

# Dissociation between 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose Positron Emission Computer Tomography, Ultrasound and Clinical Assessments in Patients with non-severe Rheumatoid Arthritis including Remission

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## Research article

**Keywords:** positron emission tomography (PET), remission, rheumatoid arthritis (RA), ultrasonography (US)

**Posted Date:** August 24th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-57444/v1>

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**Version of Record:** A version of this preprint was published at BMC Rheumatology on August 4th, 2021.

See the published version at <https://doi.org/10.1186/s41927-021-00196-1>.

# Abstract

**Background:** 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose Positron Emission Computer Tomography ([<sup>18</sup>F]FDG PET/CT) in rheumatoid arthritis (RA) visualizes and quantifies inflammation in joints of patients with severe disease activity but little is known on the metabolic status and its relationship with clinical and ultrasonography (US) metrology in patients with low/moderate activity or in remission.

**Methods:** Clinical assessments (DAS<sub>28</sub>-CRP, CDAI), [<sup>18</sup>F]FDG PET/CT, US and X-ray were performed on 63 RA patients classified into remission, low/moderate or severe disease activity. PET/CT was analyzed visually, then semi-quantitatively by determining standardized uptake value (SUV) of positive joints.

**Results:** Of the 1764 joints, 21.1% were tender only, 13.7% swollen only, 27.6% tender or swollen, 7.3% tender and swollen, 20.5% PET/CT-positive and 8.6% US-positive. PET and US-measurements correlated, albeit with poor concordance. Positive predictive value of PET/CT for clinical evaluation (tender and/or swollen) was low whereas its negative predictive value was high. Highly significant differences were found in the number of PET/CT-positive joints and in cumulative SUV between “severe and non-severe cases” (including remission and low/moderate activity together) only, but not between “remission and non-remission” or “remission and low/moderate activity”. Moreover, correlation between PET/CT measurements and clinical activity was positive only in CDAI severe disease group. In patients with remission or low/moderate activity, only 20-30% of joints were PET/CT-negative. In remission, PET/CT and US were positive in different joints and PET/CT-positive but US-negative joints mainly exhibited RA (38.1%) or normal (49.2%), and not osteoarthritis (12.7%), X-ray pattern.

**Conclusions:** [<sup>18</sup>F]FDG PET/CT was effective at distinguishing patients with a severely active disease from the others. In non-severe RA, including remission, patients, PET/CT results disconnect from US and clinical observations. A longitudinal analysis is needed to explore the clinical relevance of such infra-clinical disease.

## Background

Since the use of biologic agents in the therapeutic armamentarium of rheumatoid arthritis (RA), low disease activity (LDA) and remission are reachable targets with better outcomes including less radiographic progression (1). In clinical trials, remission is often defined as a disease activity 28-joint score (DAS<sub>28</sub>) <2.6. Although relatively lenient, this target is achieved in only 30-40 % of the patients (2-3). Within this group, the disease remains active in a significant proportion of patients as observed in the DREAM registry where 31.1% of patients had a swollen joint count ≥2 (3) and experienced joint damage progression (4). Further, imaging studies have shown at least one synovitis in 33-73 % of patients in remission by ultrasound (US) and in up to 96% of them by magnetic resonance imaging (MRI) (5). Surprisingly, even the most stringent remission criteria as the ACR/EULAR Boolean remission (6) did not decrease the prevalence of US-diagnosed synovitis (7-11). Although the relevance of US, in particular power Doppler activity, in clinical remission is widely accepted as driving radiologic progression (8-14)

and future clinical flares (7, 10, 13, 15), the relevance of other imaging techniques for assessing synovitis remains poorly understood and discordance between predictor of clinical and US remission indicates complex interactions between them (9, 16).

Our group among others (17-24) showed that 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose Positron Emission Computer Tomography ([<sup>18</sup>F]FDG PET/CT) is capable to visualize and quantify inflammation in RA synovitis. The number of PET-positive joints analyzed on the 28 joints of the DAS and the cumulative standard uptake value (CSUV) of these PET-positive joints were highly correlated with the clinical status (number of swollen joints, number of tender joints) and with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) parameters, with the DAS<sub>28</sub> (22, 24) but also with US data such as the number of US-positive joints and the cumulative synovial thickness (22). Roivanen et al (21) reported that up to 90% of the joints rated positive by clinical evaluation (swollen and tender) were also positive on [<sup>18</sup>F]FDG PET whereas a proportion of 75% was quoted by Elzinga (19). In these studies however, correlation between PET and the DAS<sub>28</sub> scores was exclusively obtained in RA patients with severe disease activity (20, 22) or in a large majority of them (21, 24). The primary objective of the present study was to compare PET/CT parameters among RA patients under remission, under low/moderate or under severe activity as defined by two classical composite indices, the DAS<sub>28</sub>-CRP score and the Clinical Disease Activity Index (CDAI).

## Methods

### Study design and patients

The cross-sectional study, approved by the ethical committee of our hospital (B70720108722), included 63 patients fulfilling the ACR/EULAR 2010 criteria for RA (25), from July 2010 to April 2012. Written informed consent was obtained for each patient. All assessments were done on the same day by the same independent experienced investigator unaware of the other results: the clinical evaluation first in the morning with a blood sample followed by the US and terminated by the PET/CT evaluation. X-rays were available as routine controls made at maximum 6 weeks around the study day. The Patient (PtGA) and the Physician Global Assessment (PGA) were determined using a Visual Analogue Scale (VAS) (0-100 mm) as well as the Health Assessment Questionnaire (HAQ) (26). Disease activity was evaluated using the DAS<sub>28</sub>-CRP (lacking PGA) (27) and the CDAI (with PGA and without CRP) (28). Each patient was categorized as in remission (DAS<sub>28</sub>-CRP<2.6, CDAI<2.8), in low to moderate disease activity (2.6-DAS<sub>28</sub>-CRP≤5.1, 2.8-CDAI≤22), or in severe disease activity (DAS<sub>28</sub>-CRP>5.1, CDAI>22) (29). The number of joints solely tender (T), solely swollen (S), "tender or swollen" (T/S) and "tender and swollen" (T&S) was recorded.

### [<sup>18</sup>F]FDG PET/CT imaging

The PET/CT studies were performed using a Gemini BigBore scanner (Philips Medical Systems, Cleveland, OH, USA). Patients fasted for 4 hours and were injected with [<sup>18</sup>F]FDG through an indwelling catheter placed in the median cubital vein and flushed with 5cc of saline solution afterwards (4 MBq/kg

body weight with a maximum of 370 MBq). Blood glucose level was lower than 140 mg/dl. The uptake time was 60 minutes and the image acquisition sequence as follows: first a scoutview CT, followed by the PET emission study that included the knees, hands, wrists, elbows and shoulders, with 2 minutes per bed position for a total scanning time ranging from 14 to 18 minutes. Finally, a low-dose CT (5-mm slice thickness, tube voltage 120 Kv, tube current–time product 80 mAs) was performed over these joints. The hands and wrists were positioned and fixated on a dedicated Plexiglas device in order to avoid movements between the PET and the CT acquisitions. PET Images were reconstructed using an iterative list mode time-of-flight algorithm and corrections for attenuation, dead-time, random and scatter events were applied. The images were first analyzed visually and joints were considered as positive for synovitis when the [<sup>18</sup>F]FDG uptake was increased compared to the background in areas corresponded to joint synovium on CT, i.e. either when thickened synovium was recognized on CT or in locations corresponding anatomically to synovium, excluding uptake in other structures such as muscle and tendons. The [<sup>18</sup>F]FDG uptake was then quantified using the maximum standardized uptake value (SUVmax). In PET-positive joints according to the visual analysis, the SUVmax was obtained by drawing a region of interest (ROI) over the most active synovial area identified. When no synovitis was identified, ROIs were placed in the corresponding areas on the CT: at the dorsal surface of the radius (on top of the lunate) for the wrists, over the lateral recess at the level of the midpatella for the knees and for the small joints as metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints, ROIs were drawn around the appropriate joint. A global metabolic assessment was obtained through the number of PET-positive joints (visual evaluation) and the sum of all SUVs (cumulative SUV, CSUV).

### **Ultrasound and X-ray examination**

US assessment was performed using a B-mode multi frequency 10-14.0 MHz transducer (Logiq 9) (GE Healthcare, Milwaukee, WI, USA). US positioning for the wrists, the MCP and the PIP joints and for the knees have been described elsewhere [22]. Proximal and distal radiocapitellar recesses were studied for the elbows and the glenohumeral joint, posterior side for shoulders. Synovial measurements were carried out systematically perpendicular to the great axis and at the point of greatest thickness. A cut-off for US positivity was defined as a synovitis of at least 1 mm thick (3 mm for the shoulders) according to US determinations in healthy controls, described elsewhere (22). In joints where 2 (wrists) or 3 (elbows, knees) scannings were performed, the joint was considered positive if at least one measurement was positive. The cumulative synovial thickness (CST), *i.e* the sum of thicknesses of all US-positive joints, is the addition of all (single or multiple) synovial measurements performed. X-ray were obtained for peripheral joints (PIPs, MCPs and wrists)

### **Statistical analysis**

Results were generally expressed as mean  $\pm$  standard deviation (SD). Correlation coefficients were calculated to measure the association between PET/CT and clinical or US parameters. The Spearman correlation was used for skewed distributions. Concordance between methods was quantified by the intraclass coefficient (ICC). Ordinal logistic regression was used to assess the relationship between

disease activity categories based on DAS<sub>28</sub>-CRP or CDAI (remission, low/moderate and severe disease activity), and PET/CT number of positive joints and CSUV. A test was performed whether all three diseases severity categories were distinguishable. If this was not the case, a classical logistic regression analysis was applied and optimal Youden cut-off values were determined from the Receiver Operating Characteristic (ROC) curve method. Results were considered significant at the 5% level ( $p < 0.05$ ). All statistical analyses were performed with SAS (version 9.4).

## Results

### Patient characteristics

The study patients (42 women and 21 men) had a mean age of  $54.8 \pm 12.3$  years and disease duration of  $7.0 \pm 6.0$  years. IgM rheumatoid factor and anti-citrullinated antibodies were positive in 49.2% and 69.8%, respectively. At baseline, 40 (63.5%) subjects had classical disease-modifying antirheumatic drugs (DMARDs), 32 (50.8%) biological agents, 19 (30.2) daily oral prednisolone and 13 (20.6%) non-steroidal anti-inflammatory drugs. Laboratory, physical examination, disease activity, US and PET-CT results are displayed in Table 1.

Variable	Patient (N=63)	Joints (N=1764)
	Mean ± SD or Number (%)	Number (%)
<u>Anamnestic disease activity</u>		
Patient global assessment - VAS (mm)	43.0 ± 30.6	
Physician global assessment - VAS (mm)	20.1 ± 26.2	
Health Quality Questionnaire	13.3 ± 13.0	
<u>Blood analysis</u>		
CRP (mg/L)	3.3 ± 4.4	
ESR (mm/h)	11.3 ± 12.1	
<u>Clinical examination</u>		
Number of tender joint	5.9 ± 8.2	373 (21.1)
Number of swollen joint	3.8 ± 4.6	242 (13.7)
Number of tender or swollen joint	7.7 ± 8.0	486 (27.6)
Number of tender and swollen joint	2.1 ± 4.3	129 (7.3)
DAS28-CRP	3.4 ± 1.5	
Remission (<2.6)	22 (34.9)	
Low /moderate activity (2.6-5.1)	31 (49.2)	
Severe activity (>5.1)	10 (15.9)	
CDAI	16.1 ± 15.2	
Remission (<2.8)	11 (17.5)	
Low /moderate activity (2.8-22)	37 (58.7)	
Severe activity (>22)	15 (23.8)	
<u>Ultrasounds</u>		
Synovitis (positive joints)	2.4 ± 3.2	152 (8.6)
Cumulative synovial thickness (mm)	8.3 ± 13.1	
<u>PET-CT</u>		
Positive joints	5.7 ± 7.9	361 (20.5)
Cumulative standard uptake value	12.8 ± 19.1	

Table 1. Patient-related and joint-related characteristics of study material. VAS: Visual Analogue Scale. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. DAS: Disease activity score. CDAI: clinical disease activity index. PET-CT: positron emission computer tomography. SD: standard deviation.

## Relation between PET/CT and US

### measurements

In total, 1764 (63 x 28) joints were analyzed. The number of positive joints and the cumulative activity (CSUV) were obtained by PET/CT on one hand and the number of positive joints and the total synovial thickness (CST) by US on the other hand. The distributions of PET/CT and US positive joints, of CSUV and of CST are illustrated in Supplementary Figure 1. Strong correlations were found between number of PET/CT-positive joints and CSUV ( $r=0.96$ ,  $P<0.0001$ ) and between number of US-positive joints and CST ( $r=0.94$ ,  $P<0.0001$ ). Significant correlations were found between number of PET-CT positive joint and US measurements (number of PET/CT-positive joints and number of US-positive joints:  $r=0.42$ ,  $P=0.0005$ ;

number of PET/CT-positive joints and CST:  $r=0.39$ ,  $P=0.0017$ ) but also between CSUV and US (CSUV and number of US-positive joints:  $r=0.41$ ,  $P=0.0009$ ; CSUV and CST:  $r=0.39$ ,  $P=0.0017$ ). Concordance between the number of PET/CT-positive and the number of US-positive joint however was poor (ICC= 0.34; 95% ICC 0.13), PET/CT-positive joints being twice more frequent than US-positive joints.

### Relationship between PET/CT and clinical measurements

Joint positivity on PET/CT was compared to clinical evaluation (tender, swollen, “tender or swollen”, “tender and swollen”) for each joint. Diagnostic efficacy of PET/CT (sensitivity, specificity, positive and negative predictive values) is presented in Table 2. PET/CT sensitivity was low with respect to clinical measurements: only 58.9% of the joints that were both tender and swollen, and only 35.8% of the joints that were tender or swollen, were positive on PET/CT. Specificity was higher: 82.6% of the joints that were not tender or not swollen, and 85.4% of the joints that were neither tender nor swollen, were PET-negative (Table 2). In accordance, the positive predictive value of PET-CT was low, while the negative predictive value was as high as 96.2% in tender and swollen joints. In other terms, when PET-CT was negative, the probability that the articulation was not tender and/or not swollen was high, while when PET-CT was positive, the probability that this articulation was tender and/or swollen was of poor value.

	Tender	Swollen	Tender or Swollen	Tender and swollen
Sensitivity	40.5 (35.5-45.5)	40.9 (34.7-47.1)	35.8 (31.5-40.1)	58.9 (50.4-67.4)
Specificity	84.9 (83.0-86.8)	82.8 (80.9-84.7)	85.4 (83.4-87.3)	82.6 (80.7-84.4)
Positive predictive value	41.8 (36.7-46.9)	27.4 (22.8-32.0)	48.2 (43.0-53.4)	21.1 (16.8-25.3)
Negative predictive value	84.2 (82.3-86.1)	89.8 (88.2-91.4)	77.8 (75.6-79.9)	96.2 (95.2-97.2)

**Table 2.** Diagnostic efficacy of PET/CT in the 1764 joints analyzed. Values are expressed in percent with 95% confidence interval

### Relationship between PET/CT parameters and disease activity threshold

The number of PET/CT-positive joints and CSUV were analyzed according to disease activity categories (based on DAS<sub>28</sub>-CRP or CDAI) and illustrated in Figure 1 and Supplementary Table 1 (e.g. there were respectively  $3.6 \pm 5.4$  PET/CT-positive joint for DAS<sub>28</sub>-CRP remission,  $4.7 \pm 6.7$  for low/moderate activity and  $13.6 \pm 11.2$  for severe disease activity). An ordinal logistic regression evidenced a significant relationship between the mean number of PET/CT-positive joints or the CSUV and clinical disease activity (Supplementary Table 1). However, “remission” and “low/moderate” disease activity categories could not be dissociated by PET/CT (the cutoff value between the two groups was negative, so that patients in remission should have a negative number of PET/CT positive joints which is impossible). Moreover, 27.3% of patients without any metabolic activity were observed in both DAS<sub>28</sub>-CRP and CDAI remission, while 25.8% and 27% in DAS<sub>28</sub>-CRP and CDAI low/moderate activity sub-groups ( $p=0.99$  for both DAS<sub>28</sub>-

CRP and CDAI subgroups) indicating that PET/CT was unable to discern remission and low-moderate activity (Supplementary Table 2).

Thus, the two categories remission and low/moderate were merged and a classical logistic regression analysis was performed between patients with severe and non-severe (including remission and low/moderate activity) disease activity (Table 3): highly significant differences were found in the number of PET/CT-positive joints and in CSUV. The optimal threshold for identifying RA patient with a clinically and biologically severe disease was at least 8 PET/CT-positive joints and a CSUV  $\geq 17.8$  for the DAS<sub>28</sub>-CRP and 6.8 and 15.0 for the CDAI, respectively. Disease activity thresholds were also studied by dividing RA patients into remission and non-remission categories (including low/moderate and severe disease), but no significant difference was observed in terms of number of PET/CT-positive joints and CSUV (data not shown).

Clinical disease activity	N	Number of PET/CT- positive joints			Cumulative SUV		
		Mean $\pm$ SD	Cut-off (AUC)	P-value	Mean $\pm$ SD	Cut-off (AUC)	P-value
DAS <sub>28</sub> -CRP			8.0 (0.77)	0.0026		17.8 (0.77)	0.0046
Non-severe $\leq 5.1$	53	4.2 $\pm$ 6.1			9.2 $\pm$ 14.1		
Severe $> 5.1$	10	13.6 $\pm$ 11.2			31.9 $\pm$ 29.9		
CDAI			6.8 (0.67)	0.023		15.0 (0.65)	0.033
Non-severe $\leq 22$	48	4.4 $\pm$ 6.3			9.7 $\pm$ 14.6		
Severe $> 22$	15	10.0 $\pm$ 10.6			22.9 $\pm$ 27.5		

**Table 3.** Association between the number of PET/CT-positive joints or cumulative SUV and disease activity based on DAS<sub>28</sub>-CRP or CDAI. DAS: disease activity score. CRP: C-reactive protein. CDAI: clinical disease activity index. PET-CT: positron emission computer tomography. SUV: standard uptake value. AUC: area under the curve. SD: standard deviation.

Supplementary Table 2 previously showed that 16/22 and 8/11 patients under remission (according to DAS<sub>28</sub>-CRP and CDAI respectively) were nonetheless PET/CT-positive for at least one joint. Of interest, 12/22 (54.5%) and 6/11 (54.5%) patients had also at least one US-positive joint, despite under remission (data not shown). As an illustration for patients in remission on DAS<sub>28</sub>-CRP, at the joint level, 75 joints were PET/CT-positive and 24 were US-positive. Moreover, in the 6 patients with strict Boolean remission (tender and joint score  $\leq 1$ , PGA  $\leq 1$  (0-10 cm), CRP  $\leq 1$  mg/dl), 20/168 joints were PET/CT-positive and 9/168 were US-positive suggesting a dissociation of PET/CT metrology and the clinical assessment in RA patients in remission. Among the patients in remission on DAS<sub>28</sub>-CRP, only 10 joints were positive for both PET/CT and US (5 wrists, 4 MCPs, 1 shoulder). The 65 PET/CT-positive remaining joints were distributed as following: 27 PIPs, 21 MCPs, 8 wrists, 7 knees, 1 elbow and 1 shoulder. Among the 6 patients under Boolean remission, only 4 wrists were both PET/CT- and US-positive, enhancing the lack of concordance between PET/CT and US.

Overall there was a significant correlation between the metabolic measurements (number of positive joint and CSUV) and the clinical assessments (DAS<sub>28</sub>-CRP and CDAI) (Table 4). However, when classifying patients in remission, low/moderate or severe category, this significant correlation between PET and clinical assessment was observed only in the subjects with severe activity according to CDAI, and not in RA patients in low/moderate disease activity or remission.

	Global	Remission	Weak/moderate	Severe
PET/CT-positive joints				
DAS <sub>28</sub> -CRP	0.34 (0.0024)	0.22 (0.33)	-0.12 (0.53)	0.17 (0.63)
CDAI	0.44 (0.0004)	-0.21 (0.54)	0.09 (0.61)	0.58 (0.024)
CSUV				
DAS <sub>28</sub> -CRP	0.37 (0.0028)	0.24 (0.28)	-0.14 (0.44)	0.22 (0.55)
CDAI	0.44 (0.0003)	-0.07 (0.85)	0.06 (0.71)	0.63 (0.012)

**Table 4.** Correlation coefficient (with P-value) between the number of PET/CT-positive joints or the cumulative SUV and clinical scores (DAS: disease activity score. CRP: C-reactive protein. CDAI: clinical disease activity index. PET-CT: positron emission computer tomography. CSUV: cumulative standard uptake value)

## Relationship between X-rays and PET/CT

The 63 peripheral joints (PIPs, MCPs and wrist) that were PET-positive but US-negative in the 16 patients in clinical remission (DAS<sub>28</sub>-CRP<2.6) were characterized with X-ray. Features of RA, i.e. symmetrical joint narrowing, bone erosion or demineralization, and of OA, i.e. asymmetrical joint narrowing, subchondral sclerosis, or osteophytes were recorded. Results were consistent with RA in 24/63 joints (38,1%) and with OA in 8/63 joints (12.7%) with OA signs. In 31/63 joints (49.2%) X-rays were normal. In particular, RA / OA / normal feature was described in 7 / 0 / 24 of the 31 PIPs, 12 / 6 / 5 of the 23 MCPs and 5 / 2 / 2 for the 9 wrists. Considering the corresponding clinical status, none of these joints were tender or swollen.

## Discussion

In line with previous work (22), we confirmed that the number of PET/CT-positive joints and the CSUV correlate significantly with the number of US-positive joints, synovial thickness and disease activity based on either on DAS<sub>28</sub>-CRP or CDAI. In addition, PET/CT was quite effective at distinguishing patients with a severely active disease from the others, as a cutoff of 8 for the number of PET-positive joints and 17.8 for the CSUV yielded an area under the curve (AUC) of 0.77 (considering DAS<sub>28</sub>-CRP as the clinical gold standard). Although the number of hypermetabolic joints and the cumulative SUV tended to be higher with increased clinical severity of the disease, one notable exception should be mentioned. There was no significant difference in the number of PET-positive joints and their CSUV between patients in clinical remission and those with a low/moderate disease activity. In both groups, only 25-27% of the patients presented with perfectly negative PET/CT findings. Clearly, PET/CT results and clinical assessment diverge in non-severe RA including remission, in agreement with previous observations made with US and MRI (3-9).

Comparing the PET and the US findings, there were twice as many PET/CT positive joints as US-positive joints. Furthermore, there was also clear evidence that PET/CT and US analysis of joints did not concur in remission. For example, out of the 22 patients in remission by DAS<sub>28</sub>-CRP, 12 were positive with both PET/CT and US, but at the joint level, only 10 of the 75 PET/CT-positive joints (5 wrists, 4 MCPs and one shoulder) were also US-positive. This divergence was also observed in patients in Boolean remission. In

other words, PET/CT was positive in a significant number of patients with no or low/moderate disease activity according to the current clinical scales, and was also positive in a significant number of joints that were not considered as inflamed according to clinical and US parameters. Two interpretations are possible for this observation. The first one would be a higher sensitivity of the metabolic measurements for identifying subclinical joint inflammation. Indeed, in inflammatory diseases, PET/CT incidental findings due to [<sup>18</sup>F]FDG accumulation is consistently associated with an enhanced glycolytic metabolism in inflammatory cellular infiltrates including activated macrophages, neutrophils and lymphocytes (30). We may therefore consider that hypermetabolic joints with normal US appearance are joints with an inflammatory component without proliferating synovitis or with a synovitis < 1 mm thickness, the cut-off retained. In a previous series of RA patients with severe disease activity, only 50% of the PIPs and 62% of the MCPs both tender and swollen were US-positive using the same cut-off (data not shown) (22). PET/CT analysis might therefore exhibit greater sensitivity than US. It is noteworthy that in the current series, the PET/CT-positive but US-negative joints within these 16 patients were mostly PIPs (31 joints in 7 patients) and MCPs (23 joints in 7 patients), joints typically involved in RA. X-ray analysis supports this hypothesis as 38% of the joints had signs of RA and 49% were normal. An alternative explanation would be to consider those joints and patients as false positive results of the PET/CT. It is indeed possible that the joints actually suffer from secondary (MCPs) or primary (PIPs) osteoarthritis. However, only 8/62 (13%) joints, 6 MCPs in 2 patients and 2 wrists in 2 patients had signs of OA. The radiological analysis is thus in favor of the first hypothesis but a longitudinal follow-up of the patients would be needed to provide definitive evidence. As a limitation, X-ray were only available for peripheral joints ((PIPs, MCPs and wrist) with systematic X-ray realisation, but not for larger joints (knee, elbow, shoulder).

## Conclusion

[<sup>18</sup>F]FDG PET/CT demonstrated a high specificity and negative predictive value compared to individual clinical evaluation of the joints. Furthermore, PET/CT is effective at differentiating “severe” from “non-severe” patients, although clinical remission was not associated with metabolic remission. Such issues are of high clinical relevance as PET/CT could possibly identify subclinical and infra-radiological inflammation worthy of treatment in order to prevent further irrevocable damages to the joints. Further studies are needed to ascertain whether this represents a clinically relevant activity of the disease or secondary degenerative changes.

## Abbreviations

RA: rheumatoid arthritis

LDA: low disease activity

DAS<sub>28</sub>: disease activity score 28-joint

US: ultrasonography

MRI: magnetic resonance imaging

<sup>18</sup>F-FDG PET/CT: <sup>18</sup>F-Fluorodeoxyglucose Positron Emission Computer Tomography

CSUV: cumulative standard uptake values

ESR: erythrocyte sedimentation rate

CRP: C-reactive protein

CDAI: Clinical Disease Activity Index

PtGA: Patient Global Assessment

PGA: Physician Global Assessment

VAS: Visual Analogue Scale

HAQ: Health Assessment Questionnaire

T: tender

S: swollen

T/S: tender or swollen

T&S: tender and swollen

SUVmax: maximum standardized uptake value

ROI: region of interest

MCP: metacarpophalangeal

PIP: proximal interphalangeal

CST: cumulative synovial thickness

SD: standard deviation

ICC: intraclass correlation coefficient

ROC: Receiver Operating Characteristic

DMARDs: disease-modifying antirheumatic drugs

ICC95%: 95% lower limit confidence

AUC: area under the curve

## Declarations

### **Ethics approval and consent to participate:**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the ethical committee of the university hospital of Liège (B70720108722). Informed consent was obtained from all individual participants included in the study.

### **Consent for publication:**

Not applicable

### **Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests:**

The authors declare that they have no competing interests

### **Funding:**

This work was supported by academic funding from “Fonds Léon Fredericq”, University of Liège, Belgium. “Fonds Léon Fredericq” had no implication in the acquisition or analyzing of the data.

### **Authors' contributions:**

CR performed the study, the US data acquisition, analyzed and interpreted the results wrote the manuscript and revised the manuscript critically. PF performed the PET-CT data acquisition, analyzed and interpreted the results and revised the manuscript critically. OM analyzed and interpreted the results, wrote the manuscript and revised the manuscript critically. NC performed the clinical evaluation and revised the manuscript critically. JH performed the X-ray data acquisition and revised the manuscript critically. LS and AA analyzed and interpreted the results, realized all the statistics analyses, and revised the manuscript critically. RH and MM designed the study, analyzed and interpreted the results, wrote the manuscript and revised the manuscript critically. All the authors approved the final manuscript for submission and publication. All co-authors take full responsibility for the integrity of the study and all parts of the final manuscript.

## Acknowledgement:

Not applicable

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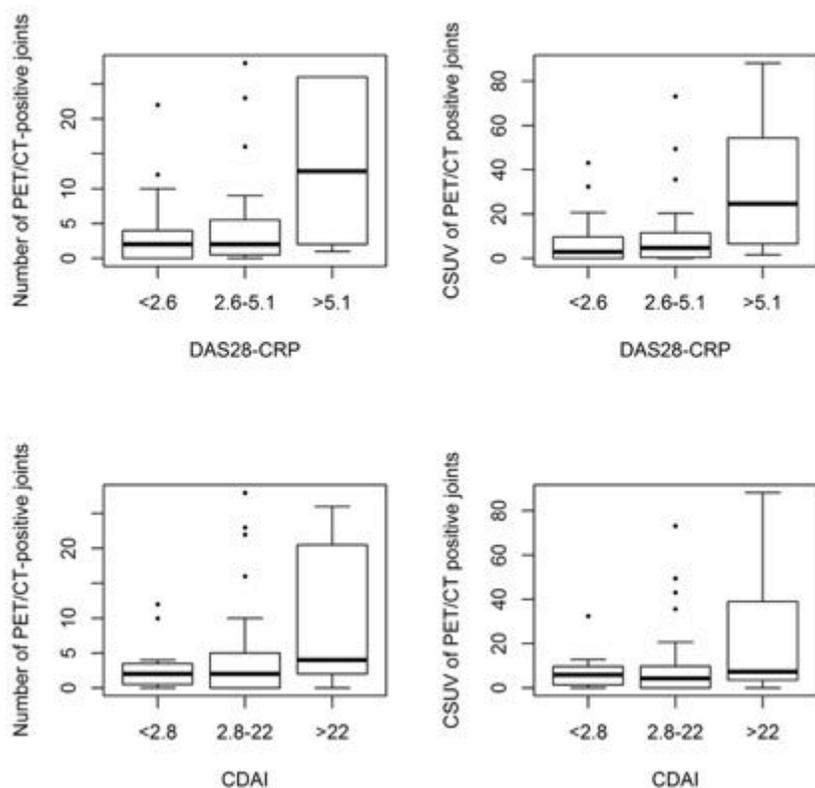
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## Figures



**Figure 1**

number of PET/CT-positive joints (left panels) and CSUV (right panels) according to disease activity categories based on DAS28-CRP (upper panels) or CDAI (lower panels). PET-CT: positron emission computer tomography. CSUV: cumulative standard uptake value. DAS: disease activity score. CDAI: clinical disease activity index. CRP: C-reactive protein.

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