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## Review article

# Positron emission tomography with $^{18}\text{F}$ -FDG in the evaluation of patients with rheumatoid arthritis - a systematic review



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## ABSTRACT

**Introduction:** Rheumatoid arthritis (RA) is a disease characterized by inflammation of the synovial membrane. Several authors have investigated the role of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) in RA.

**Objectives:** To systematically review the current literature on the role of  $^{18}\text{F}$ -FDG PET in the diagnosis, determination of disease activity and assessment of treatment response in patients with RA.

**Methods:** Searches were conducted in Medline, Cochrane Library, Lilacs, Pubmed and Scopus in Portuguese, English and Spanish languages, using the keywords «rheumatoid arthritis», «synovitis», «FDG», «PET», «glycolytic metabolism» and «disease activity».

**Results:** One hundred and forty-two articles were initially identified, of which only 40 were related directly to the subject. Twelve original articles and three case reports that met the inclusion criteria were selected.

**Discussion:** The presence of activated macrophages and fibroblasts in pannus are responsible for the intense periarticular uptake of  $^{18}\text{F}$ -FDG. The uptake patterns do not allow the differential diagnosis with other arthritides. The uptake intensity and the number of joints involved are metabolic parameters of disease activity that correlate well with the composite indices. Longitudinal studies of PET have proven useful in assessing the response to treatment with anti-TNF. When performed early, PET can predict the therapeutic response.

**Conclusion:** Although the actual role of this new technique for the investigation of RA is not yet established,  $^{18}\text{F}$ -FDG PET is a promising tool in determining the activity and prediction of response to treatment of patients with RA.

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## Tomografia por emissão de pósitrons com FDG-<sup>18</sup>F na avaliação de pacientes com artrite reumatoide – revisão sistemática

### R E S U M O

#### Palavras-chave:

Tomografia por emissão de pósitrons (PET)  
Flúor-18 (FDG-<sup>18</sup>F)  
Artrite reumatoide

**Introdução:** a artrite reumatoide (AR) é uma doença caracterizada pela inflamação da membrana sinovial. Diversos autores têm investigado o papel da tomografia por emissão de pósitrons (PET) com flúor-18 (FDG-<sup>18</sup>F) na AR.

**Objetivos:** REVISÃO sistemática da literatura atual sobre o papel do PET com FDG-<sup>18</sup>F no diagnóstico, determinação da atividade da doença e avaliação da resposta ao tratamento em pacientes com AR.

**Métodos:** Foram realizadas buscas nas bases de dados Medline, Biblioteca Cochrane, Lilacs, Pubmed e Scopus nos idiomas português, inglês e espanhol, utilizando as palavras-chave «artrite reumatoide», «sinovite», «FDG», «PET», «metabolismo glicolítico» e «atividade da doença».

**Resultados:** Cento e quarenta e dois artigos foram inicialmente identificados, dos quais apenas 40 relacionavam-se diretamente ao tema. Foram selecionados 12 artigos originais e três relatos de caso que preenchiem os critérios de inclusão.

**Discussão:** A presença de fibroblastos e macrófagos ativados no *pannus* é responsável pela intensa captação periarticular de FDG-<sup>18</sup>F. Os padrões de captação não permitem o diagnóstico diferencial com outras artrites. A intensidade de captação e o número de articulações envolvidas são parâmetros metabólicos de atividade da doença que apresentam boa correlação com os índices compostos. Estudos longitudinais de PET têm se mostrado úteis na avaliação da resposta ao tratamento com anti-TNF. Quando realizado precocemente, PET pode prever a resposta terapêutica.

**Conclusão:** Embora o real papel dessa nova técnica na investigação da AR ainda não esteja estabelecido, PET com FDG-<sup>18</sup>F é uma ferramenta promissora na determinação da atividade e na predição de resposta ao tratamento de pacientes com AR.

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## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial membrane. Its prevalence in adults is up to 1%. When not properly treated, RA can lead to osteoarticular destruction and functional limitations, with marked socioeconomic impact.<sup>1</sup>

Rheumatoid synovitis shows intense inflammatory infiltrate associated with neovascularization and proliferation of the synovial membrane. The thickened and inflamed synovial membrane, also known as *pannus*, is directly linked to bone and joint destruction.<sup>2</sup>

The diagnosis of RA in its early stages (up to 12 months after the onset of the first symptoms) is of paramount importance for a successful treatment. The establishment of an adequate treatment in this period, also known as “window of therapeutic opportunity” may prevent or limit considerably the consequences of long-term RA.<sup>3,4</sup> However, this diagnosis in an early stage can present difficulties. Multiple conditions may clinically manifest themselves in a similar manner to RA, including infectious diseases, systemic rheumatic diseases, spondyloarthritis, arthritis by crystal deposition, endocrine and neoplastic diseases.<sup>1,3,4</sup>

Laboratory tests, such as those for inflammatory activity (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) are not specific, and rheumatoid factor (RF) may be

absent in more than 30% of patients in the early phase of the disease.<sup>5</sup> The presence of anti-protein and anti-citrullinated peptides (ACPA) antibodies, including anti-citrullinated cyclic peptide (anti-CCP) antibody, is quite specific, but its sensitivity is limited (70-75%).<sup>[1,3]</sup>

Methods of diagnostic imaging such as conventional radiography have been used to aid in the diagnosis of early RA, but usually these techniques detect bony and cartilaginous structural changes that occur late in natural history of the disease. Ultrasonography (US) and magnetic resonance imaging (MRI) have also been employed, and MRI shows great potential for determining the thickness of the synovial membrane and in detecting bone marrow edema, being considered by many authors as the gold standard (in terms of imaging procedures) for the diagnosis of synovitis.<sup>1,3,6</sup>

Despite many advances in understanding the pathophysiology, diagnosis and treatment of RA, the current prognostic and diagnostic (clinical, laboratory and radiographic) indicators have limited value for early diagnosis and for establishing individual prognosis.<sup>3,7</sup>

The delay of several weeks to establish the diagnosis in patients with arthritis deprives those with RA from an adequate treatment in the therapeutic window of opportunity. In this context, other diagnostic strategies have been studied using new diagnostic imaging technologies now available.<sup>8</sup>

Positron emission tomography, also called PET, is a widely used tool in oncology. Neoplastic cells exhibit an exuberant

glycolytic metabolism and, therefore, consume great quantities of glucose. PET images of cancer patients demonstrate intense uptake of radiolabeled fluorine-18 fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) by malignant tumors and their metastases.<sup>9</sup>

$^{18}\text{F}$ -FDG is a glucose analogue linked to a radioactive isotope, fluorine-18. This molecule behaves similarly to glucose, being avidly taken up by cells with intense glycolytic metabolism. It has long been known that infectious and inflammatory processes also exhibit high uptake of  $^{18}\text{F}$ -FDG. The increased expression of glucose transporter proteins (GLUT types I and III) by membranes of leukocytes present in inflammatory sites, mainly neutrophils and macrophages, leads to this uptake. This pathophysiological mechanism explains why the intensity of  $^{18}\text{F}$ -FDG uptake is directly proportional to the intensity of the activity of inflammatory processes.<sup>10-12</sup>

Therefore,  $^{18}\text{F}$ -FDG PET is able to directly detect and quantify articular and extra-articular sites of increased inflammatory activity. That puts this tool at an advantage over other diagnostic imaging methods, which detect indirect changes of RA, such as erosions (radiography), increased blood flow (Doppler), increased thickening of the synovial membrane (ultrasonography), the presence of bone edema (MRI) or increased osteoblastic activity (bone scan).

The first reports of the use of PET in RA are dated from 1995. Researchers at Massachusetts General Hospital in Boston reported the occurrence of strong  $^{18}\text{F}$ -FDG uptake in two patients diagnosed with RA and with clinically active synovitis in their wrists.<sup>13</sup> Since then, the utility of  $^{18}\text{F}$ -FDG PET in the management of RA has been investigated by several authors.

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## Purpose

The purpose of this study was to conduct a systematic review of the current literature on the role of  $^{18}\text{F}$ -FDG PET in the diagnosis, assessment of disease activity and monitoring the efficacy of treatment with disease-modifying antirheumatic drugs (DMARDs) in patients with RA.

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## Methods

In the period from March to June 2011, searches were conducted through the following databases: Medline (1980-2012), The Cochrane Library, Lilacs, Pubmed (1980-2012) and Scopus in Portuguese, English and Spanish languages. The keywords used were "rheumatoid arthritis" (artrite reumatoide), "synovitis" (sinovite), "FDG", "PET", "glycolytic metabolism" (metabolismo glicolítico) and "disease activity" (atividade da doença).

Inclusion criteria were: original articles and case reports that addressed the role of PET in rheumatoid arthritis and that contained an adequate description of the materials, methods and results achieved. Review articles, letters to the editor and editorials were excluded.

The title and abstract of the articles obtained in the initial search were reviewed by two independent observers in order to identify those that were relevant. A review of the full version was performed on all those papers which met the inclusion

criteria; and the references of these articles were analyzed in order to draw attention to additional sources. For the purposes of this study, were considered the papers selected after mutual agreement of the two observers.

From the manuscripts selected, the following data were observed: type of study, sample size, tools used, statistical analysis and results.

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## Results

One hundred and forty-two articles were initially identified in the databases mentioned, of which only 40 were related directly to the topic searched. Of these, 14 were excluded for being review articles, six for not including patients with RA, four because they did not contain an adequate description of materials and methods, and one because it did not use  $^{18}\text{F}$ -FDG as radiotracer (Table 1). The 12 selected original articles were classified by the authors as experimental studies, diagnosis studies, assessment of disease activity, and assessment of treatment response. Table 2 summarizes the types of studies, the samples analyzed, the main technical characteristics, clinical indices and other diagnostic methods used by the different articles, as well as their primary endpoint. Three case reports were also included.

### Experimental studies

Experimental studies in animals and cell cultures have investigated the pathophysiological mechanism involved in periarticular uptake of  $^{18}\text{F}$ -FDG in patients with RA. Matsui et al.<sup>14</sup> used an animal model (rats). Arthritis was induced by intradermal injection of bovine collagen. Rats were sacrificed immediately after performing PET images. Histology and macroautoradiography of joints with arthritis were compared to PET images. It was observed that areas of marked uptake of  $^{18}\text{F}$ -FDG corresponded to areas of pannus and bone destruction; on the other hand, moderately high uptake areas were represented by hyperplasia of synovial layer cells and by the presence of inflammatory infiltrate. Neutrophils and macrophages were the predominant cells in these sites.

The authors also conducted an *in vitro* assay to determine  $^3\text{H}$ -FDG uptake by neutrophils, macrophages, fibroblasts and T cells exposed to certain pro-inflammatory cytokines ( $\text{TNF}\alpha$ , IL-1 and IL-6). The  $^3\text{H}$ -FDG uptake by macrophages was higher when stimulated by  $\text{TNF}\alpha$  versus IL-1 or IL-6. Fibroblasts exhibited a more intense uptake than that observed in macrophages, especially in response to stimulation by  $\text{TNF}\alpha$  or IL-1. In contrast, no increase in  $^3\text{H}$ -FDG uptake was observed in response to inflammatory cytokines in neutrophils and T lymphocytes. These results suggest that the glycolytic hypermetabolism observed in joints of patients with RA is closely related to the presence of pannus and to the infiltration of activated macrophages and fibroblasts.<sup>14</sup>

Thus, there is some pathophysiological substrate to explain the avidity for labeled glucose by inflammatory cells present in the pannus. Such observations justify why  $^{18}\text{F}$ -FDG PET is a method that directly detects the sites of RA activity. The changes identified in PET images reveal the protagonist of the pathophysiology of RA, which is the inflammation of the

**Table 1 – Selection process of studies according to inclusion and exclusion criteria.**

Number of studies	Type of study	Selection criteria	Status after selection process	Total
12	Original article	Met the inclusion criteria	Inclusion	15
3	Case Report	Met the inclusion criteria		
14	Review article	Review on the subject	Exclusion	25
6	Original article	Patients with RA not included		
4	Original article	Materials and methods were not described adequately		
1	Original article	The glucose analog ( <sup>18</sup> F-FDG) not used as a radiotracer for PET		

RA, rheumatoid arthritis; PET, positron emission tomography.

synovial membrane. This knowledge has led several researchers to examine <sup>18</sup>F-FDG PET as a method capable of diagnose and demonstrate the activity of AR.

### Diagnostics

Inflammatory arthritis and prolonged morning stiffness, associated with the presence of rheumatoid factor and other positive serum autoantibodies, and elevated inflammatory activity tests favor the diagnosis of RA.<sup>1,3</sup> However, often the clinical and laboratory manifestations are not typical. For this reason, RA diagnosis has been based on pre-established clinical and laboratory criteria.<sup>15</sup> Some authors have evaluated PET as a tool in the differential diagnosis of arthritides.

Okabe et al.<sup>16</sup> attempted to establish specific patterns of <sup>18</sup>F-FDG uptake for RA able to differentiate this disease from other arthritides. Seventy patients with arthritis, 30 with RA, were included in a study with the aim to establish a pattern of distribution of <sup>18</sup>F-FDG. Ninety percent of patients with RA exhibited polyarticular hypermetabolism. However, other diseases also demonstrated this pattern of polyarticular hypermetabolism, such as mixed connective tissue disease, systemic sclerosis and RS3PE syndrome (Remitting Seronegative Symmetrical Synovitis with Pitting Edema syndrome). The atlantoaxial involvement was unique to patients with RA. Some sites of hypermetabolism were characteristic of other diseases, such as sacroiliac joint uptake in patients with ankylosing spondylitis; liver, spleen and bone marrow increased uptake in patients with adult Still's disease; and arterial hypermetabolism in patients with polymyalgia rheumatica.

It should be noted that sites of extra-articular activity of AR may also exhibit hypermetabolism, such as lymph nodes and subcutaneous nodules<sup>17,18</sup> and this subject was not addressed by Okabe et al.;<sup>16</sup> this could have contributed to the differentiation of arthritides (Fig. 1).

Elzinga et al.<sup>19</sup> compared PET images in patients with RA (n=17), osteoarthritis (n=6), and fibromyalgia (n=5). As might be expected, patients with fibromyalgia showed no areas of articular hypermetabolism. The number of hypermetabolic joints in patients with RA (88) was significantly higher than in patients with osteoarthritis (12) (P < 0.001). However, uptake intensity was not statistically different between

the two groups. This indicates that PET does not work adequately as a tool for the differential diagnosis of these diseases.

### Assessment of disease activity

The activity of RA can be measured by several clinical, laboratory and radiological parameters. The composite indices of disease activity are the most used and accepted among rheumatologists. Methods of diagnostic imaging have been reserved for specific cases.<sup>3,6</sup>

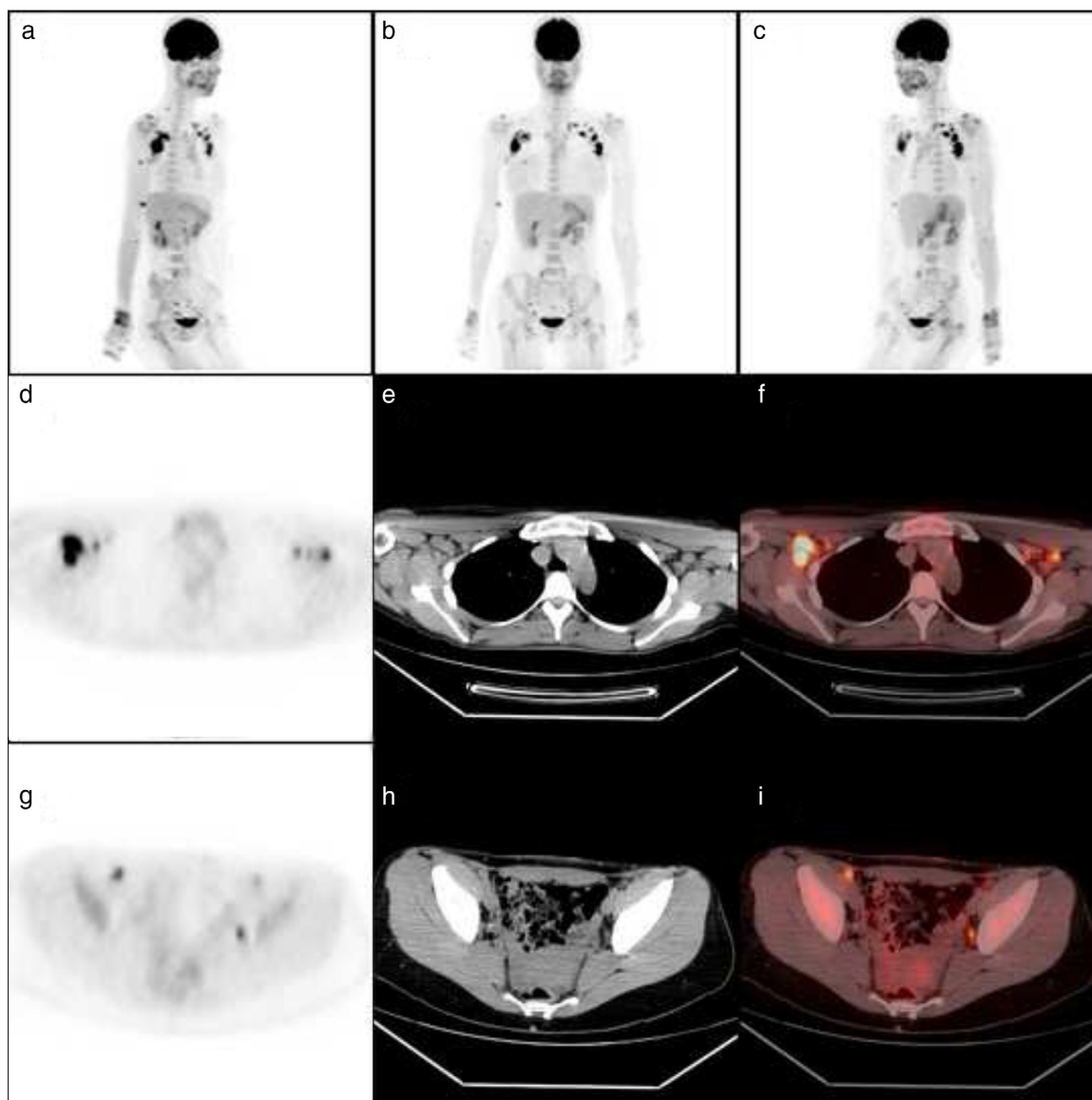
There are several studies relating the findings of PET scans with indices of disease activity and other methods of diagnostic imaging, such as ultrasonography (US) and magnetic resonance imaging (MRI). Roivainen et al.<sup>20</sup> demonstrated a good correlation between intensity of <sup>18</sup>F-FDG uptake (standard uptake value [SUV]) with the volume of the synovial membrane in 10 patients with clinically active synovitis. Palmer et al.<sup>21</sup> found a good correlation between SUV and the volume of pannus which was enhanced under the paramagnetic contrast fat-suppressed weighted MRI in 12 patients with arthritis.

Beckers et al.<sup>22</sup> compared the findings of PET scans with clinical, laboratory and ultrasonographic parameters of RA. A prospective study was conducted including 21 patients with clinically active RA (ACR criteria 1987) using <sup>18</sup>F-FDG PET. The mean DAS<sub>28</sub> was 7.4 (5.2-8.5) and mean SDAI was 60.2 (34.9-75.5). All participants were not taking any DMARDs for at least two months. Thirteen controls with no history of joint pain were included in the study. PET was negative in all controls. Of the 356 joints evaluated, 225 (63%) were positive on PET studies. The amount of metabolically positive joints was lower than the number of painful (266% vs. 75%) or swollen (282% vs. 79%) joints and higher than the number of sonographic-positive joints (199% vs. 56%). PET- and US-positive joints (n=27) had the mean thickness of the synovial membrane significantly higher (8.2 ± 0.9 mm) than PET-positive and US-negative joints (n=6) (2.9 ± 0.5 mm). A statistically significant correlation (p ≤ 0.05) between PET and all clinical parameters analyzed was observed, except for the duration of morning stiffness and for the assessment of functional capacity (HAQ). The correlation among the number of PET-positive joints and

Table 2 – Types of study, analyzed samples, main technical characteristics, clinical indices and other imaging methods used.

Author and reference	Study Design	Number of participants	Number of controls	Technical procedure used	Joints evaluated by patient	Other clinical indices or diagnostic methods	Primary Outcome
Matsui et al. <sup>15</sup>	Experimental study	5	4	PET	-	Macroautoradiography, Histology	To Compare PET with macroautoradiography and histology
Okabe et al. <sup>16</sup>	Retrospective clinical study	72 patients (30 with RA)	-	PET or PET/CT	19	-	Diagnosis
Elzinga et al. <sup>19</sup>	Crossover clinical study	14 with RA, 6 with OA	5 with FM	PET	22	-	Diagnosis
Palmer et al. <sup>21</sup>	Prospective clinical study	12 with UA	-	PET	1	MRI	Assessment of disease activity
Roivainen et al. <sup>20</sup>	Prospective clinical study	2 with RA, 6 with UA, 1 with AS, 1 USA	-	PET	1	Contrast-enhanced MRI	Assessment of disease activity
Beckers et al. <sup>22</sup>	Prospective clinical study	21 with RA	13 without arthralgia	PET	12 or 22	US, SDAI, DAS <sub>28</sub>	Assessment of disease activity
Goerres et al. <sup>23</sup>	Prospective clinical study	7 with RA	-	PET	28	DAS <sub>28</sub> , RDAI	Assessment of disease activity
Kubota et al. <sup>24</sup>	Retrospective clinical study	18 with RA	-	PET/CT	13	CRP, joint count	Assessment of disease activity
Beckers et al. <sup>25</sup>	Cohort study	16 with RA	-	PET	1	US, MRI, CRP, MMP-3	Assessment of treatment response
Okamura et al. <sup>26</sup>	Cohort study	22 with RA	-	PET/CT	12	US, MRI, DAS <sub>28</sub> , DAS <sub>28</sub> -CRP, ESR, CRP, MMP-3, RF	Assessment of treatment response
Elzinga et al. <sup>27</sup>	Exploratory study	16 with RA	-	PET	12	CRP, ESR, MHAQ, VAS	Assessment of treatment response
Sato et al. <sup>29</sup>	Prospective clinical study	6 with RA	-	PET	2	DAS <sub>28</sub> , joint count, ESR, CRP	Assessment of treatment response

RA, rheumatoid arthritis; OA, osteoarthritis; UA, undifferentiated arthritis; AS, ankylosing spondylitis; USA: undifferentiated spondyloarthritis; FM: fibromyalgia; PET, positron emission tomography; PET/CT, positron emission tomography with computed tomography; US, ultrasonography; MRI, magnetic resonance imaging; SDAI, simplified disease activity index; DAS<sub>28</sub>, disease activity score; RDAI, rheumatoid arthritis disease activity index; CRP, C-reactive protein; MMP-3, matrix metalloproteinase-3; RF, rheumatoid factor; MHAQ, modified health assessment questionnaire; VAS, visual activity score.



**Figure 1 –  $^{18}\text{F}$ -FDG PET of a female patient, 28 years old, complaining of symmetrical polyarthralgia, especially involving hands and wrists and associated with prolonged morning stiffness. Laboratory tests revealed an ESR = 81 mm, positive rheumatoid factor (40.2 IU/mL) and an anticitrullinated peptide antibody strongly positive (82.5 IU/mL). The three-dimensional reconstruction images (a, b, c) show high uptake in shoulders, wrists, metacarpophalangeal and proximal interphalangeal joints of the hands and hips. Tomographic images of PET (d, g), CT scans (e, h) and PET/CT (f, i) showing intense hypermetabolism in bilateral axillary and pelvic lymph nodes (personal file).**

composite indices of the disease activity (DAS<sub>28</sub> and SDAI) was considered significant ( $r = 0.90$ ,  $P < 0.0001$ ).

The analysis of these results suggests that the metabolic activity of synovitis demonstrated by  $^{18}\text{F}$ -FDG PET can reflect disease activity with a good correlation with DAS<sub>28</sub> and SDAI. However, the small number of patients and the prevalence of RA patients with high disease activity in this study limit its conclusions.

Goerres et al.<sup>23</sup> proposed a visual score to quantify metabolically active joints with PET. Seven patients with DAS<sub>28</sub>  $\geq 4.2$  were included. An index of zero to 4 (zero for no uptake

and 4 for a marked uptake) was assigned to each of the 28 joints usually assessed by composite indices of disease activity. The Spearman test showed a significant correlation between visual scoring by PET and DAS<sub>28</sub>. PET also revealed sites of extra-articular (tendons and bursae) uptake in six of seven patients. However, once again the small number of patients included did not allow any extrapolation of these findings.

Kubota et al.<sup>24</sup> used PET scan with a focus on large joints. Eighteen RA patients underwent  $^{18}\text{F}$ -FDG PET/CT to study the metabolism of 13 joints (atlantoaxial, shoulders, elbows,

wrists, carpals, hips and knees). PET/CT is a combination of functional positron emission tomography equipment and a computed tomography. Four patients were in clinical remission and 14 presented with clinically active RA. A modified Goerres et al.<sup>23</sup> score was used. The number of affected joints and the total score of PET were significantly different among patients in remission and with active RA. There was also a positive linear correlation between the total score with PET and serum levels of CRP ( $r=0.658$ ,  $P=0.003$ ). Five patients (28%) showed hypermetabolism in the atlantoaxial joint. The presence of hypermetabolic axillary lymph nodes was correlated with the superior limbs joints uptake ( $r=0.731$ ,  $P=0.000004$ ).

### Monitoring treatment response

The treatment with synthetic DMARDs has low cost. However, biological DMARDs have high cost and cause numerous adverse effects. In this context,  $^{18}\text{F}$ -FDG PET has been used as an attempt to discriminate those patients can benefit from this type of treatment. Beckers et al.<sup>25</sup> compared  $^{18}\text{F}$ -FDG PET with contrast-enhanced MRI and US in the treatment response evaluation. Sixteen patients with active RA underwent whole-body PET, contrast-enhanced MRI and US of one knee (i.e., the joint referred to by patients as that with more severe pain) before and after four weeks of treatment with anti-TNF (drug not specified by the authors). Metabolically positive knees showed greater synovial thickness and a more intense paramagnetic contrast enhancement. There was good correlation between the intensity of  $^{18}\text{F}$ -FDG uptake (SUV), synovial thickness with US and enhancement by paramagnetic contrast with MRI. After four weeks of treatment with anti-TNF, a significant decrease in SUV and in paramagnetic contrast enhancement occurred, but without a significant reduction in synovial thickness. These data show that the response to biological treatments can be demonstrated by PET images with respect to the metabolic aspect, before the observation of a significant reduction in synovial thickness by ultrasonography or MRI studies. However, of all possibly affected joints in these 16 patients, the study only evaluated a large joint (knee). This occurred due to a technical limitation of contrast-enhanced MRI, which is a method that studies only one joint area at a time, spending 30-40 minutes for each region. PET shows great advantage in this regard, since it can assess all joints of the body in a single examination, with similar duration.

Okamura et al.<sup>26</sup> studied 22 patients with poor response to synthetic DMARDs, including methotrexate, and with indication for treatment with biologic DMARDs (etanercept in 16 and infliximab in 6). All patients underwent  $^{18}\text{F}$ -FDG PET/CT at baseline and six months after the initiation of therapy.  $\text{DAS}_{28}$ ,  $\text{DAS}_{28}$ -CRP, ESR, CRP, matrix metalloproteinase-3 (MMP-3) and RF were determined on the same days of PET/CT. Patients had moderate to high RA activity (mean  $\text{DAS}_{28}$ :  $5.29 \pm 1.01$ ; minimum: 3.47 and maximum: 6.95). All clinical, laboratory and metabolic parameters showed significant decrease after six months of treatment (mean  $\text{DAS}_{28}$ :  $3.81 \pm 0.86$ , minimum: 2.21 and maximum: 5.33). There was good correlation among values of SUV,  $\text{DAS}_{28}$  and  $\text{DAS}_{28}$ -CRP. The decrease in SUV also correlated with the decrease in values of  $\text{DAS}_{28}$  and

$\text{DAS}_{28}$ -CRP. These results show that PET can be an alternative method for objectively measuring disease activity and determining the response to therapy with anti-TNF in a relatively simple and straightforward manner and with good correlation with the indices more commonly used by rheumatologists for such purposes.

Elzinga et al.<sup>27</sup> investigated the potential of  $^{18}\text{F}$ -FDG PET to predict the therapeutic response to infliximab. Sixteen patients with at least two swollen or painful joints (metacarpophalangeal and/or wrists) were enrolled for treatment with subcutaneous injections of infliximab at weeks 0, 2, 6, 14 and 22. The determination of the values of CRP and ESR, as well as the counting of 28 painful or swollen joints, was performed at the same intervals. The European League Against Rheumatism (EULAR) criteria<sup>15</sup> were used to classify the response to treatment as good ( $n=5$ ), moderate ( $n=8$ ) and non-responders ( $n=3$ ). PET studies of metacarpophalangeal joints and wrists were performed before the treatment and after two weeks. The results showed that the change in SUV between zero and two weeks correlated with  $\text{DAS}_{28}$  at weeks 14 and 22 ( $r=0.62$ ,  $P<0.05$ ;  $r=0.65$ ,  $P<0.01$ , respectively). The change of the components of  $\text{DAS}_{28}$  (ESR, CRP, joint counting, visual analogue scale) in the interval of two weeks did not correlate with  $\text{DAS}_{28}$  at weeks 14 and 22. A logistic regression analysis showed that SUV reduction was the only significant predictive factor for determining  $\text{DAS}_{28}$  at weeks 14 and 22 ( $\beta=0.62$ ,  $P<0.05$ ;  $\beta=0.65$ ,  $P<0.01$ , respectively). The results obtained in this small group of patients suggest that  $^{18}\text{F}$ -FDG PET of wrists and metacarpophalangeal joints, performed with only two weeks of treatment, can predict the systemic response to infliximab after 14 and 22 weeks. Considering the high cost of this treatment, this study encourages new research projects using  $^{18}\text{F}$ -FDG PET as a tool to determine which patients may benefit from the long-term treatment with infliximab, saving a lot of money for health systems, considering such a costly treatment. This strategy also could provide to non-responders to infliximab the chance of a treatment with other biological DMARDs.

The therapeutic effects of acupuncture in the treatment of patients with RA have also been under investigation. Sato et al.<sup>28</sup> included only six patients in their research. All of them reported improvement in pain, functional capacity and quality of life after two months of treatment with acupuncture. However,  $^{18}\text{F}$ -FDG PET showed no change in the metabolic activity of the affected joints. The inflammatory activity tests (CRP and ESR) did not show significant variation after acupuncture. These results suggest that acupuncture has no anti-inflammatory effect in patients with RA.

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## Conclusions

Although the number of studies on the role of  $^{18}\text{F}$ -FDG PET in RA is limited, and considering the small number of patients enrolled by most studies published with this purpose, the data presented in this review allows us to make some considerations.  $^{18}\text{F}$ -FDG PET is a non-invasive imaging method of diagnosis which is able to demonstrate disease activity in a straightforward and objective manner, with good correlation with the composite activity indices used in clinical practice.

Its high cost can be evaluated in a relative manner, when we consider that this is an assessment of the whole body, allowing the study of all joints at once. Its ability to determine and predict earlier the response to treatment with biologic DMARDs constitutes a factor that deserves a more profound analysis in future investigations. New prospective longitudinal randomized studies are needed to consolidate this method of diagnostic imaging.

Although the actual role of this new technique in the investigation of RA is not yet established, <sup>18</sup>F-FDG PET is a promising tool for the determination of disease activity and in the assessment and prediction of treatment response in patients with RA. It might be that in the future, <sup>18</sup>F-FDG PET will play a more important role in the diagnosis and assessment of disease activity.

### Conflicts of interest

The authors declare no conflicts of interest.

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