

Imaging in the preclinical phases of rheumatoid arthritis

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Received on April 11, 2019; accepted in revised form on July 8, 2019.

Clin Exp Rheumatol 2020; 38: 536-542

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EXPERIMENTAL RHEUMATOLOGY 2020.

Key words: ultrasonography, computed tomography, magnetic resonance imaging, rheumatoid arthritis, prevention

ABSTRACT

There is growing evidence that the development of rheumatoid arthritis (RA) is a multistep process. The European League Against Rheumatism (EULAR) identified different phases before the onset of RA, from the presence of genetic and environmental risk factors for RA, towards clinically suspected arthralgia and undifferentiated arthritis. Currently, a new definition of “window of opportunity” is emerging; this states that the window could even lie in preclinical phase of RA, preceding diagnosis or fulfillment of classification criteria for RA. In this scenario, the detection of subclinical inflammation by imaging tools could be useful together with autoantibodies and joint symptoms to better stratify people at high risk for developing RA and to plan prevention trials in high-risk cohorts. This review will give an overview on the use of computed tomography, magnetic resonance imaging and ultrasonography in the preclinical phases of RA.

Introduction

Rheumatoid arthritis (RA) is a debilitating, chronic inflammatory autoimmune disease. Bone erosions, especially at the bare areas of joints, are common for RA (1); synovitis and tenosynovitis, as well as bone marrow oedema can be detected frequently even at very early stages of the disease (2–6). Autoantibodies characteristic for RA such as rheumatoid factors (RF) and/or anti-citrullinated protein antibodies (ACPA) may precede the clinical manifestation of RA for years, and they have a predictive value for the manifestation of clinical arthritis (7, 8). There is growing evidence that the development of RA is a multistep process. The European League Against Rheumatism (EULAR) identified different phases (9):

1: presence of genetic and environmental risk factors for RA, 2: systemic

autoimmunity associated with RA, 3: symptoms without clinical arthritis, recently defined as clinically suspect arthralgia (CSA) (8), 4: unclassified arthritis and 5: RA (9, 10). The identification of these phases is an essential step to plan prevention trial in people at high risk for RA development. In this scenario, the detection of subclinical inflammation by imaging tools could be useful together with autoantibodies and joints symptoms to better stratify people at high risk for RA development. This review will give an overview on the use of imaging in the patient's journey towards the development of RA (Fig. 1).

Computed tomography

Computed tomography (CT) is a slice imaging technique enabling excellent three-dimensional visualisation of bone structure due to its high contrast between soft tissue and bone. Moreover, it is not prone to superimposition artifacts like conventional radiography (CR). Being more sensitive than CR and magnetic resonance imaging (MRI) regarding detection of alterations of bone structure makes CT suitable as gold standard for measuring bone erosions (11) (Fig. 2). On the other hand, CT does use radiation, which might be one of the reasons why conventional CT (cCT) is usually not widely being used for assessment of preclinical arthritis, strict radiation laws limiting a somewhat all too carefree use of radiation in a group of patients, in which other imaging techniques such as MRI or ultrasonography (US) might be more advantageous to use. CCT might however be helpful in early arthritis: Peluso *et al.* used cCT as a reference method for comparison with three-dimensional ultrasound (3DUS) in a cohort of early arthritis patients without radiographic evidence of bone erosions. CCT could detect 32 erosions in eleven patients

Competing interests: none declared.

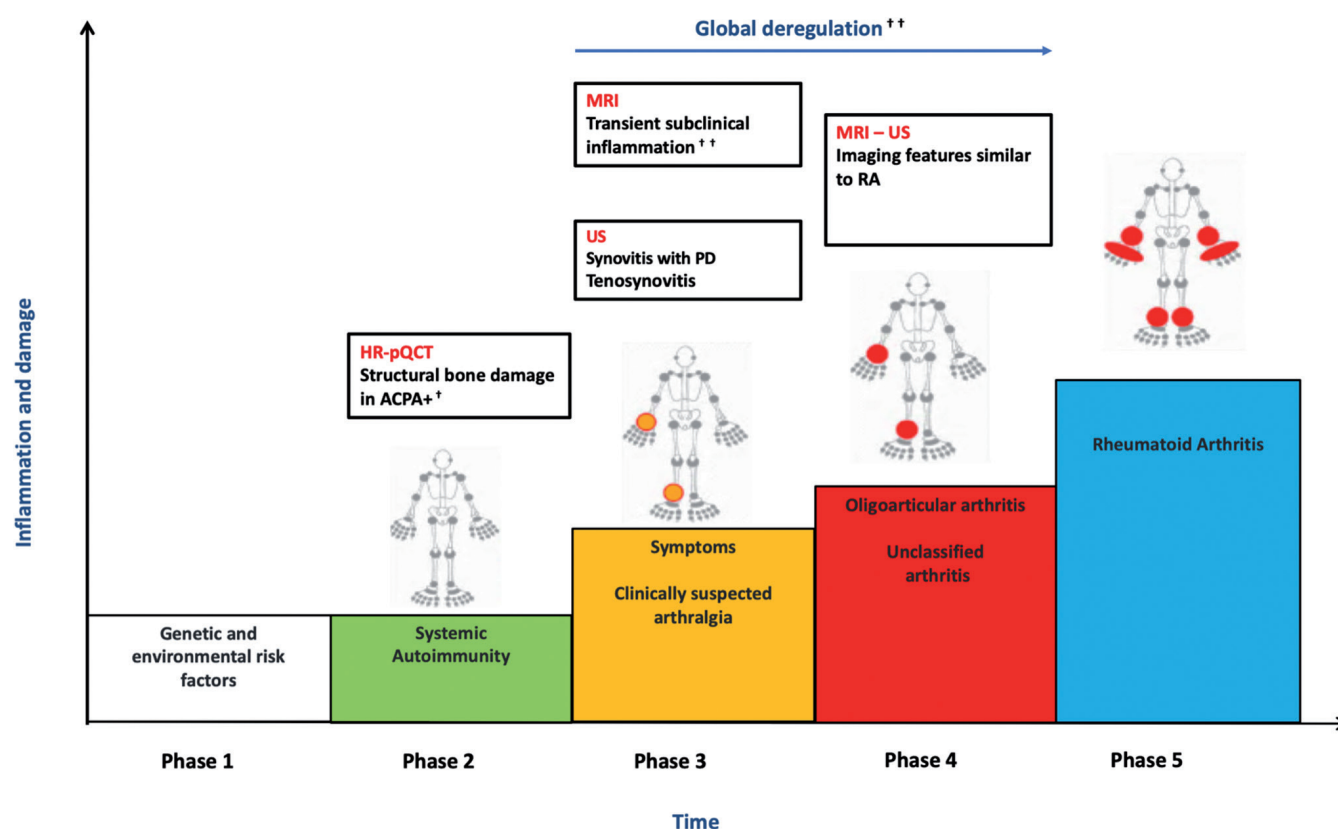


Fig. 1. The detection of inflammation and damage by imaging tools in the preclinical phases of RA.

[†]Kleyer *et al.* *Ann Rheum Dis* 2014; 73(5): 854-60; ^{††}Ten Brick RM *et al.* *RMD Open* 2018; 4: e000748. Figure 1 adapted with permission from van Steenberg HW *et al.* *Arthritis Rheum* 2013; 65: 2219-32.

and found expectedly more frequently erosions in the wrists and in the 3rd and 4th metacarpophalangeal (MCP) joints, since these were more accessible for cCT than for 3DUS (12). Combining CT to positron emission tomography (PET) offers clear advantages over use of CT alone with regards to therapy monitoring, disease quantification and detection of subclinical disease activity. However, costs and exposure to radiation is increased compared to cCT. First described in 1979 (13), the PET tracer [¹⁸F]-Fluoro-deoxy-glucose (FDG) is still the most frequently used PET tracer in daily clinical practice. [¹⁸F]-FDG is being taken up *inter alia* by cells with a high metabolic rate, such as inflammatory cells in the synovium (14). In 2012 Roivainen *et al.* (15) examined a cohort of 17 active early arthritis patients that were starting combination therapy with methotrexate, sulfasalazine, hydroxychloroquine, and low-dose glucocorticosteroids with [¹⁸F]-FDG/CT at baseline, as well as after week two and four after therapy onset. As out-

come parameters standardised uptake values (SUV), fractionised uptake rates (FUR), and glucose uptake rates (GU) were used for PET, compared to clinical (DAS28), and laboratory parameters (erythrocyte sedimentation rate, ESR, and C-reactive protein, CRP). Already two weeks after therapy onset SUV was significantly reduced in 76% of patients, and in 81% of patients from baseline to week 4. Moreover, the percentage 18F-FDG uptake values from baseline to week two correlated with DAS28 at week twelve; changes in ESR and CRP were positively associated with changes assessed by PET. The authors therefore suggested that [¹⁸F]-FDG/CT might support prediction of therapy response very early after therapy initiation. PET/CT might even also be relevant for the detection of subclinical arthritis. Recently, Gram *et al.* presented the case of a 67-year-old RF and ACPA-positive male patient with arthralgia for two years, but without clinical arthritis or any signs of pathology in US (16). The group applied a derivative of PET/CT us-

ing a tracer specific for bone metabolism, [¹⁸F]-sodium fluoride ([¹⁸F]-NaF). The patient showed FDG-uptake in a couple of joints, but increased NaF-uptake in multiple joints. Six months after the initial PET scan the patient manifested highly active RA. These findings suggest that [¹⁸F]-NaF might be a valuable tool for the detection of subclinical arthritis in patients without clinical joint swelling. High-resolution peripheral quantitative CT (HR-pQCT) is a comparatively novel variety of CT using a nominal isotropic voxel size of 82µm; the applied radiation dose for MCPs adjusted for whole body dose is very low (maximum around 15µSv for a male adult hand). Due to a very high soft tissue to bone contrast bone is depicted meticulously, while soft tissue depiction is less pronounced. The technique is still undergoing validation as an imaging outcome parameter for clinical studies (17), but quantification algorithms are underway that allow for a more or less user-independent volumetric quantification of bone erosion

volume in early RA. Peters *et al.* recently could show good reproducibility of their algorithm for bone erosion volume assessment; reproducibility of parameters of bone microstructure and bone density was excellent with ICCs ≥ 0.84 (18). These results are promising, since bone in early arthritis patients should be closely monitored for development of structural damage. The bare area of MCP joints might be a predilection site for bone erosions in inflammatory arthritis, especially the Cortical Micro-Channels (CoMiCs) System may play a crucial role: early RA-patients showed significantly more CoMiCs compared to elderly healthy volunteers > 65 years of age ($p=0.015$) (19). HR-pQCT is even able to show earliest bone changes in ACPA-positive patients without any musculoskeletal complaints: Kleyer *et al.* examined the 2nd and 3rd MCP joints of 15 ACPA positive (ACPA+) individuals and 15 healthy controls with HR-pQCT (20). Bone erosions were not detected, but bone mineral density as well as cortical thickness were significantly reduced in the ACPA+ group ($p=0.044$). Measures of trabecularity did not show any difference between the groups. Cortical porosity was more prevalent in the ACPA+ group than in the ACPA negative group ($p=0.0005$). These findings imply that structural bone alterations might start earlier than clinical manifestation of arthritis in ACPA-positive individuals (Fig. 2). As placebo-controlled phases in clinical studies are getting shorter, and since there seems to be a window of opportunity for treatment or even prevention of early RA, it is important to employ highly sensitive imaging techniques such as HR-pQCT that are able to visualise very subtle changes in bone micro architecture, even before more obvious changes such as bone erosions have occurred.

Magnetic resonance imaging

MRI is a sensitive imaging modality that allows detailed assessment of inflammation as well as structural damage in RA, with an excellent content validity where findings are highly correlated to intra-articular macroscopic alterations in the joint of RA patients (21).

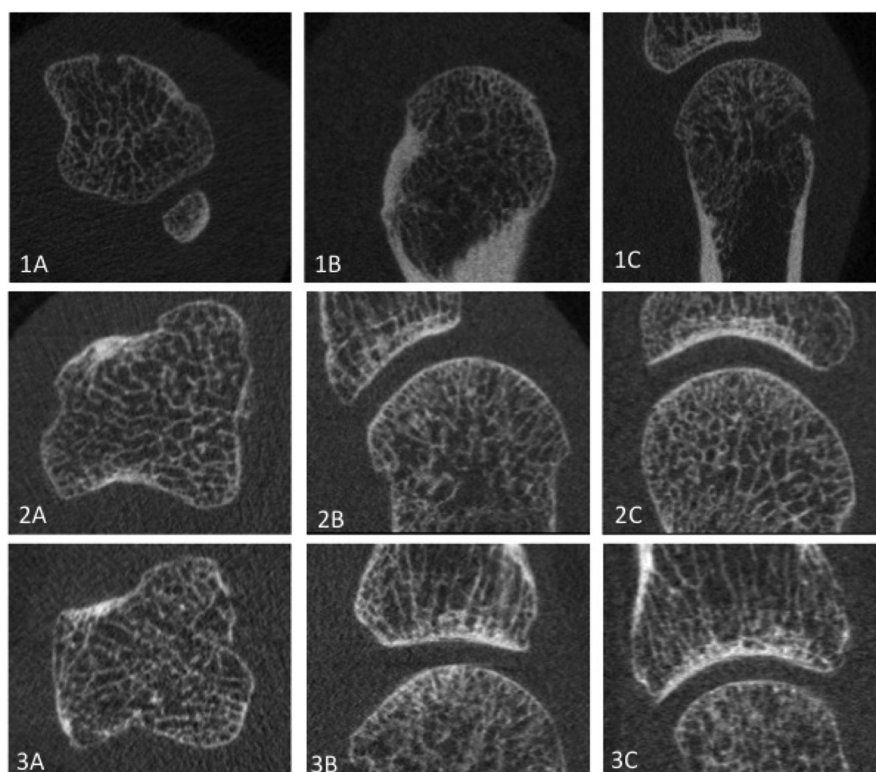


Fig. 2. Three cases visualised by HR-pQCT imaging.

Case 1: 36 year old female patient with rheumatoid arthritis. Metacarpophalangeal joint is depicted in axial (1A), sagittal (1B), and coronal (1C) plane; a clearly margined erosion is seen in the dorsal quadrant. Note, that erosion in the third plane is not visualised as a cortical break, but as absence of trabecular structure. Bone structure appears coarse (periarticular osteopenia).

Case 2: 41-year-old female patient with undifferentiated arthritis for a few weeks. Metacarpophalangeal joint is depicted in axial (2A), sagittal (2B), and coronal (2C) plane. Bone structure appears normal.

Case 3: 39-year-old, ACPA+ female patient with arthralgia for several weeks. Metacarpophalangeal joint is depicted in axial (3A), sagittal (3B), and coronal (3C) plane. Bone structure appears coarse.

Compared to physical examination and CR, MRI is a more sensitive tool for identification of disease-related tissue damage because of its direct visualisation of synovitis, cartilage destruction, bone erosion, bone marrow oedema (BME), tenosynovitis, and surrounding soft-tissue structures (22) (Fig. 3 a-c). Moreover, MRI can detect subclinical inflammation in 66% of clinically non-swollen wrist joints and 27% of non-swollen MCP joints (23).

Recently, the important role of MRI has emerged in the differential diagnosis of unclassified early arthritis and is now recommended in litigious cases when RA diagnosis is still uncertain (21). The rationale behind this is that the presence of inflammation on MRI can predict the progression from undifferentiated arthritis (UA) to clinical RA (21, 24). In this context, validated scoring systems have been developed for MRI

to quantify inflammation and structural damage in clinical trials (25-27). The OMERACT RA MRI score (RAMRIS) is the most frequently used for hands and wrists with a semi-quantitative assessment of synovitis, bone erosion and BME. However, when using MRI for diagnosis purposes, it needs to be interpreted with caution and in correlation with the clinical context and physical examination. In fact, healthy (especially older) individuals can present with bone erosions and MRI-detected inflammation resembling to RA (28-30), although some erosion sites might be more specific for RA (such as grade ≥ 2 erosions, metatarso-phalangeal-5 and metatarso-phalangeal-1 erosions) (31). In preclinical phases of RA, several studies have been conducted using objective tools such as MRI in order to identify which patients with arthralgia will develop RA. A small cohort study



Fig. 3. Magnetic resonance imaging (MRI) of a 37-year-old female patient diagnosed with early RA. Fig. 1a: Gadolinium-enhanced MRI showing inflammatory/synovitic findings in the proximal interphalangeal and metacarpophalangeal joints (*) and in the carpal area (arrowhead), together with tenosynovitis (abductor pollicis longus muscle, tick arrow) and bone marrow oedema (distal ulnar head, thin arrow). Fig. 1b: Corresponding T1-weighted MRI and Fig. 1c: corresponding conventional radiograph of the same patient without pathologic findings in this early phase of the disease.

by Krabben *et al.* showed that the MRI-combined inflammation scores (BME and synovitis) on MRI were higher in the wrists of ACPA positive patients with arthralgia, as compared to controls (32). Another small pilot study by Gent *et al.* also found that baseline MRI synovitis was present in 93% of arthralgia patients with positive anti-citrullinated protein antibodies (ACPA), but only 43% of these patients developed RA after 3 years of follow-up (33). This study raised again the question of MRI specificity and thresholds: a synovitis score of 1 (RAMRIS system) may not always be associated with subsequent development of arthritis and could be found in healthy controls, likely related to degenerative changes. When a higher arbitrary predefined cut-off score (RAMRIS ≥ 3) was used to define a positive MRI in patients with clinically suspect arthralgia, 44% had subclinical MRI inflammation and 35% of these patients progressed to clinical arthritis after 4 months (34). However, baseline subclinical MRI inflammation could not determine which patients progressed to clinical arthritis. Also, initial symptoms and serology (ACPA, rheumatoid factor, acute phase reactants) were unable to differentiate patients with CSA, with and without MRI inflammation (34). The largest published MRI study to date by Van Steenberg *et al.*, us-

ing another definition of positive MRI and a longer follow-up period, showed that 31% of 150 patients, with CSA and a positive MRI, progressed to arthritis during 1 year and 71% of these patients were ACPA positive (35). Interestingly, inflammation on MRI was associated with progression to arthritis independently of ACPA, CRP and clinical factors (35, 36). In the longitudinal study made by Ten Brinck *et al.* that included 31 patients who converted from CSA to RA, increased tenosynovitis and synovitis scores on MRI were noted at CSA onset (earliest features) followed by increased synovitis and osteitis during the progression to clinically established RA (37). These findings on serial MRIs addressed also the chronological order of joint inflammation that seem to mainly start outside the bone and subsequently in the bone (osteitis). However, when the same authors studied the progression from CSA to inflammatory arthritis (IA) at the individual joint level, the majority of clinical synovitis (69%) were intriguingly not preceded by baseline subclinical inflammation at the same joint site (38). This observation supports the hypothesis of a systemic inflammatory deregulation rather than a localised exacerbating process. From a practical point of view, clear cut-offs and specific parameters are of crucial importance to avoid over-diagnosis and

differentiate subclinical inflammation from non-specific findings on MRI. In this context, a recent study by Boer *et al.*, was made to determine which MRI scores or findings are considered normal, and which reflect pathology (39). While testing different cut-offs for positive MRI, the “5% corrected definition”, indicating the presence of inflammation at a joint in $<5\%$ of healthy persons of the same age-category at the same location, resulted in reducing false positives MRI without affecting the sensitivity. In fact, MRI specificity to detect inflammation increased from 22% to 56% in CSA patients and from 10% to 36% in UA patients. Still, larger studies on healthy individuals are awaited to better specify the cut-offs and reach a data-driven definition of a positive MRI. Overall, MRI has been of increasing interest in the past two decades with growing evidence on its validity in the detection of subclinical inflammation in patients at risk of developing RA. While more studies are needed to clarify its practical use in the preclinical stages of RA, MRI is considered as a key research tool for the upcoming years and can be used in clinical practice when there is diagnostic doubt.

Ultrasonography

Despite the difference of the US machines used and the possible different level of experience of sonographers, published data support the value of using US in the management of patients with inflammatory arthritis (IA) (21). EULAR recommendations for the management of early arthritis suggest the use of US in case of doubtful synovitis at clinical examination, highlighting previous controlled studies suggesting a greater sensitivity of US than clinical examination in detecting synovitis, particularly in the knee and in small joints (40, 41). This diagnostic role of US in clinical practice was recently showed in a multicentre study, which aimed to map the way US is used in RA (42). This real-life setting study revealed that formulating a diagnosis was the second most common indication (after monitoring disease activity) for performing an US scan (42,43). Furthermore, it is interesting to note that sonographic find-

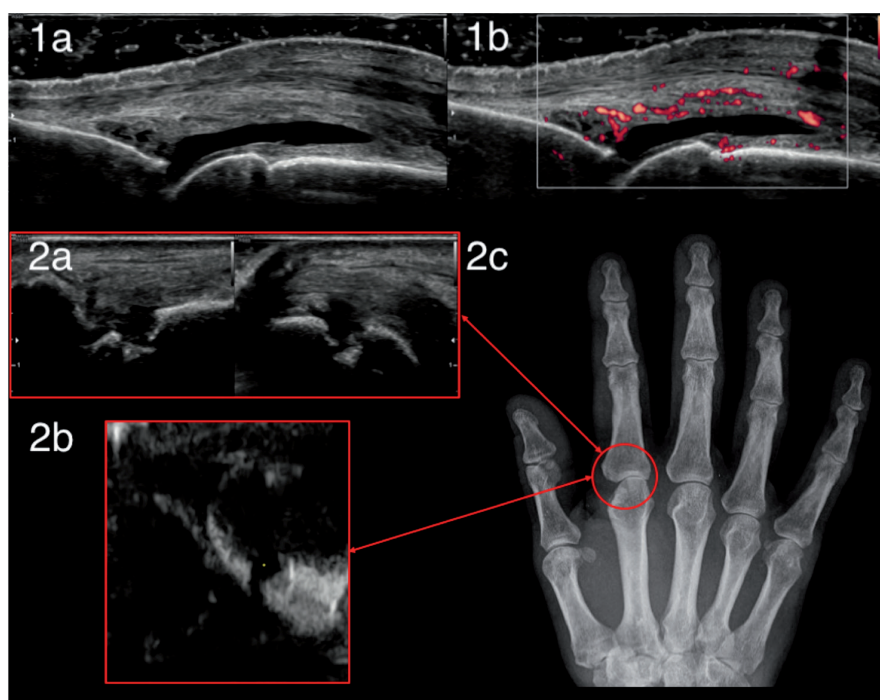


Fig. 4. 1a-b: ultrasonography of III MCP joint of a 40-year-old male diagnosed with early undifferentiated arthritis. 1a: Synovial hypertrophy with joint effusion; 1b: Synovial hypertrophy with PD signal. 2a-c: ultrasonography and conventional radiography of a 45-year-old male patient diagnosed with early RA (RF and ACPA positive). 2a: Erosion confirmed in two axes of the 2nd MCP joint right (US lateral scan); 2b: 3D US reconstruction of the erosion displayed in 2a; 2c: conventional radiography of the right hand with small erosion at 2nd MCP.

ings seemed to have better correlations with histologic scoring than serologic biomarkers of disease activity in the RA rabbit model, particularly at early stages (44). Under these premises, it clearly appears the use of US to detect signs of early inflammation and/or damage (*i.e.* erosions) in patients with or without clinical synovitis at high risk for development of RA (Fig. 4). Recently, Nam *et al* showed for the first time the predictive value of US for the development of IA (*i.e.* RA in over 85% of cases) in ACPA positive patients without clinical synovitis (45). This was seen both at a patient level and at an individual joint level (45). In this study, patients with baseline power Doppler (PD) and erosion in at least one joint were at higher risk of progression. As expected, the role of PD signal as predictor was afterwards confirmed along with morning stiffness and age at baseline as independently associated with the development of IA in patients with arthralgia without current or past synovitis (46). The same authors highlighted the positive and negative predictive value of US as predictor of IA (respectively, 26% and 89%), suggested

that US had an added value to identify which patients (*i.e.* patients without US synovitis) would not develop into IA (46). However, considering the low frequency of PD detection in the pre-clinical phases of RA, as highlighted by van Beers-Tas *et al.* in seropositive arthralgia patients (*i.e.* 4% of patients with at least one joint with PD), its role as predictor of RA needs to be further investigated (47). Recently, Horton *et al.* demonstrated the added value of US over clinical examination for identification of patients with undifferentiated arthritis (UA) at high risk for RA (48). The presence of at least five joints with GS \geq grade 2 appeared to discriminate patients with low or high risk of progression to RA, instead the presence of at least two joints with GS \geq grade 2 was clinically relevant in determining the future use of methotrexate (48). Furthermore, over the sonographic detection of synovitis, US defined tenosynovitis provided additional predictive data alongside ACPA positivity in a cohort of patients with early UA (49). In a pragmatic view of US using in patients with musculoskeletal inflammatory symptoms or

with UA, US could be more useful in the assessment of the clinically difficult ACPA negative arthritis (50). In arthralgia or UA patients, Freestone *et al.* suggested that the main role for US in the diagnosis of IA may be in the ACPA/RF negative patient group where there is still significant diagnostic uncertainty. PD positivity, GS synovitis = 3 and the presence of erosions were the selected sonographic variables that significantly changed the post test probability for the development of RA (51). The combination of US and serological findings seem to be the good way to characterise people at risk for developing RA. The best diagnostic performance in a retrospective cohort of arthralgia patients was provided by the presence of articular synovitis with PD grade ≥ 2 or by the presence of articular synovitis with PD grade ≥ 1 combined with RF and/or ACPA positivity (52). With these criteria they obtained a sensitivity of about 80% and a specificity of 92% for a diagnosis of RA (52). In conclusion, according to these preliminary evidences US confirms its role as predictor of RA development. Currently, the sonographic detection of inflammation could be an additional value in clinical practice particularly in seronegative patients with inflammatory symptoms. Conversely, the absence of US inflammation could be useful to identify patients with low risk to develop IA. The identification of the best predictive US variables for RA development and the scanning protocol needed are the necessary future steps to include US in the management of pre-RA for everyday practice but also to include such a technique in prevention clinical trials.

Conclusion

The definition of “window of opportunity” in RA is changing over the years, actually there is convincing data that earlier treatment (<6–12 months of disease duration) resulted in absolute lower radiographic joint destruction, slower progression rate and higher clinical remission rates (53). However, in the last years a “new definition” of “window of opportunity” is emerging, this states that the window could even lie in preclinical phase of RA, preceding di-

agnosis or fulfillment of classification criteria for RA (53). This possibility is not yet supported by evidence from randomised clinical trials, but different treatment management, including therapies with novel mechanisms of action could allow to prevent RA development (54). In this scenario, in which the traditional inflammatory symptoms/signs (e.g. morning stiffness, positive squeeze test) might not be present, the early visualisation of subclinical signs of inflammation, such as by HR-pQCT, MRI and US, can be crucial to assist the clinician in a better identification of people at high risk to develop RA.

Acknowledgements

The authors thank Sarah Manske (Associate Professor, McCaig Institute for Bone and Joint Health, Department of Radiology, Cumming School of Medicine, University of Calgary) and Cheryl Barnabe (Associate Professor, Departments of Medicine and Community Health Sciences, University of Calgary) for the images in Figure 2.

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