

Case Report

Comparison of Activity Score DAS28-ESR and DAS28-CRP in Moroccan Patients with Rheumatoid Arthritis

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Submitted: 03 June 2016

Accepted: 24 January 2017

Published: 25 January 2017

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OPEN ACCESS**Keywords**

- Rheumatoid arthritis
- Erythrocyte sedimentation rate
- C-reactive protein
- Disease activity score (DAS28)

Abstract

Background: Disease Activity Score-28 joints (DAS-28) is nowadays the gold standard for measuring the disease activity in patients with RA. The original DAS-28 was based on erythrocyte sedimentation (ESR), but an alternative formula incorporating C-reactive protein (CRP) [DAS-28(CRP)] has been developed.

Objectives: To compare the disease activity score DAS28-ESR versus DAS28-CRP, and to determine the factors that might influence their difference. To estimate the disease activity score DAS28-CRP threshold values that correspond to DAS28-ESR values in Moroccan patients with rheumatoid arthritis.

Patients and methods: Patients with RA were included in a cross-sectional study. We have collected the demographic characteristics and the characteristics of the RA: duration of evolution, global disease activity on a 100 mm visual analogue scale assessed both by the patient (GDAP), morning stiffness in minutes, functional impact of the disease assessed by the HAQ (Health Assessment Questionnaire), and current corticosteroid dose. The disease activity was assessed by the DAS28-ESR and DAS28-CRP. A concordance correlation between DAS28-ESR and DAS28-CRP was performed. We defined a new variable DIFDAS=DAS28-ESR – DAS28-CRP (differences between the two indexes). Factors influencing this difference were tested by univariate then multivariate logistic regression. Using DAS28-ESR as gold standard, the passing Bablok and Bland-Altman methods were used to assess the agreement between DAS28-ESR and DAS28-CRP.

Results: 103 patients were included with a female predominance (87.4 %). Mean age was 49.7 ± 11.4 years. Median disease duration was 8 years [3-14]. There was a strong positive concordance between the two indexes of 0.93 with CI 95% [0.91-0.95], although the DAS28-ESR value obtained was higher than that of DAS28-CRP at approximately 90% of the visits (n= 93). Significantly, the difference between both indexes was higher than 0.6 in 42.7% of the visits studied (n=44). In multivariate analysis, factors significantly associated with this difference were high dose of steroids and significant functional impairment ($p < 0.05$). There was a difference between DAS28-ESR and DAS28-CRP values ($p < 0.05$). Using Bland and Altman method, we found that DAS28-CRP under-estimate threshold values of DAS28-ESR by 0.49 with CI 95% [-1.96, +1.96].

Conclusion: Our study showed a positive concordance between the DAS28-ESR and DAS28-CRP. But DAS28-ESR would be higher than DAS28-CRP in patients with high dose of corticosteroids and significant functional impairment.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that causes structural joint damage, incapacitation, and alterations in quality of life. Therapeutic goals and strategies have changed over the last decade with high dose weekly methotrexate (MTX), the arrival of biological agents [1,2], and tight control strategy [3]. Importantly, these strategies aimed at achieving low disease activity and controlling progression. On the other hand, the term remission is still ill-defined, and the various remission

criteria allow different degrees of disease activity to be called remission [4,5].

Disease Activity Score-28 joints (DAS-28) is nowadays the gold standard for measuring the disease activity in patients with RA [6]. It is recommended by the European League against Rheumatism (EULAR) [7].

The DAS28 is calculated from four components: tender joint count, swollen joint count (both performed by the treating doctor), visual analogue scale (VAS) score of the patient's global

health and the laboratory parameter erythrocyte sedimentation rate (ESR). Cut-off points of 2.6, 3.2 and 5.1 have been proposed to be indicative of remission, low disease activity and high disease activity, respectively [8].

C-reactive protein (CRP) is more accurate as indicator of inflammation than ESR and it is also more sensitive to short-term changes [9,10]. Accordingly, a formula for DAS28 has been proposed whereby the index is calculated using CRP instead of ESR (<http://www.dasscore.nl>).

It was originally believed that there was a very good correlation between the DAS28-CRP and the DAS28-ESR and the formula for calculating DAS28-CRP values was designed to produce equivalent results to those of the DAS28-ESR. However DAS28-CRP values seem to be lower than DAS28-ESR values in clinical practice and some authors argue that the DAS28-CRP may need lower cut-offs for categorizing disease activity [8,11].

In the view of the above, the aim of our study was to determine which factors might account for the differences between the two versions of the DAS28 and to estimate the disease activity score DAS28-Creactive protein (CRP) threshold values that correspond to DAS28-erythrocyte sedimentation rate (ESR) values for remission, low disease activity and high disease activity in Moroccan patients with rheumatoid arthritis.

PATIENTS AND METHODS

Patients

A total of 103 RA cases were included in a cross-sectional study in the Department of Rheumatology, at El Ayachi hospital, Ibn Sina University hospital. The period of data collection was from October 2012 to March 2013. Patients were diagnosed to have RA by the rheumatologist according to American College Rheumatology (ACR) classification Criteria for RA [12]. Patients with diseases other than rheumatoid arthritis were excluded from the study. The study and the aim of the work were explained to the patients and an informed consent was obtained from all subjects. The study was approved by ethics committee of our university hospital.

Clinical and laboratory assessment

All patients were asked about their age, duration of the disease, RA treatment including dose of corticosteroid at the time of study. The patients were clinically examined: the body mass index, the morning stiffness in minutes, the number of swollen joints (0–28) and tender joints (0–28) were documented. The 28 joints included bilateral knees, shoulders, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints. The patients were asked to mark on the VAS (Visual analogue scale) of 0–100 mm according to their global assessment of disease activity (GDAP). We assessed functional impact of the disease by the HAQ (Health Assessment Questionnaire) and disease activity by disease activity score (DAS28).

DAS28 was calculated using an electronic device in the online software <http://www.4s-awn.com/DAS28/DAS28.html> [13].

Blood samples from all patients were measured on-site. CRP levels were measured by a standard method using a latex

agglutination turbidimetric immunoassay. The CRP detection level was >0 (mg/dl). Erythrocyte sedimentation rate (ESR) was measured (using Westergren's method, in mm/ hour).

Statistical analysis

Statistical analysis was done by computer using SPSS software (SPSS, Inc., Chicago, IL, USA). As DAS28 values were normally distributed, we described them using mean \pm standard deviation (SD), whereas all other variables were described using medians and interquartile range (IQR).

Coefficient of concordance [14], was used to show relationships between DAS28-CRP and DAS28-ESR values. We defined a new variable DIFDAS=DAS28-ESR-DAS28-CRP (differences between the two indexes). We considered a difference between DAS28-ESR and DAS28 -CRP as significant when it is greater than or equal to 0.6 [15]. Factors influencing this difference were tested by Univariate Logistic Regression. Then, we undertook Multivariate Logistic Regressions including all variables that reached a $p < 0.10$ at the univariate analyses. Results were reported with odds ratio (OR) and 95% confidence interval (CI). Using DAS28-ESR as gold standard, the passing Bablok [16], and bland & Altman [17], methods were used to assess the agreement between DAS28-ESR and DAS28-CRP.

RESULTS

Patient characteristics

103 patients were included with a female predominance (87.4 %). Mean age was 49.7 ± 11.4 years. Median disease duration was 8 years (3-14). Rheumatoid factor was positive in 58 patients (56.3%) and anti-cyclic citrullinated peptide antibodies in 68 (66%) of them. Median (range) Morning stiffness in these patients was 15 (0, 60). Mean DAS28-ESR was 4.2 ± 1.7 and mean DAS28-CRP was 3.7 ± 1.5 . Patients receiving corticosteroids and methotrexate were respectively 92.6% and 97.1%. Mean dose of corticosteroids was 7.5 ± 3.2 . The patient characteristics are shown in Table (1).

Table 1: Demographic and clinical characteristics of RA patients (n=103).

| Characteristics | N = 103 |
|--|-----------------|
| Age (per years) | 49,7 \pm 11,4 |
| Sex (female/male) | 90 / 13 |
| Median duration of illness (per years) | 8 (3-14)* |
| Morning stiffness | 15 (0-60)* |
| Tender joint count | 4 (1-10)* |
| Tender joint swollen | 1 (0-4)* |
| GDPA (mm) | 40 \pm 29 |
| ESR (mm/h) | 30 (14-40)* |
| CRP (mg/l) | 6.6 (5-14)* |
| DAS 28 ESR | 4,27 \pm 1,75 |
| DAS 28 CRP | 3,71 \pm 1,50 |
| HAQ | 0,5 (0-1,37)* |
| Dose of corticosteroids | 7.5 \pm 3.2 |

*median and quartiles

GDAP: Global Disease Activity Assessment by the Patient; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

Relationship between DAS28-ESR and DAS28-CRP values

The correlation coefficient of ESR versus CRP was 0.588 ($p < 0.001$) and the concordance correlation coefficient of DAS28-ESR versus DAS28-CRP was 0.93 with CI 95% [0.91-0.95], indicating that the DAS28-ESR and DAS28-CRP were strongly concordant, suggesting that the DAS28-CRP can be used as an alternative to the DAS28-ESR. Mean DIFDAS was 0.49 ± 0.3 . DAS28-ESR was higher than DAS28-CRP in 93 patients (90%) and the difference between both indexes was higher than 0.6 in 44 patients (42.7%). Furthermore, considering the cut-off points proposed by Prevo et al. [18]. Our patients were in remission at 24.8% of cases when the DAS28-CRP was applied but only in 18.4% of the patients when applying the DAS28-ESR (Table 2). Conversely, the proportion of cases with high disease activity was higher when the DAS28-ESR was applied than when the DAS28-CRP (Table 2).

DAS28-CRP threshold values

Using passing and bablok method, the regression equation was: DAS 28-CRP = $0.13 + 0.85$ DAS 28-ESR (Figure 1). The intercept of passing and bablok regression was 0.13 with CI 95% [0.03-0.23]. The slope of passing and bablok regression was 0.85 with CI 95% [0.83-0.87]. Generally in passing and bablok method, if 95% CI for intercept includes value zero it can be concluded that there is no significant difference between obtained intercept value and value zero and there is no constant difference between two indices. Respectively, if 95% CI for slope includes value one, it can be concluded that there is no significant difference between obtained slope value and value one and there is no proportional

Table 2: Classification of disease activity.

| Disease activity | Remission | Low | Moderate | High |
|------------------|-----------|-------|----------|-------|
| DAS28-CRP | 24.8% | 13.9% | 42.6% | 18.8% |
| DAS28-ESR | 18.4% | 11.7% | 37.9% | 32.0% |

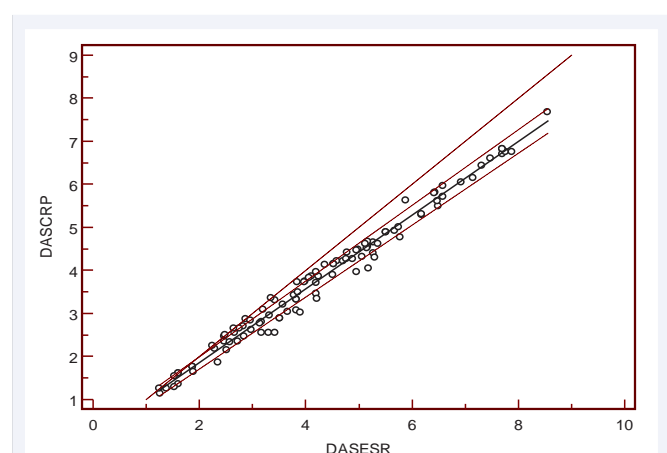


Figure 1 Passing and bablok regression analyses of DAS 28-ESR and DAS 28-CRP. Scatter diagram with regression line and confidence bands for regression line. Regression line equation: $y = 0.13 + 0.85x$; 95% CI for intercept 0.03 to 0.23 and for slope 0.83 to 0.87 indicated statistically significant difference in slope and intercept.

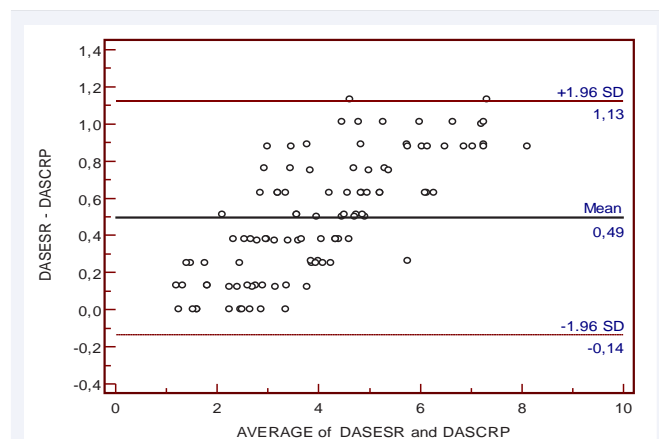


Figure 2 The Bland-Altman graph plots the difference between two indexes (DAS 28-ESR and DAS 28-CRP) against their averages.

difference between two indices. So there was a difference between DAS 28-ESR and DAS 28-CRP.

Using Bland-Altman method, we found that DAS 28-CRP under-estimate threshold values of DAS 28-ESR by 0.49 CI [-1.96, +1.96] (Figure 2).

Factors influencing DIFDAS

In the univariate analysis disease duration and morning stiffness were among factors that influence DIFDAS (Table 3). However, after adjusting for the ESR and CRP values, the multivariate analysis demonstrated that high dose of steroids and significant functional impairment were those that contributed significantly to the differences between DAS28- ESR and DAS28-CRP (Table 3).

DISCUSSION

CRP measurements are widely used in the routine evaluation of several inflammatory diseases. In addition, CRP response to treatment is faster than ESR response [19,20]. On the basis of these data, a formula to calculate DAS28 using the CRP values as the acute phase reactant variable has been proposed as beneficial in clinical practice of rheumatology [8].

Our study showed that there was direct and excellent concordance between DAS 28-ESR and DAS 28-CRP. These results agreed with other studies which showed that DAS28-CRP can be used as an alternative to the DAS28-ESR [8,15].

However, DAS28-ESR was higher than DAS28-CRP in 90% of patients and the difference between both indexes was higher than 0.6 in 42.4 % of patients. Our results are similar to those of Tamhane, Castrejon, and Eisuke, [21] and cut-off values proposed by Inoue et al., for DAS28-CRP [11], support our finding that the DAS28-CRP underestimate the disease activity of the patients and increase the proportion of patients in remission. DAS28-CRP values was, on average, 0.5 points lower than the DAS28-ESR values which joined our results.

I. Castrejón et al. [15], showed that DAS28-ESR tends to produce higher values in women and long-term disease patients. In our study gender didn't influence DIFDAS and we can relate

Table 3: Univariate and multivariate analysis of factors influencing DIFDAS.

| | Univariate analysis | | Multivariate analysis | |
|------------------------------|---------------------|------------------|-----------------------|--------------|
| | OR [95% CI] | p-Value | OR[95% CI] | p-Value |
| Gender (female) | 1.72 [0.83-3.54] | 0.141 | | |
| Age (per years) | 1.74 [0.97-1.01] | 0.541 | | |
| Disease duration (per years) | 1.05 [1.003-1.007] | 0.001 | | 0.187 |
| GDAP | 1 [0.98-1.01] | 0.72 | | |
| Morning stiffness | 1.02 [1.012-1.026] | <0.001 | | 0.507 |
| BMI | 0.99 [0.97-1.00] | 0.321 | | |
| Rheumatoid Factor | 0.55 [0.31-0.97] | 0.042 | | 0.229 |
| ACPA | 0.47 [0.26-0.85] | 0.014 | | 0.258 |
| ESR | 1.04 [1.02-1.05] | <0.001 | 1.06 [1.02-1.10] | 0.002 |
| CRP | 1.04 [1.018-1.056] | <0.001 | 0.93 [0.88-0.97] | 0.005 |
| HAQ | 5.51 [3.60-8.41] | <0.001 | 2.425 [1.05-5.59] | 0.038 |
| Therapy | | | | |
| Methotrexate | 0.5 [0.14-1.85] | 0.308 | | |
| Steroids | 1.33 [1.15-1.53] | <0.001 | 1.023 [1.05-1.37] | 0.008 |

ACPA: Anti-Cyclic Citrullinated Peptide Antibodies; GDAP: Global Disease Activity Assessment by the Patient; HAQ: Health Assessment Questionnaire; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; BMI: Body Mass Index.

that to limited number of men. Long-term disease in univariate analysis was among factors influencing this difference between DAS 28-ESR and DAS 28-CRP. But after adjusting for the ESR and CRP values, the multivariate analysis demonstrated that high dose of steroids and significant functional impairment were those that contributed significantly to the differences between DAS28- ESR and DAS28-CRP. Many studies approve the strong correlation between disease activity and low functional capacity at patients with Rheumatoid arthritis [22,23]. Previously, it has been demonstrated that corticosteroids down-regulate the production of the pro-inflammatory cytokines including IL-6 which stimulate the production of CRP [24,25]. These data may explain the role of corticosteroids in the difference found between DAS28-ESR and DAS28- CRP.

Hence, when making clinical decisions based on remission using the DAS28-CRP in the place of the DAS28-ESR, we should consider this difference between these scoring systems.

CONCLUSION

Our data show that DAS28-ESR and DAS28-CRP are not fully equivalent. DAS28-CRP produces lower values than DAS28-ESR, especially in patients with high dose of corticosteroids and high functional impairment. However, specific cutoff points should be estimated for the DAS28-CRP. As the results were derived from only Moroccan patients, other studies to compare DAS28-CRP threshold values in people of other ethnic groups are necessary.

Author's contributions

N. Hajjaj-Hassouni, F. Allali, R. Aboqual, H. Rkain: correction section of the article. L. Lakhdar, S. El kabbaj, L. Medrare, A. Ngeuleu: collection of patients and fill the questionnaire. All authors read and approved the final manuscript.

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Cite this article

Slama IB, Allali F, El kabbaj S, Lakhdar T, Medrare L, et al. (2017) Comparison of Activity Score DAS28-ESR and DAS28-CRP in Moroccan Patients with Rheumatoid Arthritis. *Ann Orthop Rheumatol* 5(1): 1078.