Concise report

Loss of metacarpal bone density predicts RA development in recent-onset arthritis

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Abstract

Objective. Serum samples taken before the onset of RA suggest that one of the first features of RA is BMD loss. We determined the ability of radiographic BMD loss to predict RA development and arthritis persistency in patients with early undifferentiated arthritis (UA).

Methods. Five hundred and seventeen patients with early UA, included in the Leiden Early Arthritis Clinic, were assessed. Of these, 101 had hand radiographs made at first visit as well as after 6 months. BMD loss was measured using digital X-ray radiogrammetry (DXR) online. The outcome measures fulfilled the 1987 ACR criteria for RA after 1 year and arthritis persistency during a mean follow-up of 7 years. Additionally, it was assessed whether BMD measurements improved predictions compared with a validated prediction rule.

Results. A total of 53.8% of UA patients developed RA and 67.5% had persistent disease after 7 years follow-up. Highly elevated BMD loss (≥2.5 mg/cm²/month) was present in 16.3% of patients and associated with RA development [odds ratio (OR) 6.1, 95% CI 1.2, 29.2, positive predictive value (PPV) 85%, negative predictive value (NPV) 52%, sensitivity 26%, specificity 95%]. BMD loss may have an independent effect of anti-CCP when tested in a logistic regression analysis (OR 4.1, 95% CI 0.8, 21.2), although the CI is large. All UA patients that were unclassified with the prediction rule and had highly elevated BMD loss progressed to RA. BMD loss was not significantly associated with arthritis persistency (HR = 0.56, 95% CI 0.14, 2.29).

Conclusion. Present data suggest that BMD loss predicts RA development. These findings need to be verified in larger studies.

Key words: computer-assisted image interpretation, diagnostic imaging, radiology, rheumatoid arthritis, undifferentiated arthritis, bone.

Introduction

The outcome of early arthritis patients is highly variable. Approximately only a third of the patients with a recent-onset undifferentiated arthritis (UA) progress towards RA as defined by the ACR 1987 criteria and 40-50% have a spontaneously remitting disease. In order to achieve individualized treatment decision making, the disease outcome needs to be estimated adequately. This is particularly relevant since it is widely acknowledged that early initiation of treatment of RA is effective in diminishing the level of joint destruction and disability [1]. Initiating DMARD therapy in all UA patients induces over-treatment in about half of the patients, arguing for a wait-and-see strategy for some time. On the other hand, studies in serum samples of patients that later have developed RA show that disease processes such as broadness of antigen recognition and isotype usage of anti-citrullinated antibodies mature very early in disease [2, 3]. Increased levels of the bone metabolism markers P1NP and osteoprotegerin have been shown in serum samples of patients, years before the onset of disease [4]. Moreover, intervention studies suggest that recent-onset disease is more sensitive to current treatment...
than later stage disease. Therefore, this early stage is sometimes referred to as the window of opportunity. The current prediction models suggest that critical disease processes that drive the development of disease processes towards RA are autoantibody responses and inflammation [5, 6]. Metacarpal BMD loss has been observed to be predictive for radiographic destruction in RA [7, 8]. Its predictive abilities in UA have not yet been investigated. Since current prediction models do not take local metacarpal or systemic bone loss into account, we hypothesized that bone loss in the three middle metacarpal bones may be of additional value to currently known predictive factors. An advantage of measuring hand BMD loss is that it is relatively easy to determine, as it uses normal hand radiographs, which are part of the standard clinical care for most RA patients.

Methods

Five hundred and sixty-seven patients with recent-onset UA who participated in the Leiden Early Arthritis Clinic (EAC) and were included between 1993 and 2006 were assessed [1]. Written informed consent was obtained from all patients in this cohort and the EAC cohort has been approved by the local medical ethical committee (ethics committee of the Leiden University Medical Center). Our study is solely based on the data and materials collected in the EAC study. Of the 567 patients with recent-onset UA, 125 had hand radiographs made at first visit as well as after 6 months and were selected for further analysis.

Digital X-ray radiogrammetry (DXR) online technology (Sectra, Sweden) was used to measure cortical DXR-BMD [7]. This technique is a computerized version of the technique of radiogrammetry developed by Barnett and Nordin [9] and has been shown to predict, among other things, joint damage in recent-onset RA [7–9]. The technique computes BMD loss by making use of the cortical thickness of the three middle metacarpal bones on hand radiographs.

The analogue radiographs were digitized with a Vidar VXR-12 Plus digitizer at 300 dots per inch (DPI) and 12 bits. The DXR-BMD technique has been described in greater detail previously [8]. In short, BMD is estimated through an automated analysis of the cortical bone at the centres of metacarpals II, III and IV on a standard projection digital radiograph. Whenever possible, mean DXR-BMD of both hands was used for the analysis to maximize accuracy of the BMD loss measurement. The reproducibility of DXR-BMD when applied to analogue and digital X-rays acquired according to the DXR protocol has been assessed in previous studies [10, 11].

BMD loss was calculated as the difference between BMD measured on the radiograph made at 6 months follow-up and the baseline radiograph. Cut-offs for the categories normal, elevated BMD loss and highly elevated BMD loss were established previously by Sectra Imtec AB and were by no means influenced by the findings of the present study (see also dxr-online.com/ReportsWebTool/ManualChange.aspx). Elevated BMD loss was defined as a change in BMD $\geq$0.25 mg/cm$^2$/month, and highly elevated BMD loss was defined as a change in BMD $\geq$2.5 mg/cm$^2$/month. Two main outcome measures were studied: fulfilling the 1987 ACR criteria for RA after 1 year and arthritis persistency during a mean follow-up period of 7 years. Persistent disease was defined as the absence of sustained DMARD-free remission, which was defined as the absence of synovitis for at least 1 year after cessation of DMARD therapy, if any. It was also assessed whether patients who could not be adequately classified using a validated prediction rule consisting of nine clinical and serological variables (those patients had a prediction score $>6$ and $<8$) could be predicted correctly using DXR [5]. In addition, the value of BMD loss for the prediction of fulfilling the 2010 ACR criteria after 1 year follow-up was tested. The discriminative ability was expressed using an area under the receiver operator characteristic curve (AUC). The value of BMD loss for the prediction of RA development after 1 year follow-up and arthritis persistency during a mean follow-up of 7 years was calculated using logistic regression and Cox regression, respectively. Calculations were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 567 patients who visited the Leiden EAC between 1993 and 2006, 125 had radiographs of the hands made at the first visit and at 6 months follow-up. Part of the radiographs could not be studied, mainly due to inadequate positioning of the hands on the radiographs. One hundred and sixty radiographs of 80 patients were of sufficient quality to be studied. Characteristics of the remaining group of 80 patients, the 125 patients with two radiographs and the whole group of 567 UA patients are depicted in Table 1. Patients with serial radiographs at 6 months had a higher number of swollen joints and were more often anti-CCP positive compared with patients for whom no radiograph at the 6-month time point was available. The patients in whom pairs of radiographs could not be studied for technical reasons were not different from the patients who had two appropriate radiographs.

Thirteen patients (16.3%) had highly elevated BMD loss, 37 (46%) had elevated BMD loss and 30 (38%) had a stable or increasing BMD. Fifty-four percent of patients whom no radiograph at the 6-month time point was available. The patients in whom pairs of radiographs could not be studied for technical reasons were not different from the patients who had two appropriate radiographs.

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have an independent association with progression to RA (OR 4.08, 95% CI 0.78, 21.22), though the CI was too wide to draw definite conclusions.

Twenty seven patients could not be classified by the prediction rule because of a score >6 and <8. All of these patients that had a highly elevated BMD loss developed RA, indicating a PPV of 100% (95% CI 85%, 100%) in this small subgroup. Sixty of the 80 patients analysed fulfilled the ACR/EULAR 2010 RA criteria within 1 year of follow-up. All 13 patients with highly elevated BMD loss fulfilled the ACR/EULAR 2010 criteria, resulting in a PPV of 100% (95% CI 72%, 100%). However, 47 patients who fulfilled the ACR-EULAR 2010 criteria had no highly elevated BMD loss. Seventy-eight percent of the patients had persistent disease. Highly elevated BMD loss was not significantly associated with persistency of arthritis after a mean follow-up of 7 years [hazard ratio (HR) = 0.57, 95% CI 0.14, 2.29].

Discussion
The concept of BMD loss is appealing, as several lines of evidence indicate that bone metabolism activity occurs very early in RA. Increased concentrations of bone metabolism markers have been found in the sera of patients before the development of RA [4, 12].

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**Table 1** Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 567)</th>
<th>Patients eligible (n = 125)a</th>
<th>P-value</th>
<th>Patients analysed (n = 80)b</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>327 (57.7)</td>
<td>78 (62.4)</td>
<td>0.33</td>
<td>57 (71.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>50.9 (16.9)</td>
<td>52.5 (14.2)</td>
<td>0.37</td>
<td>53.2 (14.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Symptom duration at baseline (days), mean (s.d.)</td>
<td>63.1 (198.1)</td>
<td>220.52 (405.2)</td>
<td>&lt;0.01</td>
<td>243.8 (175.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Swollen joint count, mean (s.d.)</td>
<td>7.3 (7.8)</td>
<td>9.0 (7.5)</td>
<td>&lt;0.01</td>
<td>8.9 (7.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>CRP, mean (s.d.), mg/l</td>
<td>22.8 (30.2)</td>
<td>22.8 (26.6)</td>
<td>0.34</td>
<td>22.3 (24.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Anti-CCP antibody positive, n (%)</td>
<td>133 (24.4)</td>
<td>46 (37.4)</td>
<td>&lt;0.01</td>
<td>30 (37.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>RA development after 1 year, n (%)</td>
<td>176 (31.0)</td>
<td>65 (52.0)</td>
<td>&lt;0.01</td>
<td>43 (53.8)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

aUA patients of whom a radiograph was made at first visit as well as at 6 months follow-up were compared with all UA patients. bUA patients of whom the radiographs were used for BMD analyses were compared with all UA patients with radiographs both at first visit and at 6 months follow-up.

**Fig. 1** ORs of various risk factors for RA development. ORs for RA development according to the 1987 ACR criteria of various disease characteristics resulting from univariate analysis. BMD loss: highly elevated BMD loss as defined by Sectra; CCP: presence or absence of anti-cyclic citrullinated antibodies; CRP: C-reactive protein; SJC: 44-swollen joint count; morning stiffness: severity of morning stiffness on visual analogue scale; gender: female gender. In order to calculate ORs for the variables CRP, SJC, age and morning stiffness, patients were divided into two groups based on the mean. The means are derived from the data of the 80 people used for analysis; CRP 22.3 mg/l, SJC 8.9, age 53.2 years and morning stiffness 7.01 cm.
In addition, within early RA BMD loss is predictive for future joint damage [7, 8]. Also, bone mineral density loss >1 year in cortical and trabecular bones of the hand, measured with dual energy X-ray absorptiometry, was demonstrated to be higher in RA patients compared with that of other inflammatory diseases [13]. It is interesting to speculate whether BMD loss is due to systemic or to local inflammatory factors. The presence of bone metabolism markers in the serum before disease onset at least points to the presence of systemically measurable phenomena.

Our study is the first to evaluate the predictive ability of measuring BMD loss using DXR in early UA. It indicates that in these patients BMD loss may be a relevant predictor for the development of RA. From several inception cohort studies it is known that ~40–50% of these UA patients remit spontaneously, whereas one-third develops RA [5]. Ideally, only the latter patients are treated with DMARDs. Our findings may be relevant for clinical practice, as they may enhance the identification of UA patients that are in an early phase of RA [5].

Nevertheless, this study has several limitations. First of all, the sample size is small; this may prevent definite conclusions to be drawn and points to the relevance of performing additional studies on BMD loss in UA patients. The sample size may be a concern for the total number of patients with BMD data (n = 80), but in particular for the patients that were studied because of being unclassified by a clinical prediction rule (n = 27). It was observed that all patients with highly elevated BMD loss, who could not be classified according to the prediction rule, developed RA. Though this may indicate that DXR can improve predictions, these initial findings should be validated in larger, independent studies.

A second limitation is the fact that the UA patients that had a repeated radiograph after 6 months, and therefore could be analysed, had more severe disease compared with the whole UA population. It is possible that some selection bias occurred here. This may limit the generalizability of our study to the standard UA population.

Third, treatment effects were not taken into consideration. Although CSs were seldom prescribed in the UA patients studied, these data are incompletely registered since no records from general practitioners are available. However, suppose that a highly elevated BMD loss is not due to the disease but to any treatment, then the true PPV would be higher than observed now.

BMD loss measured by DXR did not significantly associate with arthritis persistency. It is unknown whether this is due to insufficient power, or whether there is truly no association between BMD loss and arthritis persistency. More studies on this subject are needed. It was beyond the scope of the present study to determine the cost-effectiveness of DXR-BMD measurements for daily clinical care. This would require larger studies in unselected groups of UA patients. In conclusion, although more research into the value of BMD loss measurements in early UA is necessary, our study suggests that BMD loss may be a useful prognostic tool.

### Rheumatology key messages
- Present data suggest that BMD loss is predictive for RA development.
- BMD loss measured by DXR online may improve predictions in early arthritis.

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### References


Clinical Vignette

Canakinumab induces remission in a patient with resistant familial Mediterranean fever

Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by a defect in the regulation of caspase-1 activation leading to the cleavage of IL-1β precursor [1]. We report an FMF patient resistant to colchicine, successfully treated with canakinumab.

The patient had been taking colchicine since the age of 10. She was homozygous for the M694V mutation in the MEFV gene. At age 14, she started to have weekly attacks and her CRP gradually increased. She failed to respond to continuous NSAIDs or an anti-TNF agent along with MTX. She developed spondylitis and a chronic arthritis of the right shoulder. Subsequently she was started on anakinra. Although she initially responded, her attacks recurred and her acute-phase reactants increased after the first 9 months. She was then given canakinumab. In a week all clinical symptoms resolved and ESR, CRP and serum amyloid A (SAA) returned to normal (Fig. 1). For 2 months she was completely normal. On Day 70 joint symptoms recurred and her CRP and SAA started to rise. A second dose was administered again with full response. In the meantime she continues colchicine at 2 mg/day. We suggest that canakinumab should be considered as a potent therapeutic option for refractory FMF resistant to colchicine.

Disclosure statement: S.O. is a consultant for Novartis (Turkey). The other author has declared no conflicts of interest.

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References