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Original Article

Influence of anti-cyclic citrullinated peptide on disease activity, structural severity, and bone loss in Moroccan women with rheumatoid arthritis

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ABSTRACT

Aim of the work: The aim of this study was to assess the influence of anti-cyclic citrullinated peptide (anti-CCP) on disease activity, radiological severity, functional disability and bone loss in Moroccan women with rheumatoid arthritis (RA).

Patients and methods: One hundred and thirty-six women with RA were recruited. Age, weight, height, disease duration and steroids cumulative dose were identified. Anti-CCP and Rheumatoid factor (RF) were determined. Disease activity score (DAS28) was assessed and functional repercussion measured by the Health Assessment Questionnaire-disability index (HAQ-DI). Radiological status was assessed by the Sharp/van der Heijde (SvH) erosion and narrowing score. Bone mineral density was determined by a Lunar Prodigy Vision Dual-energy X-ray absorptiometry and vertebral fracture assessment was classified using a combination of Genant semi-quantitative approach and morphometry.

Results: Patients mean age was 49.6 ± 7.4 years and disease duration 7.7 ± 5 years. 109 (80.1%) patients were anti-CCP positive. There was no significant difference in DAS28 between patients with and without anti-CCP. Nevertheless, weight, erythrocyte sedimentation rate (ESR), rheumatoid factor titer and positivity, SvH narrowing and erosion score and osteoporosis were significantly higher in patients with positive anti-CCP. Stepwise regression analysis showed that the presence of anti-CCP was independently associated with osteoporosis and SvH erosion score.

Conclusions: Anti-CCP antibodies are strongly predictive for the development of osteoporosis and erosions in Moroccan RA patients. They not only have a valuable role in the disease prognosis prediction but also may be a relevant determinant of bone loss in RA. The presence of these antibodies warrants special attention.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint swelling, joint tenderness, progressive erosions and cartilage destruction leading to severe disability [1]. It affects approximately 1% of the world's population with a female/male ratio ranging from 2/1 to 4/1 [2]. RA is not only a risk factor for joint damage, it's also own for the development of osteoporosis, vertebral fractures (VFs), cardiovascular diseases and other organ disorders, and this risk increases more with disease duration and causes premature mortality [3–5]. Currently, the diagnosis of RA is based on the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria which combine a range of clinical, biological and immunological arguments, including anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) [6]. The interest of these criteria lies not only in their value for the diagnosis of RA but also

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in the determination of the subsequent prognosis of this disease [7,8]. Anti-CCP and RF can precede the clinical manifestation of RA by many years [9]. Indeed, in RF-negative RA patients, the anti-CCP test demonstrates sensitivity ranging from about 35% to 80% and specificity over 90% [8]. The current therapeutic strategy using increasingly aggressive regimens early in the course of the disease can lengthen life, and improve function [10]. Thus, early diagnosis is crucial [11]. Apart from its utility in predicting the development of RA in early arthritis, anti-CCP has also been associated with activity, functional impairment and disease severity in well-established RA, but data is sparse [12,13]. Thus, we wanted to assess in the present study the influence of anti-CCP on disease activity, radiological severity, functional disability and bone loss in Moroccan women with RA.

2. Patients and methods

The study group consisted of 136 consecutive women with RA who fulfilled the 2010 ACR/EULAR criteria for the classification of RA [6]. Demographic, patient and disease characteristics, including conventional RA disease core measurements, were recorded by interview and clinical examination. Disease duration was defined as the time elapsed between the onset of first disease-related symptoms and enrolment. Steroid cumulative dose was determined. Disease activity was assessed by the disease activity score-28 (DAS28) [14]. Functional repercussion was measured by the Health Assessment Questionnaire-disability index (HAQ-DI) [15]. All patients gave their informed consent to participate in the study. The procedures of the study were in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Faculty of Medicine and Pharmacy of Rabat.

Rheumatoid factors and anti-CCP were assayed in serum collected from the patients. IgM RF was determined by nephelometry. Enzyme-linked immunoassay for anti-CCP was done using the second-generation commercial kit (DIASTAT, Axis-Shield Diagnostics limited). An RF value of $\geq$20 U/ml and an anti-CCP value of $\geq$15 U/ml were considered positive according to manufacturer's specifications.

Bone Mineral Density (BMD) was determined by a Lunar Prodigy Vision Dual-energy X-ray absorptiometry (DXA) system (Lunar, Madison, WI, USA). The DXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. All BMD measurements were carried out by two experienced technicians. Daily quality control was carried out by measurement of a Lunar phantom. At the time of the study, phantom measurements showed stable results. The phantom precision expressed as the coefficient of variation percentage was 0.08. Moreover, reproducibility assessed in clinical practice showed a smaller detectable difference of 0.04 g/cm^2 (spine) and 0.02 g/cm^2 (hips) [16]. Patient's BMD was measured at the lumbar spine (anteroposterior projection at L1-L4) and at the femurs (femoral neck, trochanter and total hip) [17]. Using the Moroccan female normative data [18], The World Health Organization classification system was applied, defining osteoporosis (OP) as T-score ≤ -2.5 and osteopenia as -2.5 < T-score ≤ -1. Study participants were categorized by the lowest T-score of the L1-L4 lumbar spine, femur neck, or total femur.

Imaging performance could be obtained by lateral spine imaging when performing BMD measurement using DXA, with specific software, the so-called Vertebral Fracture Assessment (VFA). VF evaluation was performed (T4 to L4) qualitatively and then semiquantitatively using the Genant classification [19]. VFA was classified using a combination of the Genant semiquantitative approach and morphometry. Each VFA image was inspected by two trained readers (IG & AM) to decide if there were any VFs (decision by consensus). Grade 1 (mild) fracture is a reduction in vertebral height of 20–25%, grade 2 (moderate) a reduction of 26–40%, and grade 3 (severe) a reduction of over 40% [19]. In the case of doubt regarding fracture grade, the vertebrae in question were measured using built-in morphometry. Automatic vertebral recognition by the software was used. The positioning of the six morphometry points was modified by two experienced investigators only when the software failed to correctly recognize vertebral heights. The intra-rater reproducibility was evaluated using the kappa score to 0.9 ($p < 0.0001$). Subjects with grade 1 or higher fractures were included in the fracture group. However, as many studies rarely report mild deformities as "fractures", and to realize comparisons with the literature, we performed a double analysis including and excluding grade 1 fractures from the fracture group.

Radiographs of both hands (posteroanterior view) were assessed and scored by the same readers for joint damage using Sharp/van der Heijde (SvH) scoring [20] wherein 16 joints of hands were assessed for erosions (range 0–5/joint, maximum score 80 for each hand) and 15 joints for joint space narrowing (range 0–4/joint, maximum score 60 for each hand). The cumulative score is obtained by adding these 2 components (maximum score 280). Readers were blinded to each subject's identity and clinical status. Inter-observer reliability was found to be very good (unweighted mean kappa = 0.78, mean percentage agreement = 95%).

Results are expressed as mean ± SD and range. Risk factors related to the presence or absence of anti-CCP were tested for significance using the Student's *t*-test for quantitative variables and chi-square test for qualitative variables. Analysis of variance ANOVA was used to compare patients according to RF and anti-CCP combined status [positive anti-CCP (+) and positive RF (+); anti-CCP+ and negative RF(−); negative anti-CCP (−) and RF+; and anti-CCP− and RF−]. Multivariate regression analysis was used to estimate the independent effects of some clinical, laboratory, and radiological variables on the presence of anti-CCP. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) was used for statistical analyses. The level of significance was $P < 0.05$.

3. Results

In this cohort of 136 female patients with RA, the mean age, weight and disease duration were 49.6 ± 7.4 years (27–64 years), 66.5 ± 11 kg (44–104 kg) and 7.7 ± 5 years (1–25 years) respectively. The majority of our patients were treated by methotrexate (MTX) 121 (88.9%), and only 8 (5.8%) were taking leflunomide (LEF) and 5 (3.6%) were taking sulfasalazine (SAS). Two (1.4%) patients were taking a combination of hydroxychloroquine (HCQ), MTX and SAS. None of our patients was treated by biologics. The mean DAS28 was 4.8 ± 0.9. In our cohort, no patient was in a state of clinical remission, 8 (5.9%) with low activity, 76 (55.9%) with moderate activity, and 52 (38.2) with high activity.

The mean HAQ score was 1.2 ± 0.9, indicating moderate disability. Moreover, 109 (80.1%) patients had positive anti-CCP and 114 (83.8%) had positive RF. The mean SvH narrowing and erosion score was 56 ± 32.7 and 29.8 ± 35.9, respectively. OP was observed in 55 (40.4%) patients and VFs were detected in 21 (15.4%). Other details of clinical, biological parameters of these patients are reported in Table 1.

Table 2 shows the difference between patients with and without anti-CCP. The weight, erythrocyte sedimentation rate (ESR), RF positivity and titer, SvH narrowing and erosion score and OP were significantly higher in patients with positive anti-CCP. However, disease duration, HAQ, DAS28 and frequency of VFs were comparable in both groups.

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