and FAPI uptake was related to higher clinical activity scores and, therefore, disease severity.[34] In a further study, a cohort of 27 patients with IgG_4-related disease underwent consecutive FAPI and ^{18}F-FDG-PET/CT, MRI and histopathological assessment to assess inflammatory and fibrotic activity. The study found that ^{68}Ga-FAPI-PET/CT could effectively discriminate fibrosis from inflammation, as ^{18}F-FDG highlighted inflammatory areas with IgG_4-positive plasma cell infiltration, while FAPI identified regions with activated fibroblasts. Interestingly, ^{68}Ga-FAPI uptake did not correlate with ^{18}F-FDG uptake and FAPI-positive fibrotic lesions responded less to immunotherapy.[30]

Synovial fibroblasts are also known to be key mediators of synovitis in RA and the expression of FAP is strongly upregulated in the inflammatory activated fibroblasts.[35] Interestingly, FAP expression in the synovial tissues of patients with RA has been found to be significantly higher than that in patients with osteoarthritis, suggesting a certain specificity for inflammatory tissue remodelling.[33] Supporting this, in a preclinical study on murine models of collagen-induced arthritis and on fibroblast-like synoviocytes isolated from patients with RA, ^{68}Ga-FAPI-PET imaging revealed a non-physiologically high ^{68}Ga-FAPI uptake in the synovium of arthritic joints.[36] Notably, Rauber *et al* could demonstrate that ^{68}Ga-FAPI tracer uptake in inflamed joints strongly correlates with erosive joint damage and clinical disease activity (measured by Tender and Swollen Joint Count (TJC, SJC), Disease Activity in PsA score (DAPSA), and by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)), and responds to targeted biological treatment.[29] Furthermore, a recent longitudinal study on 20 patients with RA who underwent dual-tracer ^{68}Ga-FAPI/^{18}F-FDG-PET/CT, ^{68}Ga-FAPI uptake correlated with most clinical and laboratory disease activity variables as well as with radiographic disease progression. Furthermore, a higher positivity rate (^{68}Ga-FAPI: 77.7% vs ^{18}F-FDG: 72.9%; p<0.001) and uptake intensity (^{68}Ga-FAPI: 9.54±4.92 vs ^{18}F-FDG 5.85±2.81; p<0.001) was found in the clinically affected joints compared with FDG.[37] Lastly, in a preliminary study which is currently available as an abstract, an increased ^{68}Ga-FAPI uptake at synovial and entheseal sites in a cohort of 10 patients with psoriasis was associated with a higher risk of developing PsA, as all patients with synovio-entheseal ^{68}Ga-FAPI uptake eventually progressed to PsA as opposed to only one patient without any signs of ^{68}Ga-FAPI-PET/CT activity.[38] As such, if these results are confirmed, ^{68}Ga-FAPI-PET/CT activity could represent a potential imaging biomarker for defining patients with psoriasis at high risk of transition to PsA. Panel A of figure 3 shows examples of ^{68}Ga-FAPI/PET-CT images from patients with IA.

It is essential to note that research efforts on the use of ^{68}Ga-FAPI-PET/CT in IA are still limited, and the clinical utility and broader applications of ^{68}Ga-FAPI-PET in this area have yet to be fully explored. As early studies have yielded very encouraging results, further analysis is needed on the role of ^{68}Ga-FAPI-PET/CT in diagnosing and monitoring arthritis. These should be aimed at (1) assessing the specificity and eventually defining cut-offs of ^{68}Ga-FAPI uptake that enables to differentiate arthritis from other non-inflammatory conditions; (2) validating ^{68}Ga-FAPI-PET/CT on larger cohorts of patients with various forms of arthritis and on at-risk populations to determine its value as a risk stratification tool; (3) assessing the reliability of ^{68}Ga-FAPI-PET/CT for monitoring disease activity and therapeutic response over time compared with other established forms of conventional

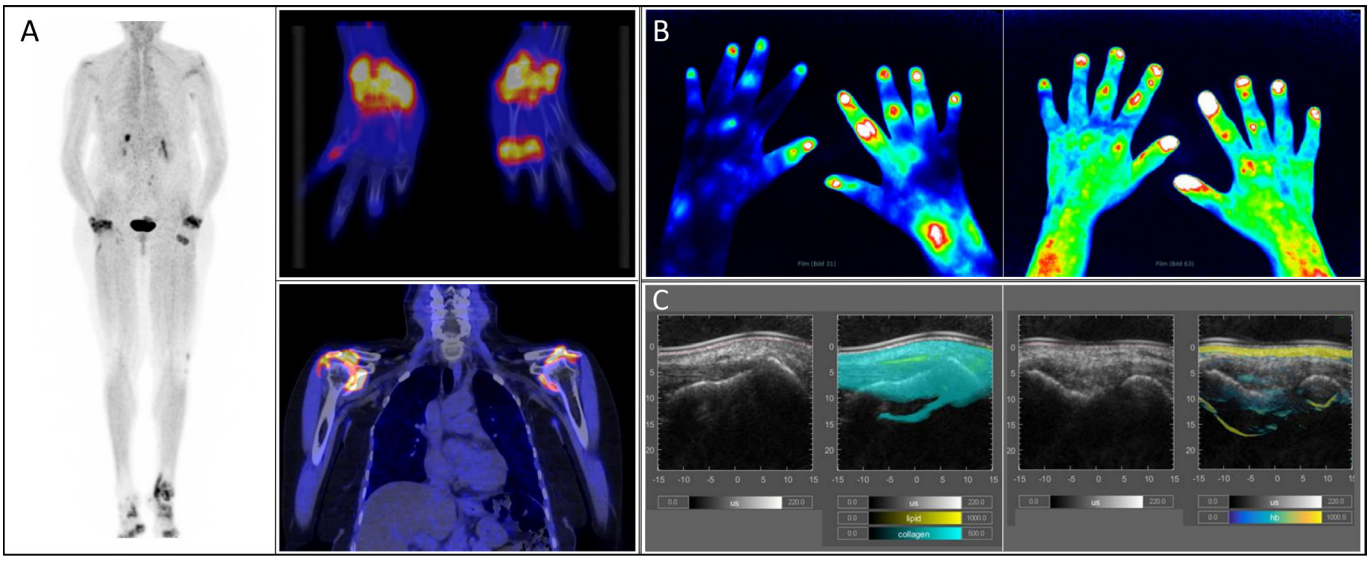

Figure 3 Examples of applied metabolic imaging to joints and entheses. Panel (A)[67]Ga-FAPI-04-positron emission tomography/CT scans showing avid intra-articular[67]Ga-FAPI uptake in the wrist, metacarpophalangeal and ankle joints (left and upper quadrant) and in the shoulder joints of patients with rheumatoid arthritis. Panel (B) fluorescence optical imaging acquisitions showing changes in micro vascularisation and increased blood flow in the finger joints of a patient with rheumatoid arthritis (left) and early psoriatic arthritis (right). Panel (C) multispectral optoacoustic tomography scans of the Achilles tendon enthesis (left) and of the lateral humeral epicondyle enthesis of a patient with psoriatic arthritis showing the distribution of lipid and collagen (left) and haemoglobin (right) superimposed to ultrasound. Ga-FAPI, ^{68}Ga-fibroblast activation protein inhibitor.

imaging. Indeed, it is pivotal to address the potential issue of oversensitivity, as performing whole-body imaging with a tracer such as F^{68}Ga-FAPI that has shown to be more sensitive—but not necessarily more specific—than ^{18}F-FDG[38] might detect transient inflammatory processes that do not represent pathology.

Macrophage-targeted PET/CT

Macrophage-targeted PET/CT imaging in IA represent a further new frontier in the field for which some promising preliminary studies have been conducted. Macrophages are central players in the immune system's response to inflammation and especially in joints, where resident macrophages of the synovial lining constitute a protective barrier and, when activated by inflammatory stimuli such as damage or autoimmunity, they release pro-inflammatory cytokines such as TNF-alpha and IL-1 leading to sustained inflammation.[14 15] Therefore, they represent ideal targets for imaging in arthritis. Macrophage-targeted PET/CT imaging has seen the emergence of three prominent radiotracers: ^{124}I-DPA-713, Ga-DOTA and ^{11}C-R-PK11195, each exploiting a distinct binding mechanism to target activated macrophages and thus providing researchers with a range of options for tailoring radiotracers to specific conditions. ^{124}I-DPA-713 employs a small molecule ligand that binds to the translocator protein (TSPO), which is upregulated in activated macrophage cell membranes during inflammation.[39] Ga-DOTA, on the other hand, uses the chelator tetraxetan complexed with gallium-68, which selectively binds to macrophage receptors such as integrins.[40] ^{11}C-R-PK11195 uses an antagonist of the peripheral-type benzodiazepine receptor that is expressed by activated glial cells and by macrophages.[41]

Recently, preliminary studies from Binsbergen *et al* have shown a remarkable correlation between clinical response and ^{11}C-DPA713 PET/CT joint assessment not only at baseline, but also at 4 weeks during anti-TNF treatment.[42] However, the short half-life of ^{11}C-labelled and ^{18}F-labelled radioligands has been limiting the use of TSPO-specific DPA-713, which recently led Foss *et al* to conduct the first human study on the bioavailability of a radioiodinated tracer with a longer half-life and increased affinity for macrophages, ^{124}I-DPA-713 using PET/CT,[39] which had previously been studied on murine models for tuberculosis and SARS-CoV2 infection.

^{68}Ga-DOTA PET/CT has been used to trace the activity of tumour-associated macrophages in colorectal cancer and neuroendocrine tumours,[43 44] but its potential role as an important marker of inflammation is emerging. An emblematic case was shared by Xu *et al*, where a patient with prostate cancer undertook a ^{68}Ga-DOTA-FAPI-04 PET/CT imaging that also highlighted intense uptake on the shoulder, corresponding to known arthritis.[45] While this might indicate a reduced sensitivity for oncological uses, this has brought attention to this specific marker for imaging inflammation. ^{68}Ga-DOTA conjugated with containing tyrosine-octreotate (^{68}Ga-DOTA-TATE) and extracellular-loop-1-inverso (^{68}Ga-DOTA-ECL1), has recently been used successfully in preclinical studies to visualise lung inflammation[46] and heart muscle inflammation after myocardial injury.[47]

^{11}C-R-PK11195 PET/CT had previously found application in visualising activated glial cells and macrophages

in patients with ischaemic stroke, neuro-AIDS and large vessel vasculitis.[48–50] More recently, ^{11}C-R-PK11195 PET/CT has also been studied on a series of patients with established RA,[51 52] with promising evidence on its potential for monitoring disease activity and therapy response. Significant ^{11}C-R-PK11195 accumulation could be demonstrated in clinical as well as subclinical rheumatoid synovitis even before changes became visible in MRI, and was related to the occurrence of flares and increased disease activity in the short-term.[51 52] Furthermore, Verweij *et al* were able to develop a multivariable predictive model of treatment response based on clinical data (DAS44) and whole-body ^{11}C-R-PK11195 PET/CT scans which correlated with clinical response after 3 months of treatment.[53] To mitigate the issue of background uptake observed with ^{11}C-R-PK11195, a small number of exploratory studies on individuals with RA have introduced a further macrophage tracer binding to the β-folate receptor, ^{18}F-fluoro-PEG-folate (polyethylene glycol folate) which exploits the increased expression of folate receptors by activated macrophages.[41 54] Compared with ^{11}C-R-PK11195, it possesses substantial pharmacokinetic advantages, including rapid clearance and minimal background uptake, enabling a more accurate detection of inflammatory activity in all districts.[54]

Macrophage-targeted PET/CT imaging offers a unique opportunity to experimentally visualise macrophage-driven inflammation. By binding selectively to activated macrophages, these tracers could enable the selective visualisation of synovitis by distinguishing it from other kinds of articular inflammatory processes such as enthesitis or osteoarthritis. As such, though in its nascent stages, this approach might allow a more comprehensive understanding of immune responses in arthritis and holds the potential to identify specific targets for therapeutic interventions like corticoid tapering[55] or TNF therapy.[42]

Fluorescence optical imaging

FOI relies on the principle that inflamed tissues exhibit increased vascular permeability and accumulate fluorescent contrast agents more readily than healthy tissues. These contrast agents, such as indocyanine green (ICG) or newer molecular probes, are administered intravenously and distributed throughout the body, accumulating in regions of altered circulation. On exposure to specific light wavelengths, these contrast agents emit fluorescent signals, which are then captured by a specialised camera and quantified. The resulting images highlight areas of increased fluorescence, pinpointing regions of inflammation, including those situated within the joints.

FOI has emerged as a valuable technique in the study and management of IA by leveraging the properties of fluorescent agents to visualise joint inflammation, vasculopathic changes and skin involvement.[56] In the first proof-of-concept study, ICG-enhanced FOI demonstrated greater sensitivity in detecting arthritis when compared with clinical examination.[57] Notably, it displayed a robust agreement with both MSUS-Power-Doppler (PD) (88%) and MRI (83%) and there was a significant correlation with the DAS28 (r=0.41). An important finding was that in 97.8% of joints in control subjects, FOI produced normal results,[57] underlining its specificity and reliability in distinguishing healthy joints from those affected by arthritis. Indeed, FOI changes of the finger joints have been found to coincide with MRI findings on RA also in other studies, and a comparative analysis between FOI and MRI on early and very early arthritis found that FOI has good sensitivity (86%) and specificity (63%) in detecting both clinical and subclinical inflammatory synovial changes.[58] In a study by Glimm *et al*, patients with early RA who were either initiating or escalating antirheumatic therapy were monitored for 1 year using FOI and showed a noteworthy reduction in signal intensity during FOI.[59] Similarly, Meier *et al* conducted a study involving patients with different IA who were followed for 6 months after initiating or escalating treatment,[60] and found that that quantitative analysis of FOI enhancement exhibited a significant correlation with MRI (ρ=0.80; p<0.001) and disease activity (ρ=0.61; p<0.001). In particular, responders showed a notable reduction in signals (−21.5%, p<0.001), while non-responders exhibited an increase (+10.8%, p=0.075),[60] underscoring the feasibility of using FOI for monitoring therapy response.[56]

In another study on patients with SSc, FOI revealed a decrease in microcirculation within the hands and fingers of patients with SSc compared with healthy controls (limited SSc −15.1%, diffuse SSc −50.6%). This reduction was found to be significantly associated with capillaroscopic changes, the presence of disseminated SSc features, a diffuse SSc subtype and the occurrence of digital ulcers or pitting scars.[61] The same research team, in their subsequent 12-month follow-up report, noted that fingers with pathological staining by FOI at baseline had a higher risk for new ulcer development in the same finger (p=0.0153).[62]

Schmidt *et al* retrospectively compared inflammatory skin enhancements in patients with psoriasis vulgaris and PsA versus RA versus healthy controls and found that subclinical hand skin enhancement was notably more prevalent in patients with Psoriasis (PsO) and PsA (72.5%) than in RA (20.5%) or healthy individuals (28.0%) (p<0.001). FOI patterns accurately classified a significant percentage of PsO/PsA (72.5%), RA (76.9%) and healthy control (68.0%) cases, underscoring FOI's potential for the assessment of rheumatic diseases with skin involvement.[63] Still regarding PsA, in a study focusing on patients with suspected or confirmed diagnosis, FOI exhibited higher sensitivity compared with MSUS in detecting inflammation within Proximal and distal interphalangeal joints (p=0.035) and revealed distinct patterns of pathological enhancement for confirmed and suspected PsA.[64] Recently, a multicentre study was conducted in Germany to assess the value of FOI in identifying preclinical musculoskeletal inflammation, as an early indicator of PsA in individuals with

psoriasis who are at risk of developing PsA.[65] In this study involving 389 patients, 20% (n=77) were determined to have psoriasis only, based on comprehensive clinical, MSUS and FOI evaluations. PsA was diagnosed in half of the patient cohort, with 36% identified through clinical examination and an additional 14% through supplementary MSUS assessment. Among the 116 patients without clinical or MSUS evidence of PsA but found to be FOI-positive, 37% also tested positive with MRI. During the 2-year follow-up of FOI-positive patients lacking clinical/MSUS/MRI evidence of PsA, clinical PsA was confirmed in an additional eight patients, representing 42% of assessed patients (or 12% when considering the 72% drop-out rate).[65] These findings underscore the promise of FOI as a method for early detection of musculoskeletal inflammation in the hands, potentially serving as a valuable imaging biomarker for the transition from psoriasis to PsA,[65] and expediting its diagnosis in at-risk patients and ultimately enhancing outcomes. Panel B of figure 3 shows some examples of FOI acquisition in patients with RA and early PsA.

Standardising FOI protocols and interpretation criteria is crucial for widespread clinical adoption. Its non-invasive, real-time imaging and potential for detecting subclinical inflammation without radiation exposure make it a valuable tool in IA diagnosis and management. However, FOI has limitations due to its limited penetration depth (less than 2 cm) and susceptibility to confounders, such as minor skin issues, or background noise due to autofluorescence of the nearby tissues, which potentially lead to overestimating arthritic involvement. Also, using an exogenous agent for FOI scans carries inherent risks such as hypersensitivity reactions, but documented cases generally report good patient tolerance and safety.[56]

Optoacoustic imaging

Optoacoustic imaging (OAI) is a non-invasive imaging modality that combines optical illumination and ultrasound detection by using the photoacoustic effect to derive information on tissue composition. The photoacoustic effect is elicited when tissues are exposed to and absorb energy from laser light pulses, leading to brief thermoelastic expansion and contraction and thus generating ultrasound waves depending on the molecular properties of their components.[66–68] These ultrasound waves are then detected and used to reconstruct high-resolution images of the internal structures.[67] An OAI system comprises three primary elements: (1) a light source (usually a pulsed laser) with illumination optics, delivering light energy to the tissue; (2) one or more ultrasound detectors measuring the generated acoustic signals; and (3) a signal processing and reconstruction unit for image creation.[69] In medical applications, OAI[69 70]may be particularly useful in oncology, where it can aid in cancer detection, monitoring treatment response and guiding targeted therapies.[71–73] So far, various OAI techniques have been explored in dermatological,[74 75] metabolic,[76] gastrointestinal[77–79] and musculoskeletal diseases.[80–83]

MSOT is a technique that combines ultrasound and multi-wavelength OAI. (NO_PRINTED_FORM) Therefore, MSOT offers a non-invasive in vivo approach for imaging clinically relevant structures and deriving information for individual light-absorbing target molecules (ie, chromophores).[84–87] Through MSOT various endogenous tissue chromophores such as oxygenated and non-oxygenated haemoglobin, melanin, lipids and collagens can be visualised, as well as exogenous contrast agents targeted to specific molecules or cells. Target tissues are illuminated with a near-infrared laser at multiple wavelengths and the corresponding optoacoustic signals at each wavelength are detected and reconstructed into single-wavelength MSOT images that are superimposed to a coregistered ultrasound image. To distinguish the estimated concentration of the single chromophores, spectral identification (ie, 'unmixing') is applied based on the single absorbance spectra of the chromophores.[69] Thus, MSOT's ability to visualise both anatomical structures and molecular processes makes it a versatile tool that is able to enrich conventional ultrasound images with a spatial representation of metabolic activity.[88] Notably, MSOT is handled similarly to a standard ultrasound device and the examination time does not exceed that of a typical ultrasound examination, making it suitable for bedside use.[89]

The potential clinical impact of this imaging modality has been shown in various studies outside rheumatology, including the visualisation of disease activity in inflammatory bowel diseases, malignant features in several oncological pathologies, vascular damage in systemic sclerosis, severe anaemia in vivo and muscle degeneration degenerative muscular diseases.[70 90 91] Of note, in patients with Crohn's disease examination of the intestinal wall by MSOT found significant optoacoustic differences and particularly in the total haemoglobin content between active and non-active disease, and was thus able to distinguish remission from inflammation.[92] Also relevant for its implications on the use MSOT on the musculoskeletal system, Regensburger *et al* explored the role of endogenous collagens detected by MSOT as imaging biomarkers of Duchenne muscular dystrophy, and found that MSOT-measured collagen content in skeletal muscle was strongly correlated to the patients 'functional status and to MRI findings'.[81] Furthermore, the authors described excellent longitudinal reproducibility and repeatability of the MSOT findings, suggesting it is suitable for the prospective examination of musculoskeletal structures.[93] Lastly Masthoff *et al* conducted a proof of concept assessment of microvascular dysfunction, a key physiopathological element of systemic sclerosis, examining endogenous oxyhaemoglobin and haemoglobin levels in subcutaneous finger tissue by MSOT and revealed that individuals with SSc exhibited reduced optoacoustic signals compared with healthy controls.[89] Altogether, these studies highlight MSOT's capabilities to

Table 1 Overview of the main advantages and limitations, current research applications and future perspectives of metabolic and molecular imaging techniques used in inflammatory arthritis

	Advantages	Limitations	Current main application in research	Future perspectives
GAG-CEST MRI	▲ High spatial resolution. ▲ Functional and molecular imaging capabilities. ▲ In vivo quantification of glycosaminoglycan content. ▲ No ionising radiation.	▲ Requirement of ultra-high field MRI. ▲ Extended scanning time and susceptibility to motion artefacts. ▲ High costs of installation and maintenance. ▲ Limited number of metabolites detectable. ▲ No whole-body imaging. ▲ Reproducibility still under investigation. ▲ Lack of validation.	▲ Assessment of early cartilage damage in osteoarthritis. ▲ Investigating the molecular changes associated with osteoarthritis.	▲ Very early and in-depth identification of cartilage changes associated with degenerative and inflammatory joint conditions.
Fibroblast-targeted and macrophage-targeted PET/CT	▲ Whole body scan. ▲ Fast scanning time. ▲ Discerning inflammatory and fibrotic changes.	▲ Ionising radiation. ▲ Need for short-lived radiotracers. ▲ High device and maintenance costs. ▲ Lack of validation.	▲ Monitoring of disease progression and therapeutic response. ▲ Stratification of individuals at-risk of developing arthritis.	▲ Multitracer approaches, combining different radiotracers to capture diverse aspects of rheumatic disorders. ▲ Theranostic applications.
MSOT	▲ Non-invasive evaluation of tissue metabolic profile. ▲ Real-time molecular imaging combined with ultrasound. ▲ Non-ionising radiation.	▲ No cut-off values for metabolites available. ▲ High costs of the device. ▲ Limited use in patients with increased body hair or darker skin colour. ▲ Limited depth penetration. ▲ Lack of validation.	▲ Monitoring of disease progression and therapeutic response. ▲ Early diagnosis of synovitis and enthesitis.	▲ Advancements in hardware and software to improve usability and allow bedside use. ▲ Use of additional agents (eg, indocyanine green) to enable the visualisation of specific structures and or/phenomena associated with arthritis.
FOI	▲ Visualisation of microcirculatory changes. ▲ Real-time imaging. ▲ No ionising radiation.	▲ Possible hypersensitivity reactions to indocyanine green. ▲ Contraindications in case of hepatic and renal insufficiency. ▲ Artefacts due to background noise from auto-fluorescence of surrounding tissues. ▲ No whole-body imaging. ▲ Lack of validation.	▲ Early detection of synovial inflammation. ▲ Monitoring of therapeutic response. ▲ Detection of disease-specific inflammation patterns.	▲ Exploration of novel fluorescent markers with high affinity for specific inflammatory targets.

FOI, fluorescence optical imaging; GAG-CEST-MRI, Glycosaminoglycans-chemical exchange saturation transfer-MRI; MSOT, multispectral optoacoustic tomography; PET/CT, positron emission tomography/CT.

provide unique insights into tissue characteristics that are otherwise unobservable through conventional imaging techniques, and which are highly likely to be exploitable for the rheumatological imaging of arthritis as well. Panel C of figure 3 shows examples of MSOT images of the entheses of patients with PsA.

MSOT in inflammatory arthritis

So far, only a limited amount of studies has investigated MSOT in patients with IA. An early study showed a strong correlation between power-doppler ultrasound anomalies and optoacoustic parameters measured by a handheld OAI system in the inflamed joints of patients with RA.[94] Hallasch *et al* were the first to demonstrate the feasibility of using OAI via MSOT for the assessment and monitoring of arthritis in a cohort of patients with PsA compared with healthy controls.[95] Without using external contrast agents, the study found higher oxyhaemoglobin and deoxyhaemoglobin signals at the finger joints of patients with PsA, which are consistent with signs of an increased vascularisation. Interestingly, higher optoacoustic signal intensities for haemoglobin were also found in a subset of patients with no morphological changes consistent with PsA detected on X-rays. Additionally, a case of finger joint arthritis examined by MSOT before and 3 months after starting treatment with a biological agent is presented, in which a decrease of haemoglobin signals was observed, aligning with the patient's subjective reduction in pain.[95] Altogether, these observations imply that OAI of arthritis in general and PsA in particular is feasible by MSOT and that there are some measurable metabolic changes that might be present before the onset of structural joint damage that allow to distinguish healthy controls from patients with arthritis. A recent cross-sectional study on a large cohort of patients with RA and PsA and healthy controls, MSOT was used to investigate the metabolic profile of synovitis and enthesitis and its relation to clinical disease activity and ultrasound changes. The analysis revealed the presence of specific changes in haemoglobin, lipids and collagen that allowed to distinguish arthritis from enthesitis. Specifically, entheseal tenderness was not associated with significant metabolic changes, whereas ultrasound signs of enthesitis were associated with increased total haemoglobin, oxygen saturation and collagen content.[96] In contrast, the presence of synovitis-related clinical and sonographic findings showed increased haemoglobin levels, reduced oxygen saturation and collagen content, while synovial hypertrophy was associated with increased lipid content in the joints.[96] These findings are most likely to be interpreted as signs of increased metabolic demand and cellularity in synovial tissues of active arthritis accompanied by increased collagen breakdown. Conversely, enthesitis had a more bradytrophic profile, with signs of increased collagen apposition and vascularisation, possibly reflecting local remodelling.[96] Therefore, these observations imply that synovitis and enthesitis do not only differ at the clinical and anatomical-functional level but also exhibit divergent measurable metabolic patterns.

Taken together, evidence accumulated so far suggests that OAI is a promising imaging technique for the assessment and diagnosis of IA even in its earlier stages. Despite its promising potential, however, the use of MSOT in the field of rheumatology is still in the early stages of validation and is still burdened by some technical limitations. For instance, the penetration depth of the laser is currently limited to 3–4 cm, which hampers its use on larger joints and in overweight patients in whom target structures are located deeper.[97] Furthermore, since melanin constitutes one of the endogenous contrast agents, different skin tones may condition some measurement results[98]; however, specific studies addressing these topics are missing. Lastly, MSOT quantifies chromophores in arbitrary units that reflecting relative quantities within a specified region of interest. Still, the associations between these relative quantities and actual analytical concentrations in tissues, as well as the establishment of normal ranges for these measurements, are yet to be established. All these issues relate to the requirement for further standardisation, which is currently addressed by the International Photoacoustic Standardisation Consortium.[99 100]

Further research and validation studies are needed to establish MSOT's clinical utility, optimise imaging protocols and validate its role in routine rheumatological practice. Key areas for future investigation include establishing age-adjusted and sex-adjusted cut-offs for normal MSOT measurements; evaluating its effectiveness in early arthritis detection, and diagnosis of arthritis in at-risk patients before the onset of overt inflammation; differentiating inflammatory from non-inflammatory joint conditions; and monitoring disease activity and treatment response. These efforts aim to enhance understanding of disease mechanisms and therapy effects, potentially offering a non-invasive diagnostic and risk-stratification tool for arthritis assessment at all activity stages.

CONCLUSIONS

In conclusion, metabolic imaging techniques are emerging as promising new approaches for the assessment of IA. By providing insights into the metabolic activity of articular structures, this form of imaging complements conventional methods by offering a more comprehensive assessment of the molecular, functional and structural aspects of inflammation. Such metabolic changes can be found at all stages of arthritis and abide with the resolution of inflammation. However, they are particularly relevant in the early stages of arthritis before the onset of visible inflammation on conventional imaging and clinical symptoms.

^{18}F-FDG-targeted, FAPI-targeted and macrophage-targeted PET/CT imaging stand out as whole-body imaging tool that allow a comprehensive staging of, respectively, the metabolic and tissue remodelling activity

in all synovio-entheseal structures at once with an overall low exposure to ionising radiation. Thus, integrating this in the clinical routine alongside the established disease activity measures would enable a more accurate quantification of patients' inflammatory burden and improve the evaluation of treatment response. Furthermore, the ability of FAPI-PET/CT to differentiate between active inflammation and chronic changes and the specificity of macrophage-targeted tracers for synovitis detection might also prove useful for the differential diagnosis of non-inflammatory conditions such as osteoarthritis. FOI and OAI with MSOT on the other hand have shown remarkable potential in the assessment of subclinical and early arthritis and might be a helpful tool for detecting subclinical tissue-level metabolic changes before the onset of inflammation, aiding in the implementation of preventive treatment strategies. Finally, GAG-CEST MRI allows for high-resolution mapping of molecular concentrations of GAGs in the cartilage and is being investigated for osteoarthritis, but holds great potential for the identification of early non-bony structural changes in inflammatory joint conditions as well.

Whether these cutting-edge techniques will be up to the task of addressing these unmet clinical needs and effectively change the future management of arthritis remains to be determined, as most of these find themselves in the earliest stages of validation and still need to overcome certain limitations. A systematic overview of the advantages and disadvantages as well as on the current uses and future perspectives of the metabolic and molecular imaging techniques cited in this review is provided in table 1.

For now, research continues to explore the applications of metabolic imaging, as their future integration into routine clinical practice might offer unprecedented opportunities to transform the management of IA at all levels from disease detection, monitoring and treatment planning by shifting the paradigm from the treatment of established disease to the primary and secondary prevention of inflammation and disability.

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REFERENCES

1 Hazes JMW, Luime JJ. The epidemiology of early inflammatory arthritis. *Nat Rev Rheumatol* 2011;7:381–90.
2 Sieper J, Rudwaleit M, Baraliakos X, *et al*. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1–44.
3 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
4 McQueen FM. Imaging in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2013;27:S1521-6942(13)00069-7:499–522.:.
5 Just SA, Nielsen C, Werlinrud JC, *et al*. Six-month prospective trial in early and long-standing rheumatoid arthritis: evaluating disease activity in the wrist through sequential synovial histopathological analysis, RAMRIS magnetic resonance score and EULAR-OMERACT ultrasound score. *RMD Open* 2019;5:e000951.
6 Zabotti A, Mandl P, Zampogna G, *et al*. One year in review 2018: ultrasonography in rheumatoid arthritis and psoriatic arthritis. *Clin Exp Rheumatol* 2018;36:519–25.
7 Bøyesen P, Haavardsholm EA, Østergaard M, *et al*. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. *Ann Rheum Dis* 2011;70:428–33.
8 Bøyesen P, Haavardsholm EA, van der Heijde D, *et al*. Prediction of MRI erosive progression: a comparison of modern imaging modalities in early rheumatoid arthritis patients. *Ann Rheum Dis* 2011;70:176–9.
9 Faustini F, Simon D, Oliveira I, *et al*. Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis. *Ann Rheum Dis* 2016;75:2068–74.
10 Minopoulou I, Kleyer A, Yalcin-Mutlu M, *et al*. Imaging in inflammatory arthritis: progress towards precision medicine. *Nat Rev Rheumatol* 2023;19:650–65.
11 Maroudas A, Venn M. Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. II. Swelling. *Ann Rheum Dis* 1977;36:399–406.
12 Wu B, Warnock G, Zaiss M, *et al*. An overview of CEST MRI for non-MR physicists. *EJNMMI Phys* 2016;3:19.
13 Ntziachristos V, Pleitez MA, Aime S, *et al*. Emerging Technologies to Image Tissue Metabolism. *Cell Metab* 2019;29:S1550-4131(18)30569-2:518–38.:.

14 Boissier M-C, Semerano L, Challal S, *et al*. Rheumatoid arthritis: from autoimmunity to synovitis and joint destruction. *J Autoimmun* 2012;39:222–8.
15 Culemann S, Grüneboom A, Nicolás-Ávila JÁ, *et al*. Locally renewing resident synovial macrophages provide a protective barrier for the joint. *Nature* 2019;572:670–5.
16 Schett G, Lories RJ, D'Agostino M-A, *et al*. Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol* 2017;13:731–41.
17 van de Sande MG, Baeten DL. Immunopathology of synovitis: from histology to molecular pathways. *Rheumatology (Oxford)* 2016;55:599–606.
18 Wójcik P, Biernacki M, Wroński A, *et al*. Altered Lipid Metabolism in Blood Mononuclear Cells of Psoriatic Patients Indicates Differential Changes in Psoriasis Vulgaris and Psoriatic Arthritis. *Int J Mol Sci* 2019;20:4249:17.:.
19 Slart RHJA, Writing group, Reviewer group, *et al*. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging* 2018;45:1250–69.
20 Schierz JH, Sarikaya I, Wollina U, *et al*. Immune Checkpoint Inhibitor-Related Adverse Effects and ^{18}F-FDG PET/CT Findings. *J Nucl Med Technol* 2021;49:324–9.
21 Palmer WE, Rosenthal DI, Schoenberg OI, *et al*. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1995;196:647–55.
22 Chaudhari AJ, Ferrero A, Godinez F, *et al*. High-resolution (18) F-FDG PET/CT for assessing disease activity in rheumatoid and psoriatic arthritis: findings of a prospective pilot study. *Br J Radiol* 2016;89:20160138:20160138.:.
23 Roivainen A, Hautaniemi S, Möttönen T, *et al*. Correlation of 18F-FDG PET/CT assessments with disease activity and markers of inflammation in patients with early rheumatoid arthritis following the initiation of combination therapy with triple oral antirheumatic drugs. *Eur J Nucl Med Mol Imaging* 2013;40:403–10.
24 Raynor WY, Jonnakuti VS, Zirakchian Zadeh M, *et al*. Comparison of methods of quantifying global synovial metabolic activity with FDG-PET/CT in rheumatoid arthritis. *Int J Rheum Dis* 2019;22:2191–8.
25 Kubota K, Ito K, Morooka M, *et al*. FDG PET for rheumatoid arthritis: basic considerations and whole-body PET/CT. *Ann N Y Acad Sci* 2011;1228:29–38.
26 Takata T, Taniguchi Y, Ohnishi T, *et al*. (18)FDG PET/CT is a powerful tool for detecting subclinical arthritis in patients with psoriatic arthritis and/or psoriasis vulgaris. *J Dermatol Sci* 2011;64:144–7.
27 Bouman CAM, van Herwaarden N, Blanken AB, *et al*. 18F-FDG PET-CT in rheumatoid arthritis patients tapering TNFi: reliability, validity and predictive value. *Rheumatology (Oxford)* 2022;61(SI):SI):SI6–13.:.
28 Ulijn E, den Broeder AA, Boers N, *et al*. Extra-articular findings with FDG-PET/CT in rheumatoid arthritis patients: more harm than benefit. *Rheumatol Adv Pract* 2022;6:rkac014.
29 Rauber S, Mohammadian H, Schmidkonz C, *et al*. Molecular imaging with fibroblast activation protein tracers depicts inflammatory joint damage and its transition to resolution of inflammation. *Immunology* [Preprint] 2023.
30 Schmidkonz C, Rauber S, Atzinger A, *et al*. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. *Ann Rheum Dis* 2020;79:1485–91.
31 Kratochwil C, Flechsig P, Lindner T, *et al*. ^{68}Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *J Nucl Med* 2019;60:801–5.
32 Laverman P, van der Geest T, Terry SYA, *et al*. Immuno-PET and Immuno-SPECT of Rheumatoid Arthritis with Radiolabeled Anti-Fibroblast Activation Protein Antibody Correlates with Severity of Arthritis. *J Nucl Med* 2015;56:778–83.
33 Croft AP, Campos J, Jansen K, *et al*. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* 2019;570:246–51.
34 Bergmann C, Distler JHW, Treutlein C, *et al*. ^{68}Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. *Lancet Rheumatol* 2021;3:S2665-9913(20)30421-5:e185–94.:.
35 Lindner T, Loktev A, Giesel F, *et al*. Targeting of activated fibroblasts for imaging and therapy. *EJNMMI Radiopharm Chem* 2019;4:16.
36 Ge L, Fu Z, Wei Y, *et al*. Preclinical evaluation and pilot clinical study of [^{18}F]AlF-NOTA-FAPI-04 for PET imaging of rheumatoid arthritis. *Eur J Nucl Med Mol Imaging* 2022;49:4025–36.
37 Luo Y, Pan Q, Zhou Z, *et al*. ^{68}Ga-FAPI PET/CT for Rheumatoid Arthritis: A Prospective Study. *Radiology* 2023;307:e222052.
38 Fagni F, Simon D, Kleyer A, *et al*. Fibroblast Activation in Psoriasis Patients Assessed by 68Ga-FAPI-04 PET-CT Is Associated with Progression to Psoriatic Arthritis. *Arthritis Rheumatol* 2022.
39 Foss CA, Plyku D, Ordonez AA, *et al*. Biodistribution and Radiation Dosimetry of ^{124}I-DPA-713, a PET Radiotracer for Macrophage-Associated Inflammation. *J Nucl Med* 2018;59:1751–6.
40 Decristoforo C, Hernandez Gonzalez I, Carlsen J, *et al*. 68Ga- and 111In-labelled DOTA-RGD peptides for imaging of alphavbeta3 integrin expression. *Eur J Nucl Med Mol Imaging* 2008;35:1507–15.
41 Steinz MM, Ezdoglian A, Khodadust F, *et al*. Folate Receptor Beta for Macrophage Imaging in Rheumatoid Arthritis. *Front Immunol* 2022;13:819163.
42 Binsbergen W, De Jongh J, Pieplenbosch S, *et al*. POS0153 MACROPHAGE [11c]-dpa-713 pet-ct imaging to predict early anti-tnf treatment outcome in rheumatoid arthritis. EULAR 2023 European Congress of Rheumatology, 31 May - 3 June. Milan, Italy; June 2023:1–298
43 Kömek H, Can C, Kaplan İ, *et al*. Comparison of [^{68} Ga]Ga-DOTA-FAPI-04 PET/CT and [^{18}F]FDG PET/CT in colorectal cancer. *Eur J Nucl Med Mol Imaging* 2022;49:3898–909.
44 Ambrosini V, Campana D, Tomassetti P, *et al*. PET/CT with 68Gallium-DOTA-peptides in NET: an overview. *Eur J Radiol* 2011;80:e116–9.
45 Xu T, Zhao Y, Ding H, *et al*. [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT imaging in a case of prostate cancer with shoulder arthritis. *Eur J Nucl Med Mol Imaging* 2021;48:1254–5.
46 Puuvuori E, Liggieri F, Velikyan I, *et al*. PET-CT imaging of pulmonary inflammation using [^{68}Ga]Ga-DOTA-TATE. *EJNMMI Res* 2022;12:19.
47 Heo GS, Kopecky B, Sultan D, *et al*. Molecular Imaging Visualizes Recruitment of Inflammatory Monocytes and Macrophages to the Injured Heart. *Circ Res* 2019;124:881–90.
48 Gerhard A, Schwarz J, Myers R, *et al*. Evolution of microglial activation in patients after ischemic stroke: a [11C](R)-PK11195 PET study. *Neuroimage* 2005;24:591–5.
49 Venneti S, Lopresti BJ, Wang G, *et al*. PET imaging of brain macrophages using the peripheral benzodiazepine receptor in a macaque model of neuroAIDS. *J Clin Invest* 2004;113:981–9.
50 Pugliese F, Gaemperli O, Kinderlerer AR, *et al*. Imaging of vascular inflammation with [11C]-PK11195 and positron emission tomography/computed tomography angiography. *J Am Coll Cardiol* 2010;56:653–61.
51 Gent YYJ, Ter Wee MM, Voskuyl AE, *et al*. Subclinical synovitis detected by macrophage PET, but not MRI, is related to short-term flare of clinical disease activity in early RA patients: an exploratory study. *Arthritis Res Ther* 2015;17:266.
52 van der Laken CJ, Elzinga EH, Kropholler MA, *et al*. Noninvasive imaging of macrophages in rheumatoid synovitis using 11C-(R)-PK11195 and positron emission tomography. *Arthritis Rheum* 2008;58:3350–5.
53 Verweij N, Zwezerijnen G, Ter Wee M, *et al*. Early prediction of treatment response in rheumatoid arthritis by quantitative macrophage PET. *RMD Open* 2022;8:e002108.
54 Verweij NJF, Yaqub M, Bruijnen STG, *et al*. First in man study of [^{18}F]fluoro-PEG-folate PET: a novel macrophage imaging technique to visualize rheumatoid arthritis. *Sci Rep* 2020;10:1047.
55 Verweij NJF, Ter Wee M, De Jongh J, *et al*. OP0189 Macrophage pet/ct imaging of the feet can contribute to early prediction of therapy outcome in rheumatoid arthritis. *Ann Rheum Dis* 2021;80(Suppl 1):114.
56 Ohrndorf S, Glimm AM, Ammitzbøll-Danielsen M, *et al*. Fluorescence optical imaging: ready for prime time? *RMD Open* 2021;7:e001497.
57 Werner SG, Langer H-E, Ohrndorf S, *et al*. Inflammation assessment in patients with arthritis using a novel in vivo fluorescence optical imaging technology. *Ann Rheum Dis* 2012;71:504–10.
58 Werner SG, Langer H-E, Schott P, *et al*. Indocyanine green-enhanced fluorescence optical imaging in patients with early and very early arthritis: A comparative study with magnetic resonance imaging. *Arthritis Rheum* 2013;65:3036–44.
59 Glimm A-M, Sprenger LI, Haugen IK, *et al*. Fluorescence optical imaging for treatment monitoring in patients with early and active rheumatoid arthritis in a 1-year follow-up period. *Arthritis Res Ther* 2019;21:209.
60 Meier R, Thuermel K, Noël PB, *et al*. Synovitis in patients with early inflammatory arthritis monitored with quantitative analysis of dynamic contrast-enhanced optical imaging and MR imaging. *Radiology* 2014;270:176–85.
61 Friedrich S, Lüders S, Werner SG, *et al*. Disturbed microcirculation in the hands of patients with systemic sclerosis detected by

fluorescence optical imaging: a pilot study. *Arthritis Res Ther* 2017;19:87.
62 Friedrich S, Lüders S, Glimm AM, *et al*. Association between baseline clinical and imaging findings and the development of digital ulcers in patients with systemic sclerosis. *Arthritis Res Ther* 2019;21:96.
63 Schmidt A, Glimm AM, Haugen IK, *et al*. Detection of subclinical skin manifestation in patients with psoriasis and psoriatic arthritis by fluorescence optical imaging. *Arthritis Res Ther* 2020;22:192.
64 Erdmann-Keding M, Ohrndorf S, Werner SG, *et al*. Fluorescence optical imaging for the detection of potential psoriatic arthritis in comparison to musculoskeletal ultrasound. *J Deutsche Derma Gesell* 2019;17:913–21. 10.1111/ddg.13931 Available: https://onlinelibrary.wiley.com/toc/16100387/17/9
65 Koehm M, Ohrndorf S, Foldenauer AC, *et al*. Fluorescence-optical imaging as a promising easy-to-use imaging biomarker to increase early psoriatic arthritis detection in patients with psoriasis: a cross-sectional cohort study with follow-up. *RMD Open* 2022;8:e002682.
66 Ntziachristos V, Razansky D. Molecular imaging by means of multispectral optoacoustic tomography (MSOT). *Chem Rev* 2010;110:2783–94.
67 Tzoumas S, Deliolanis N, Morscher S, *et al*. Unmixing Molecular Agents From Absorbing Tissue in Multispectral Optoacoustic Tomography. *IEEE Trans Med Imaging* 2014;33:48–60.
68 Beard P. Biomedical photoacoustic imaging. *Interface Focus* 2011;1:602–31.
69 Regensburger AP, Brown E, Krönke G, *et al*. Optoacoustic Imaging in Inflammation. *Biomedicines* 2021;9:483.
70 McNally LR, Mezera M, Morgan DE, *et al*. Current and Emerging Clinical Applications of Multispectral Optoacoustic Tomography (MSOT) in Oncology. *Clin Cancer Res* 2016;22:3432–9.
71 Xiang L, Xing D, Gu H, *et al*. Real-time optoacoustic monitoring of vascular damage during photodynamic therapy treatment of tumor. *J Biomed Opt* 2007;12:014001.
72 Lin L, Wang LV. The emerging role of photoacoustic imaging in clinical oncology. *Nat Rev Clin Oncol* 2022;19:365–84.
73 Stoffels I, Morscher S, Helfrich I, *et al*. Metastatic status of sentinel lymph nodes in melanoma determined noninvasively with multispectral optoacoustic imaging. *Sci Transl Med* 2015;7:317ra199:317.:.
74 He H, Schönmann C, Schwarz M, *et al*. Fast raster-scan optoacoustic mesoscopy enables assessment of human melanoma microvasculature in vivo. *Nat Commun* 2022;13:2803.
75 Nau T, Schönmann C, Hindelang B, *et al*. Raster-scanning optoacoustic mesoscopy biomarkers for atopic dermatitis skin lesions. *Photoacoustics* 2023;31:100513.
76 He H, Fasoula N-A, Karlas A, *et al*. Opening a window to skin biomarkers for diabetes stage with optoacoustic mesoscopy. *Light Sci Appl* 2023;12:231.
77 Regensburger AP, Eckstein M, Wetzl M, *et al*. Multispectral optoacoustic tomography enables assessment of disease activity in paediatric inflammatory bowel disease. *Photoacoustics* 2024;35:100578.
78 Paulus L-P, Wagner AL, Buehler A, *et al*. Multispectral optoacoustic tomography of the human intestine - temporal precision and the influence of postprandial gastrointestinal blood flow. *Photoacoustics* 2023;30:100457.
79 Paulus L-P, Buehler A, Wagner AL, *et al*. Contrast-Enhanced Multispectral Optoacoustic Tomography for Functional Assessment of the Gastrointestinal Tract. *Adv Sci (Weinh)* 2023;10:e23025622302562.
80 Träger AP, Günther JS, Raming R, *et al*. Hybrid ultrasound and single wavelength optoacoustic imaging reveals muscle degeneration in peripheral artery disease. *Photoacoustics* 2024;35:100579.
81 Regensburger AP, Fonteyne LM, Jüngert J, *et al*. Detection of collagens by multispectral optoacoustic tomography as an imaging biomarker for Duchenne muscular dystrophy. *Nat Med* 2019;25:1905–15.
82 Günther JS, Knieling F, Träger AP, *et al*. Targeting Muscular Hemoglobin Content for Classification of Peripheral Arterial Disease by Noninvasive Multispectral Optoacoustic Tomography. *JACC Cardiovasc Imaging* 2023;16:S1936-878X(22)00682-9:719–21.:.
83 Regensburger AP, Wagner AL, Danko V, *et al*. Multispectral optoacoustic tomography for non-invasive disease phenotyping in pediatric spinal muscular atrophy patients. *Photoacoustics* 2022;25:100315.
84 Wang LV, Yao J. A practical guide to photoacoustic tomography in the life sciences. *Nat Methods* 2016;13:627–38.
85 Mercep E, Dean-Ben XL, Razansky D. Combined Pulse-Echo Ultrasound and Multispectral Optoacoustic Tomography With a Multi-Segment Detector Array. *IEEE Trans Med Imaging* 2017;36:2129–37.
86 Merčep E, Jeng G, Morscher S, *et al*. Hybrid optoacoustic tomography and pulse-echo ultrasonography using concave arrays. *IEEE Trans Ultrason Ferroelectr Freq Control* 2015;62:1651–61.
87 Weber J, Beard PC, Bohndiek SE. Contrast agents for molecular photoacoustic imaging. *Nat Methods* 2016;13:639–50.
88 Karlas A, Pleitez MA, Aguirre J, *et al*. Optoacoustic imaging in endocrinology and metabolism. *Nat Rev Endocrinol* 2021;17:323–35.
89 Masthoff M, Helfen A, Claussen J, *et al*. Multispectral optoacoustic tomography of systemic sclerosis. *J Biophotonics* 2018;11:e201800155:11.:.
90 Ganzleben I, Klett D, Hartz W, *et al*. Multispectral optoacoustic tomography for the non-invasive identification of patients with severe anemia in vivo. *Photoacoustics* 2022;28:100414.
91 Paltauf G, Nuster R, Frenz M. Progress in biomedical photoacoustic imaging instrumentation toward clinical application. *J Appl Phys* 2020;128:18.
92 Knieling F, Neufert C, Hartmann A, *et al*. Multispectral Optoacoustic Tomography for Assessment of Crohn's Disease Activity. *N Engl J Med* 2017;376:1292–4.
93 Wagner AL, Danko V, Federle A, *et al*. Precision of handheld multispectral optoacoustic tomography for muscle imaging. *Photoacoustics* 2021;21:100220.
94 van den Berg PJ, Daoudi K, Bernelot Moens HJ, *et al*. Feasibility of photoacoustic/ultrasound imaging of synovitis in finger joints using a point-of-care system. *Photoacoustics* 2017;8:8–14.
95 Hallasch S, Giese N, Stoffels I, *et al*. Multispectral optoacoustic tomography might be a helpful tool for noninvasive early diagnosis of psoriatic arthritis. *Photoacoustics* 2021;21:100225.
96 Tascilar K, Fagni F, Kleyer A, *et al*. Non-invasive metabolic profiling of inflammation in joints and entheses by multispectral optoacoustic tomography. *Rheumatology (Oxford)* 2023;62:841–9.
97 Helfen A, Masthoff M, Claussen J, *et al*. Multispectral Optoacoustic Tomography: Intra- and Interobserver Variability Using a Clinical Hybrid Approach. *J Clin Med* 2019;8:63.
98 Mantri Y, Jokerst JV. Impact of skin tone on photoacoustic oximetry and tools to minimize bias. *Biomed Opt Express* 2022;13:875–87.
99 Assi H, Cao R, Castelino M, *et al*. A review of A strategic roadmapping exercise to advance clinical translation of photoacoustic imaging: From current barriers to future adoption. *Photoacoustics* 2023;32:100539.
100 Gröhl J, Hacker L, Cox BT, *et al*. The IPASC data format: A consensus data format for photoacoustic imaging. *Photoacoustics* 2022;26:100339.