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Association of Anti-citrullinated Protein Antibody Positivity and Titer Levels to Low Hand BMD, and the Consequence of Low Hand BMD on DAS28 (CRP) Remission in Established RA: Findings from a US Observational Cohort

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Introduction

- The presence of bone erosions in RA correlates with low bone mineral density (BMD) levels.[1]
- Hand BMD loss as measured by digital X-ray radiogrammetry (DXR), a sensitive quantitative method for detecting early bone loss, is an independent predictor of radiographic joint damage progression.[2–4]
  - Studies have established low hand BMD as a potential indicator of the risk of vertebral and non-vertebral fractures.[5,6]
- Anti-citrullinated protein antibody (ACPA) positivity is associated with poor prognosis in RA.[7]
  - In patients who are positive (+) for anti-cyclic citrullinated peptide-2 (anti-CCP2, a surrogate of ACPA), structural bone damage can start before the clinical onset of RA.[8]
  - In patients with early RA, elevated anti-CCP2 levels have been found to be independent predictors of localized DXR–BMD loss.[9]
- The relationship between hand BMD loss and anti-CCP2 antibodies in patients with established RA is unclear.

Objectives

- To assess the relationship between hand DXR–BMD and anti-CCP2 antibodies, and the association with joint progression and fracture risk in patients with established RA in a real-world setting.

Methods

Study population

- The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry was initiated in 2003. Details regarding the design of the registry have been reported previously.[10–12] (see http://www.brassstudy.org).
  - BRASS is a single-center, prospective, observational, longitudinal cohort of >1400 adults with established or recent-onset RA who are being followed in a hospital-based practice of 21 rheumatologists in Boston, MA, USA.
  - For the present study, eligible patients had DXR–BMD and anti-CCP2 measurements at the same time point or within 6 months.

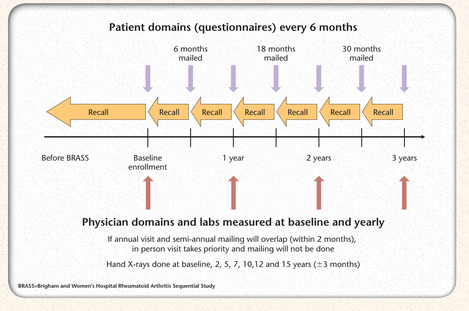
Measurements and data collection

- Patient demographic data and clinical characteristics, disease activity and laboratory parameters were assessed at baseline and annually thereafter.
- Digitized hand radiographs were collected at baseline and at 2, 5, 7 and 10 years (Figure 1).
- Hand BMD was measured at the metacarpal bones of the second, third and fourth digits using DXR–BMD (DXR-online, Sectra Imtec AB, Linköping, Sweden).
- Anti-CCP2 was measured using a validated ELISA (Inova Diagnostics, San Diego, CA, USA until its discontinuation in 2011; thereafter Euro-Diagnostica [distributed by IBL-America, Minneapolis, MN, USA]).
- Patient-reported outcomes were assessed with a follow-up questionnaire every 6 months (Figure 1).

Study outcomes

- Patient demographic data, baseline characteristics and clinical outcomes were reported by anti-CCP2 status (anti-CCP2+ and anti-CCP2 negative [–]) and anti-CCP2 titer group (Group [Gp] 1–3):
  - anti-CCP2+ status was defined either as anti-CCP2+ (≥20 units/mL) or anti-CCP2– (<20 units/mL)
  - anti-CCP2+ patients were divided equally into three subgroups as Gp 1, 20–96.6 units/mL; Gp 2, 96.7–309.6 units/mL; or Gp 3, 309.7–580 units/mL.
- Mean DXR–BMD was reported by anti-CCP2 status and titer group.
- The association between achievement of DAS28 (CRP) <2.6 and bone loss was analyzed in patients with DXR–BMD <0.5 g/cm² (left or right hand) versus ≥0.5 g/cm² (both hands).

Figure 1. BRASS Study Design



Statistical analysis

- Cross-sectional analysis was performed on available data for DXR–BMD and anti-CCP2 measured within 6 months of the DXR–BMD measurement.
- For descriptive statistics, Wilcoxon rank-sum test (or Kruskal–Wallis test) was used for continuous variables and Pearson's chi-square test for categorical variables.
- Associations between DXR–BMD (left, right and combined [average of left and right hands]) and anti-CCP2 status and titer (Gp1–3) were explored in multivariate analyses using linear regression controlling for covariates (age, RA duration, BMI, DAS28 [CRP], smoking status, use of steroids, biologic DMARD and osteoporosis medication):
  - model 1 explored anti-CCP2 as a continuous variable (linear trend) in relation to DXR–BMD
  - model 2 explored anti-CCP2 as a categorical variable and included different anti-CCP2 groups as reference groups.
- Associations between BMD–DXR and DAS28 (CRP) <2.6 in patients with DXR–BMD ≥0.5 g/cm² and <0.5 g/cm² were explored using a logistic model controlling for covariates (age, RA duration, BMI, smoking status, use of steroids, biologic DMARD and osteoporosis medication).

Results

Patient disposition and patient characteristics by anti-CCP2 status and titer group

- A total of 149 patients (all post-menopausal women) had an anti-CCP2 measurement within 6 months of a DXR–BMD measurement: 47 (31.5%) were anti-CCP2–; 102 (68.5%) were anti-CCP2+ [34 per titer group].
- Patient characteristics by anti-CCP2 status and titer group are shown in Table 1.
  - Age, BMI, DAS28 (CRP), smoking status, use of steroids, biologic DMARD and osteoporosis medication and biologic DMARD use did not differ significantly by anti-CCP2 status (+/–) or between groups.
  - Mean RA duration was different between the groups ($p<0.05$); a longer RA duration was also reported in anti-CCP2+ patients versus anti-CCP2– patients ($p<0.05$).

DXR–BMD by anti-CCP2 group

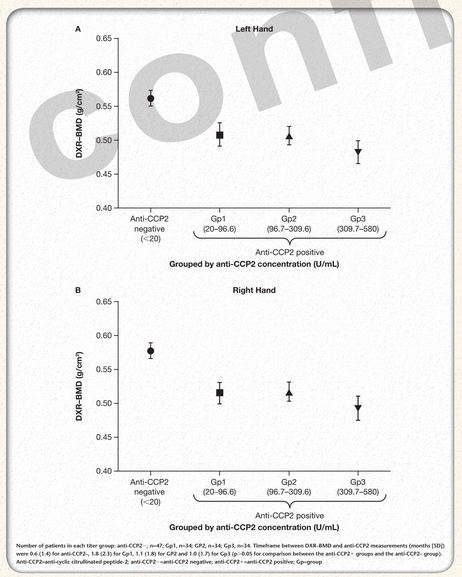
- DXR–BMD was higher in the anti-CCP2– group versus the anti-CCP2+ groups (anti-CCP2– versus Gp1–3: $p<0.0001$ for left and right hand).
- DXR–BMD decreased with increasing anti-CCP2 titer (Figure 2).

Table 1. Baseline Characteristics by Anti-CCP2 Status and Titer Group

	Anti-CCP2– n=47	Anti-CCP2+ n=102	Anti-CCP2+, Gp1 n=34	Anti-CCP2+, Gp2 n=34	Anti-CCP2+, Gp3 n=34	Overall population N=149
Anti-CCP2 range	3.0–15.43	15.44–580	15.44–96.6	96.7–302.1	302.2–580	3–580
Anti-CCP2 level, units/mL, mean (SD)	5.1 (2.9)**	226.4 (157.0)**	55.2 (21.4)**	208.1 (61.4)**	415.7 (61.2)**	156.6 (165.7)
Age, years, mean (SD)	60.3 (8.4)	61.9 (9.6)	60.4 (9.0)	62.0 (9.5)	63.4 (10.3)	61.4 (9.3)
RA duration, years, mean (SD)	12.2 (12.0)*	16.7 (10.8)*	18.0 (11.3)*	15.1 (8.7)*	17.0 (12.1)*	15.3 (11.3)
BMI, kg/m², mean (SD)	27.3 (5.8)	26.9 (5.9)	26.0 (4.8)	25.6 (4.9)	29.2 (7.1)	27.0 (5.9)
DAS28 (CRP), mean (SD)	3.5 (1.4)	4.0 (1.5)	3.9 (1.5)	4.0 (1.6)	4.1 (1.5)	3.8 (1.5)
Steroid use, n (%)						
Never	10 (21.3)	18 (17.6)	6 (17.6)	6 (17.6)	6 (17.6)	28 (18.8)
1–6 months	12 (25.5)	29 (28.4)	8 (23.5)	13 (38.2)	8 (23.5)	41 (27.5)
>6 months	25 (53.2)	55 (53.9)	20 (58.8)	15 (44.1)	20 (58.8)	80 (53.7)
Ever/current smoker, n (%)	23 (48.9)	55 (53.9)	16 (47.1)	19 (55.9)	20 (58.8)	78 (52.3)
Biologic DMARD, n (%)	20 (42.6)	51 (50)	17 (50.0)	19 (55.9)	15 (44.1)	71 (47.7)
Osteoporosis medication, n (%)	6 (12.8)	15 (14.7)	6 (17.6)	7 (20.6)	2 (5.9)	21 (14.1)

*p<0.05, **p<0.001 comparing anti-CCP2– versus anti-CCP2+ or between the four anti-CCP2 groups. Anti-CCP2 status was defined as either anti-CCP2+ (≥20 units/mL) or anti-CCP2– (<20 units/mL). Anti-CCP2+ titer groups were either defined as Gp 1, 20–96.6 units/mL; Gp 2, 96.7–309.6 units/mL; or Gp 3, 309.7–580 units/mL. Anti-CCP2=anti-cyclic citrullinated peptide-2; anti-CCP2–=anti-CCP2 negative; anti-CCP2+=anti-CCP2 positive; Gp=group

Figure 2. Mean DXR–BMD by Anti-CCP2 and Titer Group



Number of patients in each titer group: anti-CCP2– : n=47; Gp1, n=34; GP2, n=34; Gp3, n=34. Timeframe between DXR-BMD and anti-CCP2 measurements (months [SD]) were 0.6 (1.4) for anti-CCP2–, 1.8 (2.3) for Gp1, 1.1 (1.8) for GP2 and 1.0 (1.7) for Gp3 ($p<0.05$ for comparison between the anti-CCP2+ groups and the anti-CCP2– group). Anti-CCP2=anti-cyclic citrullinated peptide-2; anti-CCP2–=anti-CCP2 negative; anti-CCP2+=anti-CCP2 positive; Gp=group

Associations between DXR–BMD and anti-CCP2 – multivariate analysis

- Using model 1, combined hand DXR–BMD was negatively associated with anti-CCP2. For every 10-unit increase in anti-CCP2, DXR–BMD decreased by 0.0014 units ($p<0.001$; Table 2). R^2 adjusted for the total hand DXR–BMD model was 0.406.
- Using model 2, combined hand DXR–BMD was negatively associated with anti-CCP2 Gp1, Gp2 and Gp3 versus anti-CCP2– ($p<0.05$; Table 3). R^2 adjusted for the total hand DXR–BMD model was 0.426.
- Results for individual hands were similar to those for the combined analysis (Tables 2 and 3).

Association between achievement of DAS28 (CRP) <2.6 and bone loss

- Patients with low DXR–BMD were less likely to achieve DAS28 (CRP) <2.6 (Figure 3).
- After controlling for baseline confounding factors, the odds of achieving DAS28 (CRP) <2.6 were significantly lower for patients with DXR–BMD <0.5 (n=64) versus ≥0.5 (n=85; odds ratio 0.355 [95% CI: 0.126, 0.998]; p=0.0496).

Table 2. Associations Between DXR–BMD and Anti-CCP2, Multivariate Model 1

	Left-hand DXR-BMD		Right-hand DXR-BMD		Average of left and right hand	
Variable	Coefficient	p value	Coefficient	p value	Coefficient	p value
Model 1*						
Anti-CCP2 per 10-unit increase*	–0.0014	<0.001	–0.0014	<0.001	–0.0014	<0.001
Age, years	–0.0036	<0.001	–0.0035	<0.001	–0.0035	<0.001
RA duration, years	–0.0015	0.01	–0.0016	0.008	–0.0012	0.034
BMI, kg/m²	0.0019	0.089	0.0023	0.043	0.0018	0.100
DAS28 (CRP)	–0.0036	0.415	–0.0027	0.545	–0.0025	0.570
Steroid use 1–6 months (vs never)	–0.022	0.231	0.0004	0.984	–0.0055	0.757
Steroid use >6 months (vs never)	–0.0335	0.055	–0.0297	0.09	–0.0311	0.065
Smoker (ever/current vs never)	–0.0085	0.497	–0.0149	0.247	–0.0133	0.283
Biologic DMARD (yes vs no)	–0.0128	0.339	0.0105	0.436	0.0042	0.750
Osteoporosis medication (yes vs no)	–0.0481	0.008	–0.0493	0.008	–0.499	0.005
R^2, adjusted	0.388		0.399		0.406	

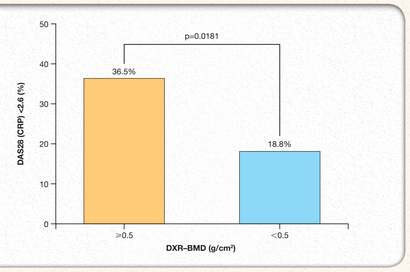
*Model 1 explored anti-CCP2 as a continuous variable (linear trend) in relation to DXR–BMD. Anti-CCP2=anti-cyclic citrullinated peptide-2; BMD=bone mineral density; DXR=digital X-ray radiogrammetry

Table 3. Associations Between DXR–BMD and Anti-CCP2, Multivariate Model 2

	Left-hand DXR-BMD		Right-hand DXR-BMD		Average of left and right hand	
Variable	Coefficient	p value	Coefficient	p value	Coefficient	p value
Model 2*						
Anti-CCP2+ Gp1 (vs anti-CCP2–)	–0.0475	0.007	–0.0555	0.002	–0.0542	0.002
Anti-CCP2+ Gp2 (vs anti-CCP2–)	–0.0394	0.02	–0.0477	0.006	–0.0464	0.005
Anti-CCP2+ Gp3 (vs anti-CCP2–)	–0.0683	<0.001	–0.0715	<0.001	–0.0686	<0.001
Anti-CCP2+ Gp 1 (vs Gp 3)	0.0208	0.268	0.0161	0.395	0.0144	0.442
Anti-CCP2+ Gp 2 (vs Gp 3)	0.0289	0.113	0.0238	0.201	0.0221	0.215
Anti-CCP2– (vs Gp 2–3)	0.0523	<0.001	0.0586	<0.001	0.0568	<0.001
Anti-CCP2+ Gp 3 (vs anti-CCP2–, Gp 1 and Gp 2)	–0.0442	0.004	–0.0433	0.006	–0.0422	0.006
Age, years	–0.0037	<0.001	–0.0036	<0.001	–0.0036	<0.001
RA duration, years	–0.0013	0.03	–0.0013	0.026	–0.001	0.081
BMI, kg/m²	0.0018	0.112	0.0021	0.063	0.0016	0.148
DAS28 (CRP)	–0.0023	0.603	–0.0014	0.76	–0.0015	0.736
Steroid use 1–6 months (vs never)	–0.0248	0.174	–0.0014	0.94	–0.0076	0.664
Steroid use >6 months (vs never)	–0.0358	0.04	–0.0324	0.061	–0.0346	0.038
Smoker (ever/current vs never)	–0.0059	0.637	–0.0125	0.324	–0.0103	0.400
Biologic DMARD (yes vs no)	–0.013	0.332	0.0118	0.378	0.0042	0.746
Osteoporosis medication (yes vs no)	–0.0481	0.008	–0.0477	0.009	–0.0469	0.008
R^2, adjusted	0.399		0.421		0.426	

*Model 2 explored anti-CCP2 as a categorical variable. Anti-CCP2 status was defined as either anti-CCP2+ (≥20 units/mL) or anti-CCP2– (<20 units/mL). Anti-CCP2+ titer groups were defined as Gp 1, 20–96.6 units/mL; Gp 2, 96.7–309.6 units/mL; or Gp 3, 309.7–580 units/mL. Anti-CCP2=anti-cyclic citrullinated peptide-2; anti-CCP2–=anti-CCP2 negative; anti-CCP2+=anti-CCP2 positive; BMD=bone mineral density; DXR= digital X-ray radiogrammetry Gp=group

Figure 3. Association Between DXR–BMD and DAS28 (CRP) <2.6



Conclusions

- Our results show that, in a real-word setting, hand DXR–BMD is negatively associated with anti-CCP2.
- These results suggest that anti-CCP2+ patients with established RA, particularly those with high anti-CCP2 titers, have lower hand BMD.
- Furthermore, patients with lower hand BMD are less likely to achieve DAS28 (CRP) <2.6, suggesting an association between disease activity and bone loss. Such patients could have an increased risk of joint progression and fracture.
- Interestingly, although there is evidence that hand joint damage in RA is related to use and hand dominance,[13] our data show that bone loss occurs in both hands, which is consistent with RA being defined as a symmetrical disease.

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