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ORIGINAL ARTICLE

Opportunistic screening for osteoporosis using thoraco-abdomino-pelvic CT-scan assessing the vertebral density in rheumatoid arthritis patients

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Abstract

Introduction Screening for osteoporosis is crucial in rheumatoid arthritis (RA) patients. The aim of this study was to assess the value of thoraco-abdomino-pelvic CT-derived bone mineral density (BMD) results in L1, compared to dual energy X-ray absorptiometry (DXA) results for osteoporosis screening in rheumatoid arthritis patients.

Methods Consecutive RA patients who underwent a CT-scan and DXA within a 2-year period were retrospectively included. The CT sagittal images were then evaluated for vertebral fractures from T4 to L5 using the Genant classification. The CT-attenuation values (in Hounsfield units (HU)) of trabecular bone in L1 were measured on axial images and compared to the DXA results.

Results This study included 105 patients (mean age 61.1 years (± 9.5), 78.1% women). There were 28 patients (26.7%) with DXA-defined osteoporosis and 32 (30%) with osteoporotic fractures (vertebral and/or non-vertebral). The CT assessment indicated that the mean (SD) vertebral L1 attenuation was 142.2 HU (± 18.5). The diagnostic performance for the vertebral CT-attenuation measurement was acceptable: the AUC was 0.67 for predicting osteoporotic fractures and of 0.69 for predicting vertebral fractures. Among patients with osteoporotic fractures, there were 23 (74%) patients categorized as osteoporotic with a L1 CT-attenuation of 135 HU or less, whereas there were only 13 patients (42%) identified by DXA.

Conclusion CT offers a combined opportunistic screening for osteoporosis by assessing both vertebral fractures and bone density on routine CT-scans. This approach may be particularly interesting for RA patients with a high osteoporosis risk.

Keywords Bone mineral density · CT-attenuation · DXA · Osteoporosis · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is the most common form of inflammatory rheumatism [1]. RA is characterized by chronic and systemic inflammation, which is known to promote bone loss. Osteoporosis is the main extra-articular complication of RA and has a multifactorial underlying mechanism (proinflammatory cytokines, menopausal status, and glucocorticoids) [2]. The main consequences of reduced bone mineral density (BMD) are osteoporotic fractures, which are associated with pain, disability, and death [3]. The prevalence of vertebral fractures is nearly 22% in rheumatoid arthritis [4].

Although osteoporosis is a common complication of RA, it remains substantially underdiagnosed and undertreated [5]. Planned screening for osteoporosis may involve various imaging techniques. Dual-energy X-ray absorptiometry (DXA) is widely recognized as the reference standard for diagnosing osteoporosis [6]. Therefore, alternative techniques are needed to increase osteoporosis detection.

Vertebral fracture assessment (VFA) is often described as an opportunistic screening technique for osteoporosis in RA patients [7, 8]. It offers a global evaluation of the vertebral morphology and can detect unknown vertebral fractures.

Measuring BMD by using quantitative computed tomography (QCT) was suggested in 1970 [9]. In Gausden et al. systematic review of the MEDLINE database performed in 2016 [10], 10 studies correlated HU (Hounsfield units) measurements of trabecular bone with DXA-based bone assessment. This is a wide subject of investigation because there is an

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enormous patient volume of body CT scanning currently performed in older adults for a wide variety of clinical indications in the general population [11]. International Society for Clinical Densitometry (ISCD) Official Positions mentioned that CT values could be used instead of BMD values, under the assumption of a constant calibration and a stable scanner [12]. Official Positions also highlight that the generalization of screening thresholds reported in previous studies [9, 13] needs further validation.

Systematic screening for osteoporosis is often forgotten in the follow-up of RA patients, who regularly undergo many exams for their disease and comorbidities [14]. In this context, patients receive CT-scans for various clinical indications (intercurrent diseases) or before starting biological disease-modifying anti-rheumatic drugs (bDMARD). However, the proportion of patients imaged with CT-scan during RA follow-up is not known. Many studies have raised the possibilities to estimate BMD using diagnostic CT images [10, 11, 15–18], providing the opportunity to measure bone attenuation values of vertebral bodies expressed in Hounsfield units (HU) by using a region-of-interest (ROI) measurement. The ROI measurement is integrated onto the axial plane of the first lumbar vertebra (L1) body, which is mainly composed of trabecular bone and is preferentially affected by osteoporosis. The L1 is used in this method because it is easily identified as the first non-rib-bearing vertebra and because focusing on this vertebra appears to be the most relevant technique [13, 16].

There are currently no studies in a RA population that assess this method of opportunistic screening for osteoporosis. Considering that CT-attenuation values could be machine-specific and that relevant thresholds seem to differ according to the osteoporotic risk of the population, we first determined our own threshold in this study.

The aim of this study was to assess the value of thoraco-abdomino-pelvic CT-derived BMD assessment in L1 compared with DXA for osteoporosis screening in rheumatoid arthritis patients.

Materials and methods

Patient cohort

The study group consisted of 105 consecutive RA patients who fulfilled the ACR/EULAR criteria [19] for the classification of RA. We reviewed the cases of patients eligible for bDMARD between January 2010 and December 2014. All patients who underwent a thoraco-abdomino-pelvic CT and also received a DXA test within 2 years (before or after the CT) were retrospectively included. CT examinations were acquired during the course of routine care using multi-detector CT systems.

The detailed data collected from all subjects included the following: demographics, such as age, gender, smoking and alcohol status, menopausal status, body height, weight and body mass index (BMI), and history of osteoporotic fractures; RA clinical characteristics, such as disease duration, rheumatoid factors (RF) or ACPA status, CRP and ESR, joint erosion, and disease activity score (DAS 28); and history of RA treatments, such as glucocorticoids, csDMARD (conventional synthetic disease modifying activity drugs) and bDMARD.

Three profiles of patients were determined as follows: those with DXA-defined osteoporosis, patients with osteoporotic vertebral fractures (detected on CT-scans), and patients with osteoporotic fractures (vertebral and/or non-vertebral).

CT-scan procedure

TAP CT-scans were routinely done using standardized procedure (GE Medical Systems LightSpeed VCT; 120 kV; 1.25–5 mm axial slices and 3 mm sagittal slices; systematic use of IV contrast in the absence of contraindications, daily calibration controls).

Attenuation assessment on CT-scans

We retrospectively assessed the CT images. The L1 vertebra was identified in the axial plane and viewed in bone tissue windows. We assessed the vertebral BMD by placing the largest elliptical ROI over an area of the central part of the vertebral body trabecular bone of L1, excluding the cortical margins to prevent volume averaging, as previously described [13, 16, 20] and as shown in Fig. 1. This process was sequentially performed for all patients by a single observer (who was blind to the patients' DXA scores), ensuring that the same region is consistently evaluated in different scans. We avoided placing the ROI over areas of attenuation heterogeneity, such as the posterior venous plexus, focal heterogeneity, lesion or fracture (in case of fracture of L1, the ROI is placed on L2), to avoid distortion of the attenuation measurements. The mean CT-attenuation for each patient was measured in HU.

The inter-observer concordance of the technique was previously evaluated on 30 CT-scans by two independent readers in an independent study. The kappa coefficient was excellent at 0.933 ($p = 0.0001$) [21].

Vertebral fractures assessment on CT-scans

We also assessed the presence of vertebral fractures by using multiplanar reconstructions from sagittal CT views of the thoraco-lumbar spine. Each vertebra between the fourth thoracic vertebra (T4) and L5 was judged and assigned a grade using the Genant visual semi-quantitative method [22] as shown in Fig. 2. All vertebral fractures defined by a grade ≥ 1 were recorded and verified in a separate reading session for final confirmation.

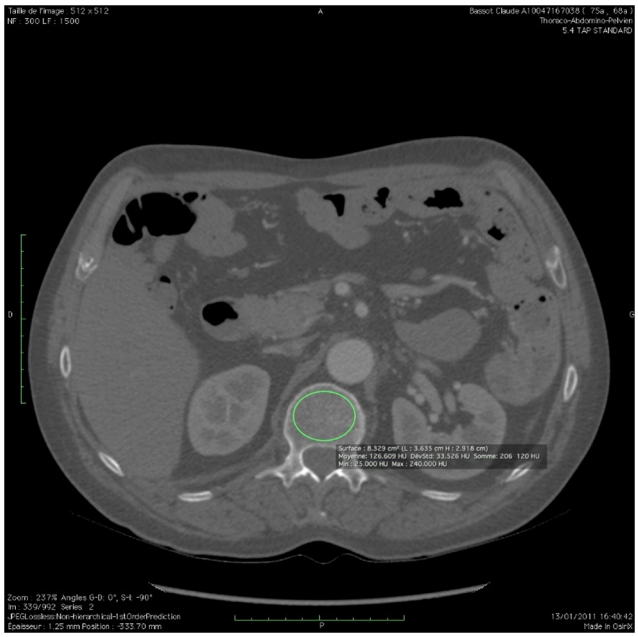

Fig. 1 Axial image through the vertebral body of L1 on a thoraco-abdomino-pelvic CT-scan. Placement of the region of interest within the trabecular bone and assessment of the CT-attenuation value in Hounsfield units (126.6 HU in this example)

BMD assessment by dual-energy X-ray absorptiometry

DXA of the lumbar spine and proximal femur was performed using standard techniques on a Lunar Prodigy densitometer *(Advance* PA + 301010, enCORE, version 14.10.022) (Madison, WI, 53718, USA). The cutoff for osteoporosis was set as a T-score ≤ -2.5 at any measured location as per common practice. Osteopenia was defined as a T-score between -1 and -2.5, and normal BMD was defined as a T-score ≥ -1 using the lowest reported T-score [6]. Furthermore, in a substantial subset of cases, the T-scores for one of the two central sites were not reported for various technical reasons. At least one valid reported T-score for the lumbar spine or hips was required for study inclusion.

Statistical analysis

The baseline sociodemographic and clinical characteristics are described as the mean ± standard deviation (SD) for continuous variables and as a percentage for categorical variables. We determined the thresholds of L1 CT-attenuation (in HU), defined as the 75th percentile of the distribution of BMD, for each of the following profiles of patients: DXA-defined osteoporosis, osteoporotic vertebral fractures (detected on CT-scans), and osteoporotic fractures (vertebral and/or non-vertebral). We then determined the diagnostic accuracy by calculating the sensitivity, specificity, positive predictive (PPV) and negative values (NPV), and the area under the curve (AUC) for each threshold. Associations between RA disease phenotypes and CT vertebral attenuation measurement were evaluated using linear regression model.

Statistical analysis was performed using SAS 9.4™ (SAS v9.4, SAS Inst., Cary, NC, USA).

Results

Characteristics of the study population

There were 105 patients (82 women) with a mean (SD) age of 61.1 (± 9.5) years evaluated in this study. The details of the clinical, therapeutic, biological, and radiological parameters for all patients are reported in Table 1. The CT assessment showed that the mean (SD) vertebral L1 attenuation was 142.2 HU (± 18.5) in the population. According to the DXA results, 28 patients (26.7%) had osteoporosis and 36 (34.3%) were osteopenic. The remaining 41 (39%) cases had normal BMD. Vertebral fractures were found on CT-scans in 18 (17.1%) patients. There were 32 patients with osteoporotic fractures (14 had only non-vertebral fractures, 13 had only vertebral fractures, and five had both vertebral and non-vertebral fractures).

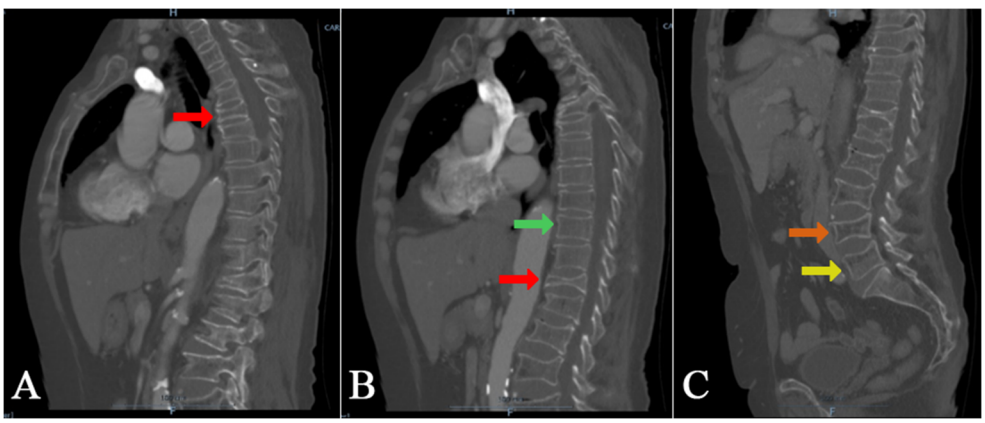

Fig. 2 Sagittal reconstructions from CT views of the thoraco-lumbar spine (**a**, **b**: thoracic view, **c**: abdominal view). Grade 3 fractures of T5 and T12 (red arrows), grade 2 fracture of L4 (orange arrow), grade 1 fracture of L5 (yellow arrow), normal vertebrae (green arrow)

Table 1 Characteristics of RA patients

		N (%)	Mean (± SD)
Age			61.1 (9.5)
Female gender (%)		82 (78.1)	
RA disease duration (years)			13.4 (11.5)
RF positive		80 (76.9)	
ACPA positive		88 (85.4)	
Erosions		83 (79)	
DAS 28			4.8 (1.1)
	< 2.6	1 (0.96)	
	2.6–3.2	7 (6.7)	
	3.3–5.1	57 (54.8)	
	> 5.1	39 (37.5)	
CRP (mg/L)			20.1 (29.6)
ESR (mm)			32.8 (22.8)
Glucocorticoids[a]		86 (81.9)	
Glucocorticoids dose (mg/day)			7.8 (7.4)
Methotrexate[a]		99 (94.2)	
Other csDMARD[b]		57 (54.3)	
bDMARD[a]		46 (43.8)	
Number of previous bDMARD			0.8 (1.3)
Smoking, yes[a]		51 (51)	
Alcohol, yes[a]		5 (5.2)	
BMI (kg/m^2)			27.5 (6.6)
Menopausal women		71 (86.6)	
Previously known vertebral fracture		7 (6.7)	
Previous non-vertebral fracture[c]		19 (18.3)	
Patients with vertebral fractures on CT		18 (17.1)	
Patients with DXA-defined osteoporosis		28 (26.7)	

SD, standard deviation; *RA*, rheumatoid arthritis; *RF*, rheumatoid factors; *ACPA*, anti-citrullinated protein antibody; *DAS 28*, disease activity score 28; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *csDMARD*, conventional synthetic disease-modifying anti-rheumatic drug; *bDMARD*, biological disease modifying anti-rheumatic drug; *BMI*, body mass index

[a] Current or previous

[b] ARAVA®, SALAZOPYRINE®, or PLAQUENIL®

[c] Major osteoporotic fractures (humerus, ribs, femoral neck, distal femur, proximal tibia)

Table 2 CT-attenuation values in L1 and fracture status according to DXA results

	All patients with CT-attenuation measurement (*N* = 101)	Patients with normal BMD on DXA (*N* = 40)	DXA-defined osteopenic patients (*N* = 33)	DXA-defined osteoporotic patients (*N* = 28)
Mean CT-attenuation, HU (SD)	142.2 (18.5)	168 (53.1)	134.2 (33.3)	113.7 (36.4)
Patients with vertebral fractures on CT (N)	17	0	9	8
Patients with osteoporotic fractures[a] (N)	30	5	12	13

CT, computed tomography; *HU*, Hounsfield unit; *SD*, standard deviation; *DXA*, dual energy X-ray absorptiometry; *BMD*, bone mineral density

[a] Vertebral or non-vertebral fractures

BMD assessment by CT-attenuation

There were 105 TAP CT-scans analyzed (102 with IV contrast administration). The CT vertebral attenuation was determined for 101 patients (four CT-scans could not be assessed for technical reasons; one of these four patients had an osteoporotic vertebral fracture). The results are presented in Table 2.

There were 31 patients with osteoporotic fractures (among 101 patients with available CT-attenuation results): 23/31 (74%) patients were osteoporotic using the threshold proposed by Pickhardt et al. (L1 attenuation ≤ 135 HU) [16] and only 13/31 patients (42%) were considered to be osteoporotic according to the DXA definition.

Among RA clinical characteristics and history of treatment, RA disease duration was the only factor associated with a CT-attenuation variation. Each additional year of disease was associated with a decrease in CT-attenuation value ($\beta = -1.31$ HU) (95% CI, −2.14 to −0.49).

Threshold analysis for osteoporosis detection

In DXA-defined osteoporotic patients, the vertebral L1 attenuation was 134.6 HU or less (95% CI, 124.6 to 156) in 75% of these patients. Figure 3 a shows the cumulative proportion of osteoporotic patients based on the CT-attenuation results. The data indicate that 75% of patients with vertebral fractures detected on CT-scans had a L1 CT-attenuation of 131 HU or less (95% CI, 121.4 to 155.9). Finally, in patients with any osteoporotic fractures, the vertebral L1 attenuation was 139.3 HU or less (95% CI, 125.7 to 150.5) in 75% of these patients. Figure 3 shows the cumulative proportion of patients with vertebral fractures detected on CT-scans (b) and the incidence of patients with osteoporotic fractures (c) according to the CT-attenuation results. Table 3 summarizes the sensitivity, specificity, PPV, NPV, and AUC for each group of patients at the 75th percentile threshold.

Using a higher sensitivity of 80%, the CT-attenuation thresholds for vertebral fractures and osteoporotic fractures were 139.3 HU and 142.8 HU, respectively. In this case, the specificity values were 51% and 49%, respectively.

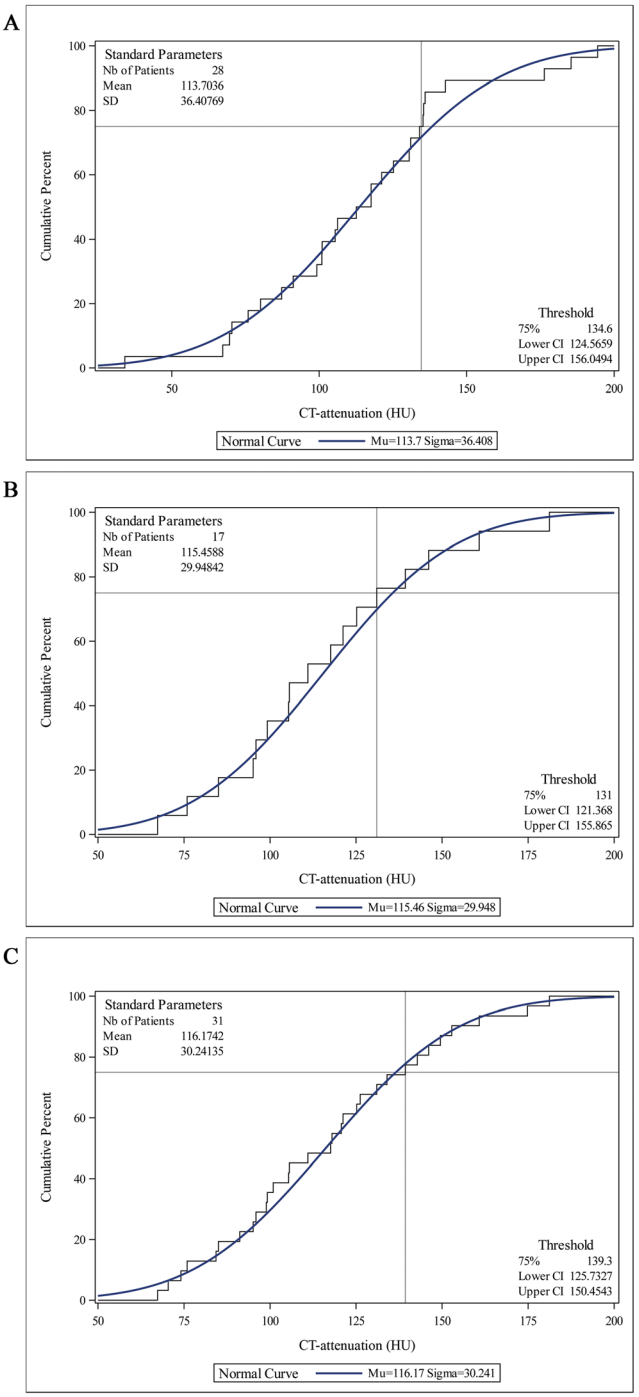

Fig. 3 Cumulative proportion of osteoporosis (**a**), osteoporotic vertebral fractures detected on CT-scans (**b**), and osteoporotic fractures (**c**) according to the L1 CT-attenuation results. CT, computed tomography; HU, Hounsfield unit; SD, standard deviation; CI, confidence interval

Discussion

This is the first study assessing the value of thoraco-abdomino-pelvic CT-attenuation for osteoporosis screening in RA patients. Many previous studies have demonstrated the interest of assessing lumbar trabecular BMD via a simple ROI attenuation measurement on routine CT [10, 13, 15–18, 20, 23, 24].

Our findings in RA patients suggest that the bone density values measured using CT have a moderate correlation with the DXA results. Then, CT-assessed BMD may complement DXA for assessing deteriorating bone quality. Vertebral fractures frequently occurs in patients with osteopenic or normal T-scores [16]. These findings highlight a frequent difficulty of DXA, which overestimates BMD in cases with degenerative changes [25]. The 3D nature of CT data limits the potential misclassification problem in degenerative and scoliotic spines and minimizes the false-negative results linked to

Table 3 Performance values of CT-attenuation thresholds at the 75th percentile

	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
CT-attenuation threshold for DXA-defined osteoporosis (134.6 HU)	0.75	0.62	0.43	0.87	0.68 (0.58–0.78)
CT-attenuation threshold for vertebral fractures detected on CT-scans (131 HU)	0.76	0.62	0.29	0.93	0.69 (0.58–0.81)
CT-attenuation threshold for osteoporotic fractures (139.3 HU)	0.77	0.56	0.44	0.85	0.67 (0.57–0.76)

CT, computed tomography; *DXA*; dual energy X-ray absorptiometry; *HU*, Hounsfield unit; *PPV*, positive predictive value; *NPV*, negative predictive value; *AUC*, area under the curve; *CI*, interval confidence

vertebral osteoarthritis [26]. Moreover, the CT-based technique directly measures trabecular bone density and the results may better reflect the true BMD status than DXA. Our findings confirm the results of Pickhardt et al. that suggest that CT vertebral attenuation has a high correlation with vertebral fractures [16]. Our study is the first report to highlight the correlation between L1 CT-attenuation and osteoporotic fractures in general (vertebral and non-vertebral). In our study, 74% of patients with a prior history or current osteoporotic fractures were well categorized as osteoporotic using the CT-attenuation results, whereas only 42% of patients were categorized as osteoporotic using DXA.

This technique could be used in practice depending on the clinical objectives. Pickhardt et al. suggested that the detection of a very low BMD by CT (< 100 HU) could allow for a faster identification of high-risk patients who require further osteoporosis investigation. However, high L1 CT-attenuation (> 200 HU) could make DXA unnecessary [16]. Between 100 and 200 HU, various thresholds could be considered, depending on the a priori risk of osteoporotic fracture in the studied population. In the cohort of patients with abdominal CT-scans for various clinical indications, Pickhardt et al. found a sensitivity of 76% and specificity of 75% at a 135 HU threshold for distinguishing osteoporosis [16]. These results are consistent with our findings. However, we suggest that in a high-risk cohort, such as rheumatoid arthritis patients [27, 28], the aim of the screening technique should be to minimize false-negative results by using a higher sensitivity threshold (at 80% for example). In our RA patients, the lower specificity observed compared to the general population [16] is probably related to the multifactorial process of osteoporosis in RA, including both quantitative (decrease of BMD) and qualitative (alterations of microarchitecture) bone tissue disorders [29, 30].

The use of CT-attenuation provides a simple and accessible way of broadening access to BMD measurements in this population. This technique requires a negligible amount of training and time, has acceptable intra and inter-observer reproducibility [20], and can be applied prospectively. It adds no cost and requires no additional time for examination, equipment, or radiation exposure for patients. Previous studies showed that the overall performance for predicting osteoporosis is similar for enhanced and unenhanced scans [31]. Finally, the vertebral attenuation results do not suffer from advances in CT technology or procedures and do not change according to the CT window used for viewing [16]. These findings show that the CT-attenuation technique is a reliable method. Moreover, one advantage of CT compared to DXA is its ability to accurately identify unsuspected osteoporotic vertebral fractures [32], which clearly diagnoses osteoporosis independent of the patient's DXA T-score.

This is the first study in RA patients and could contribute to establish specific thresholds for predicting osteoporosis in this high-risk population. Moreover, in our CT-based study, all patients had a correlative DXA performed within 2 years of the CT used for BMD measurements. All of the DXA assessments were performed on the same osteodensitometer, which decreased the measurement biases. We used a manual ROI-placement method on CT images to avoid distortion of the attenuation measurements.

There are several limitations to our study. First, there was a selection bias inherent in the study because we included a convenient sample of patients who received DXA and CT for a clinical indication. Second, there were four CT-attenuation results lost due to the retrospective analysis of CT-scans. Last, this was a single-center study conducted on a limited number of patients. As mentioned in ISCD Official Positions, the generalization of screening thresholds reported in our study and in previous works needs further validation. For the identification of subjects with high or low fracture risk according to low (or high) CT-derived BMD measures, machine-specific cutoff values are required [7, 8]. In the special RA population, thresholds and diagnostic performance measures require larger cohorts and external validation.

BMD assessment is a serendipitous screening potential offered by CT-scans. This technique provides a combined assessment of vertebral fractures and density on routine thoraco-abdomino-pelvic CT-scans. This opportunistic strategy will allow clinicians to increase the detection of osteoporosis in RA patients and to initiate appropriate management in order to reduce the likelihood of any other osteoporotic fracture in the future. These changes could limit the high morbidity and mortality of osteoporosis in this population [33]. We did not assess the potential benefits and economic implications of using CT for detecting osteoporosis. However, the technique

is expected to yield substantial health cost savings. CT-attenuation measurements could be automated or computer-assisted in the future, and the data could be incorporated into fracture risk assessment tools such as the FRAX® tool [34]. Automating the process could allow for large-scale opportunistic screening for osteoporosis in rheumatoid arthritis patients and in the general population. Furthermore, prospective studies could also determine the predictive value of routine CT for future fractures.

Compliance with ethical standards

Conflicts of interest None.

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