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**Title:** Genes and environmental factors associated with the severity of progression of rheumatoid arthritis  
**Issue Date:** 2014-01-23
Loss of metacarpal bone density predicts RA development in recent onset arthritis

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Rheumatology, 2012 Jun;51(6):1037-41
ABSTRACT

Objective
Serum samples taken prior to the onset of Rheumatoid Arthritis (RA) suggest that one of the first features of RA is Bone Mineral Density (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
517 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 six months and were studied. BMD loss was measured using DXR-online. The outcome measures were fulfilling 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 prediction making compared to a validated prediction rule.

Results
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 per month) was present in 16.3% of patients and associated with RA development (OR 6.1 (95%CI 1.2-29.2), PPV 85%, 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.
INTRODUCTION

The outcome of early arthritis patients is highly variable. Approximately only one-third of the patients with a recent-onset Undifferentiated Arthritis (UA) progresses towards Rheumatoid Arthritis (RA) as defined by the ACR-1987 criteria and 40-50% has 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. Initiating Disease Modifying Anti-Rheumatic (DMARD) Therapy in all UA patients induces overtreatment 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. Increased levels of the bone metabolism markers P1NP and osteoprotegerin have been shown in serum samples of patients years before the onset of disease.

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 which drive the development of disease processes towards RA are autoantibody responses and inflammation. Metacarpal Bone Mineral Density (BMD) loss has been observed to be predictive for radiographic destruction in RA. Its predictive abilities in Undifferentiated Arthritis have not been investigated yet. 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

567 patients with recent onset UA who participated in the Leiden Early Arthritis Clinic and were included between 1993 and 2006 were assessed. Written informed consent was obtained from all patients in this cohort and the cohort has been approved by the local medical ethical committee (ethics committee of the Leiden University Medical Center). Of the 567 patients with recent onset UA, 125 had hand radiographs made at first visit as well as after six months and were selected for further analysis.

Digital X-ray radiogrammetry online technology (DXR) (Sectra, Sweden) was used to measure cortical DXR-BMD (BMD). This technique is a computerized version of the
technique of radiogrammetry developed by Barnett and Nordin and has been shown to predict, among others, joint damage in recent onset rheumatoid arthritis\textsuperscript{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 DPI and 12 bit. The DXR-BMD technique has been described in greater detail previously\textsuperscript{8}. In short, BMD is estimated through an automated analysis of the cortical bone at the centers 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\textsuperscript{10,11}.

BMD loss was calculated as the difference between BMD measured on the radiograph made at six 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, 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 one 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 one year after cessation of DMARD-therapy, if any. It was also assessed whether patients that 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\textsuperscript{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 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 Early Arthritis Clinic between 1993 and 2006, 125 had radiographs of the hands made at first visit and at six months follow-up. Part of the radiographs could not be studied, mainly due to inadequate positioning of the hands
on the radiographs. 160 radiographs of 80 patients were of sufficient quality to be studied. Characteristics of the remaining group of 80 patients, and the 125 patients with two radiographs and the whole group of 567 UA patients are depicted in Table 1. Patients with serial radiographs in 6 months had a higher number of swollen joints and were more often anti-CCP positive compared to patients of whom no radiograph at the 6 months time point was available. The patients 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. 54% of patients fulfilled the ACR 1987 criteria for RA within the first year. Patients with highly elevated BMD loss (>2.5 mg/cm² per month) had a six-times increased odds to develop RA, which was significant (95% CI 1.24-29.24). The PPV was 85% (95% CI 54-97%), the NPV 52% (95% CI 40-64%), the sensitivity 26% (95% CI 14-41%), the specificity 95% (95% CI 80-99%) and the AUC 0.6 (95% CI 0.48-0.93). The OR's for RA-development of BMD loss were compared to the OR's of other known risk factors that were determined on the same dataset. The odds ratio's of these risk factors were lower than that of highly elevated BMD loss (see Figure 1).

When adjusting for the presence of anti-CCP antibodies in logistic regression analysis, BMD loss still tended to have an independent association with progression to RA (OR 4.08, 95% CI 0.78-21.22), though the confidence interval was too wide to draw definite conclusions.

27 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. 60 of the 80 patients analyzed fulfilled

<table>
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<th>Table 1. Characteristics of the study population</th>
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<td>All patients (n=567)</td>
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<td>Female (%)</td>
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<td>Age, mean ± SD</td>
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<td>Symptom duration at baseline</td>
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<td>Anti-CCP antibody positive, n (%)</td>
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* UA-patients of whom a radiograph was made at first visit as well as at six months follow-up were compared to all UA-patients.

** UA-patients of whom the radiographs were used for BMD analyses were compared to all UA-patients with radiographs both at first visit and at six months follow-up.
the ACR-EULAR 2010 RA criteria within one 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 which 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 seven years (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 prior to the development of RA\(^4,12\). In addition, within early RA BMD loss is predictive for future joint damage\(^7,8\). Also, bone mineral density loss over 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 to 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 about 40-50% of these UA patients remit spontaneously, whereas one-third develops RA. 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.

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 that could not be classified according to the prediction rule, developed RA. Though this may indicate that DXR can importantly improve prediction making, 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 six months and therefore could be analyzed had more severe disease compared to 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 corticosteroids were seldom prescribed in the UA patients studied, these data are incompletely registered since e.g. no records from GP’s are available. However, supposed that a highly elevated BMD loss is not due to the disease but to any treatment, the true positive predictive value would be higher than observed now.

BMD loss measured by DXR did not significantly associate with arthritis persistency. It is undecided 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 an useful prognostic tool.
CONFLICTS OF INTEREST

J.K is an employee of Sectra Imtec AB. The other authors declare no conflicts of interest.

FUNDING STATEMENT

The work of A.H.M van der Helm- van Mil is supported by the Dutch Organization of Health Research and Development. Sectra Imtec AB supported this study by performing the DXR measurements free of charge.
REFERENCE LIST


