

Are the C-reactive protein values and erythrocyte sedimentation rate equivalent when estimating the 28-joint disease activity score in rheumatoid arthritis?

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Abstract

A formula for calculating disease activity score with 28 joint counts (DAS28) with C-reactive protein (CRP) instead of the erythrocyte sedimentation rate (ESR) has been proposed.

Objective

Here we analyze the factors that contribute to the differences in the DAS28 when calculated using either the ESR (DAS28-ESR) or the CRP values (DAS28-CRP).

Methods

We analyzed the data from 587 visits made by 220 patients with early arthritis. The age at the onset of the disease was 51±16 years old and 76.3% of the patients were women. The disease evolution at the first visit was 5 months and at each visit information related to several variables was collected, including that necessary to calculate the DAS28-ESR and DAS28-CRP. We defined a new variable DIFDAS=DAS28-ESR – DAS28-CRP to analyze which independent variables account for differences between the two indexes.

Results

There was a correlation between the two indexes of 0.91 ($p<0.0001$), although the DAS28-ESR value obtained was higher than that of DAS28-CRP at approximately 90% of the visits. Significantly, the difference between both indexes was higher than 0.6 in 44% of the visits studied. A multivariate analysis showed that female gender and disease duration were associated with the higher values obtained for DAS28-ESR when compared to those of DAS28-CRP.

Conclusion

Our data show that DAS28-ESR and DAS28-CRP are not fully equivalent, because the former usually produces higher values. This finding is particularly relevant in females and patients with a long disease duration.

Key words

Rheumatoid arthritis, erythrocyte sedimentation rate, C-reactive protein, outcome measures.

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This study was funded by grants from the Instituto de Salud Carlos III: FIS 05/2041 and 05/2044 to IGA.

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Received on August 20, 2007; accepted in revised form on January 22, 2008.

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Introduction

Rheumatoid arthritis (RA) may cause severe and irreversible joint destruction leading to functional disability, impaired quality of life and increased comorbidity and mortality (1). Lately, the development of new therapeutic strategies has improved the prognosis of patients with RA. However such therapies are not free of serious adverse events and they are also very costly, posing a substantial economic burden to health care systems (2). It is therefore necessary to establish an accurate risk/benefit ratio for these agents as well as to quantify patients' response to these treatments, both in clinical trials and in daily practice.

The DAS is a combined index that incorporates, in a continuous score, the Ritchie articular index, the 44 swollen joints count, the global disease activity as assessed by the patient, and the erythrocyte sedimentation rate (ESR) as an acute phase reactant. The DAS has been proved to be a sensitive and specific tool to measure disease activity in RA (3). Moreover, when DAS is used to monitor treatment response together with monthly visits, the level of disease control achieved is greater than when more traditional schedules are utilized (4).

One of the major downsides of the DAS is that its joint counts are time consuming. A simplified version of the DAS that uses 28-joint counts, the DAS28, was then developed. The DAS28 certainly improves the feasibility of the index without losing any significant information of the original DAS (5, 6). An additional problem associated with the DAS or DAS28 index is that although the ESR is extensively used to assess disease activity in RA, it can be influenced by several conditions such as age, female gender, anemia, serum fibrinogen levels, immunoglobulins and rheumatoid factor (7). C-reactive protein (CRP) is more accurate as indicator of inflammation than ESR and it is also more sensitive to short-term changes (7-9). Discrepancies between ESR and CRP values may result from the effect of blood constituents that are not related to inflammation but that can interfere with the ESR. Accordingly, a

formula for DAS28 has been proposed whereby the index is calculated using CRP instead of ESR (<http://www.das-score.nl>). Although it was originally believed that there was a very good correlation between the DAS28-CRP and the DAS28-ESR, some authors argue that the DAS28-CRP may need lower cut-offs for categorizing disease activity (10, 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 what extent these factors had any consequences into the assessment of RA activity in daily clinical practice.

Patients and methods

This is a prospective longitudinal observational study in which all patients attending the Early Arthritis Clinic in our center from September 2001 to June 2006 were included. To be referred to the clinic, patients had to have two or more swollen joints for at least four weeks and symptoms for less than one year. Patients were excluded if they had been diagnosed of gouty arthritis, septic arthritis, spondyloarthropathies or connective tissue diseases during the follow-up. The study protocol was reviewed and approved by the Local Research Ethics Committee and all patients who entered the study signed a written consent form after being informed about the details of the protocol.

At each visit, the following data are collected per protocol and entered into an electronic database: clinical and demographic information, data about treatments with disease modifying anti-rheumatic drugs, 28 tender and swollen joint counts (TJC and SJC, respectively), global disease activity on a 100 mm visual analogue scale assessed both by the patient (GDAP) and by the physician (GDAPh), and basic laboratory tests including ESR and CRP. DAS28 indexes, with ESR and with CRP were calculated as previously described:

$$\text{DAS28-ESR} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot (\text{GDAP}) \quad (5)$$

$$\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP}+1) + 0.014 \cdot (\text{GDAP}) + 0.96$$

(<http://www.das-score.nl>)

Conflict of interest:

Dr. I. Gonzalez-Alvaro has received unrestricted research funding from Abbott Laboratories, Sanofi-Aventis and Bristol-Myers Squibb. However, these research projects have no relation with this study; the other co-authors have declared no competing interests.

Statistical procedures

All statistical analyses were performed using Stata 9.2 for Windows (StataCorp LP, College Station, TX, USA). We first compared the distribution of DAS28-ESR and DAS28-CRP using graphic tools such as the *kdensity* command that provides kernel density estimations. Then, to compare how both indexes evaluated disease activity at each visit, we created the DIFDAS variable:

$$\text{DIFDAS} = \text{DAS28-ESR} - \text{DAS28-CRP}$$

We used the Mann-Whitney-U or Pearson correlation tests to determine whether there was any association between DIFDAS and independent categorical or continuous factors, respectively. Then, we undertook multivariate linear regressions by using the *glm* command of Stata (Gaussian as *family* option and identity as *link* option) including all variables that reached a $p < 0.05$ at the bivariate analyses. Best fit models were obtained by stepwise backward estimation, removing all variables with a $p > 0.05$.

Results

A total of 220 patients (76.4% female) were included in the study. We analyzed the data from 587 structured visits in a follow-up period of two years, including 220 initial visits, 139 second visits, 125 third visits and 103 fourth visits after 6, 12 and 24 months of follow-up, respectively. The age at the onset of the disease was 51 ± 16 years old and the mean disease duration at the first visit 5.1 ± 2.9 months. Rheumatoid factor was positive in 128 patients (58.2%) and anti-cyclic citrullinated peptide antibodies in 70 (31.2%) of them. They represent a fairly average early arthritis cohort, with more than half of the patients (57.3%) already fulfilling ACR criteria for RA at entry.

The values of DAS28-ESR in our cohort ranged from 0 to 8.2, with a median of 3.4 and an IQR of 2.5–4.4. In contrast, the DAS28-CRP values ranged from 0.2 to 7.7 and showed a median of 2.8 (IQR: 1.9–3.9). Although the correlation coefficient of the two indexes was 0.91 ($p < 0.001$), the value of DAS28-ESR was higher than DAS28-CRP in approximately 90% of the visits. The distribution of the values for both indexes

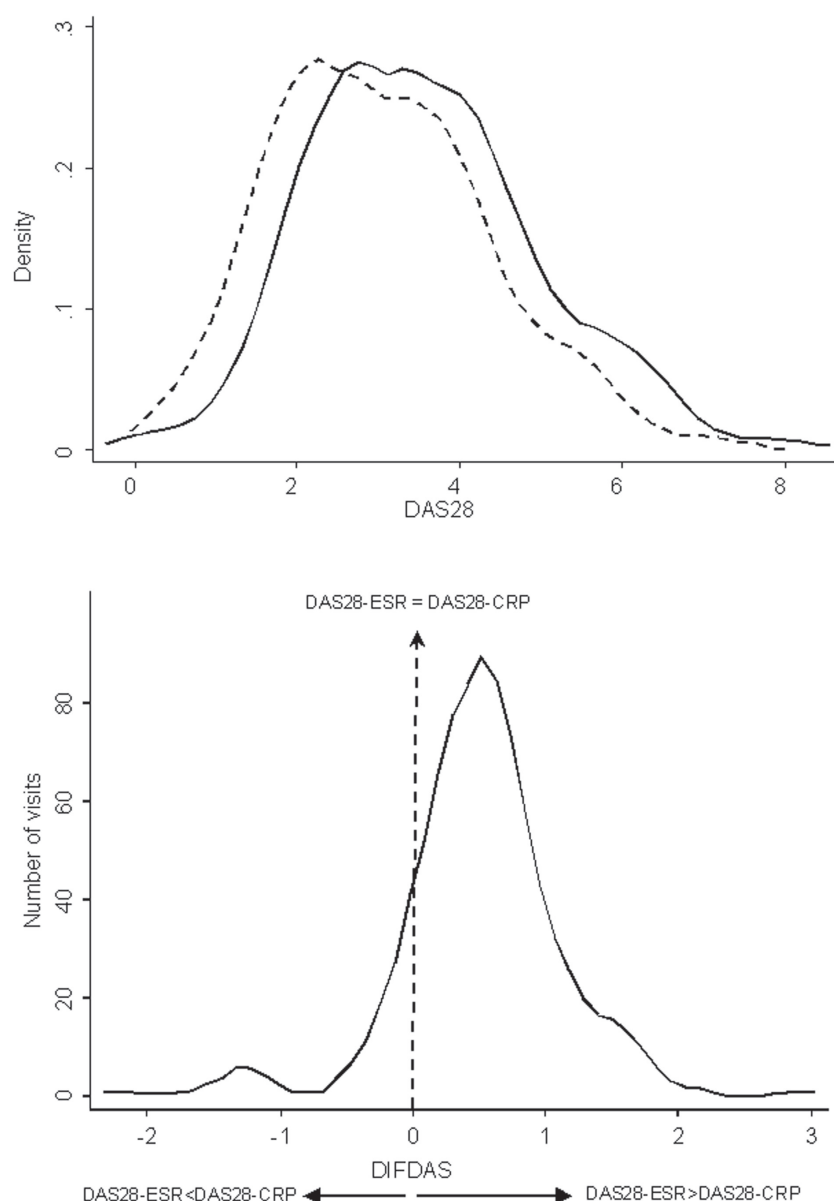


Fig. 1. A: Distribution of the DAS28 index calculated with the ESR (solid line) and CRP (dotted line) values in our population. B: Distribution of the DIFDAS values (see *Materials and methods* for definition) at all the visits analyzed in our cohort.

produced similar shapes, although the distribution curve for the DAS28-ESR was displaced toward higher values (Fig. 1A).

The difference between both indexes was higher than 0.6 at 44% of the visits and higher than 1.2 at 26% of the visits. These represent the minimum relevant variation in response to treatment depending on initial DAS28 value (less than 5.1 or higher than 5.1 respectively) according to the EULAR criteria (12). Furthermore, considering the cut-off points proposed by Prevoo *et al.* (5) our patients were in remission at 41%

of the visits when the DAS28-CRP was applied but only in 26% of the visits when applying the DAS28-ESR (Table I). Conversely, the proportion of cases with low, moderate or high disease activity was higher when the DAS28-ESR was applied than when the DAS28-CRP (Table I).

Then, we studied which variables could explain these differences by generating a new variable, DIFDAS, as defined in the Methods. The distribution of DIFDAS was displaced towards positive values, indicating that DAS28-ESR renders a higher value than DAS28-CRP in most

Table I. Classification of disease activity.

Disease activity	Remission	Low	Moderate	High
DAS28-CRP	41.3%	14.4%	35%	9.3%
DAS28-ESR	26%	17.9%	40.8%	15.2%

visits (Fig. 1B). As shown in Table II, several variables were associated with differences in DIFDAS in the bivariate analysis. However, after adjusting for the ESR and CRP values, the multivariate analysis demonstrated that the variables of gender and disease duration were those that contributed significantly to the differences between DAS28-ESR and DAS28-CRP. Indeed, women showed higher DAS28-ESR values than those obtained with the DAS28-CRP (Fig. 2), and the contribution of gender to the differences between both indexes was 0.2 points higher for women in the DAS28-ESR index (Table II).

With regards to disease duration, the multivariate analysis suggested that the difference in the DAS28-ESR increased with respect to the DAS28-CRP, with a regression coefficient of 0.02 per month of disease duration (Table II), although this effect was not linear (Fig. 3A). The differences between the two indexes was 0.5 points on average in the first 20

months of disease duration and thereafter, the differences increased continuously over time due to the increasing relative DAS28-ESR values. Regarding the clinical consequences of this finding, it seems that after two years of disease duration, disease activity estimated by DAS28-ESR tends to reach a plateau (Fig. 3B) whereas when estimated with CRP the disease activity of the cohort continues to improve (Fig. 3C).

Nevertheless, since the DAS score was developed and validated to be used in rheumatoid arthritis patients, we reanalyzed our data separately both in the RA patients and in patients with undifferentiated arthritis (UA). Coefficients for gender were 0.19 ± 0.06 ($p=0.002$) for RA patients and 0.26 ± 0.09 ($p=0.005$) for UA patients and for disease duration were 0.018 ± 0.002 ($p<0.001$) for RA and 0.021 ± 0.002 ($p<0.001$) for UA patients. In both cases, the coefficients were like those described for the whole population (Table II).

Discussion

A formula to calculate DAS28 using the CRP values as the acute phase reactant variable has been proposed on the basis that CRP response to treatment is faster than ESR response (13, 14). Accordingly, DAS28-CRP has been included as an outcome variable in some clinical trials, although there is still insufficient information about how the DAS28-CRP index behaves in comparison with DAS28-ESR. In this regard, this study shows that the DAS28-ESR and DAS28-CRP values are not interchangeable and that DAS28-ESR tends to produce higher values in women and long-term disease patients.

With regards the first of these issues, in 44% and 26% of the visits analyzed in our study the differences between both indexes were greater than 0.6 and 1.2 points respectively, the minimal improvements considered to be relevant by EULAR criteria depending on baseline DAS28 measurement (12). Therefore, our data suggest that despite the good correlation between both indexes, if we evaluate disease activity with the DAS28-ESR in one visit and then with DAS28-CRP in the next, we may incorrectly consider the patient to

Table II. Bivariate and multivariate analysis.

	Bivariate analysis		Multivariate analysis	
	DIFDAS	p-value	Coef. of regression	p-value
Gender (male vs. female)	0.24 [-0.10-0.52] / 0.58 [0.35-0.86]	<0.05	0.199	0.001
Disease (RA vs. UA)	0.51 [0.20-0.83] / 0.52 [0.23-0.80]	0.82		
Therapy: None	0.49 [0.17-0.75]		0.110	0.011
MT	0.51 [0.24-0.80]	0.015		
CT	0.63 [0.34-1.17]		0.142	0.017
CCP (+) vs. (-)	0.49 [0.17-0.77] / 0.53 [0.28-0.94]	0.006	-----	-----
RF (+) vs. (-)	0.54 [0.26-0.96] / 0.53 [0.19-0.96]	0.49	-----	-----
GDAP	0.0092	0.828	-----	-----
GDAPh	-0.0005	0.991	-----	-----
Pain	0.034	0.415	-----	-----
HAQ	0.118	0.005	-----	-----
ESR	0.381	<0.001	0.23	0.001
CRP	-0.118	0.005	-0.84	0.001
Age (years old)	0.007	0.862	-----	-----
Disease duration	0.402	<0.001	0.024	0.001

RA: rheumatoid arthritis; UA: undifferentiated arthritis; MT: monotherapy; CT: combined therapy; CCP: anti-cyclic citrullinated peptide antibodies; RF: rheumatoid factor; GDAP: global disease activity assessment by the patient; GDAPh: global disease activity assessment by the physician; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

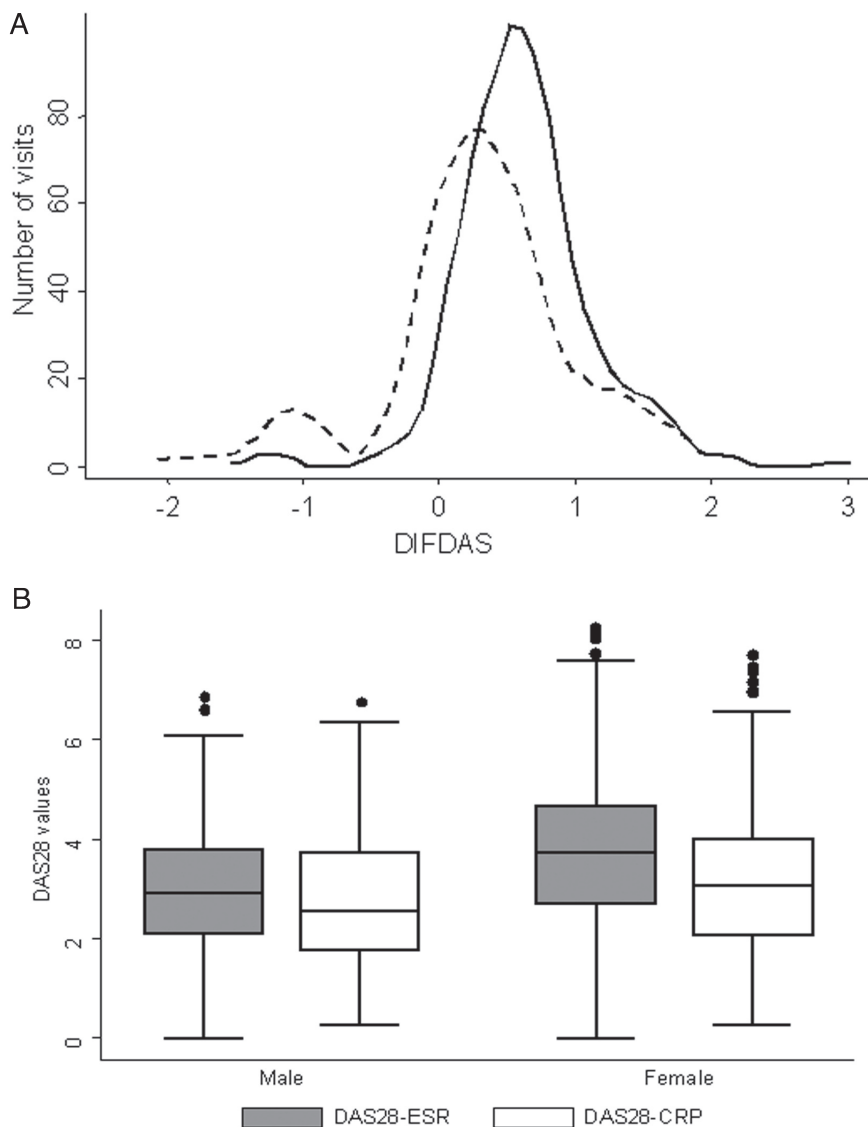


Fig. 2. Effect of gender on the evaluation of disease activity estimated with ESR and CRP. **A:** Distribution of the DIFDAS variable in female (solid line) or male patients (dotted line: see *Materials and methods* for definition). **B:** Distribution of the DAS28 values calculated with ESR (grey boxes) or CRP (white boxes) according to gender. Data are presented as the interquartile range (p75 upper edge of the box, p25 lower edge, p50 midline in the box), as well as the p95 (upper line from the box) and p5. Dots represent the outliers.

have improved. In addition, if we apply the cut-off values proposed for the DAS28-ESR to DAS28-CRP, we might underestimate the disease activity of the patients and increase the proportion of patients in remission or with weak disease activity. Indeed, the estimated cut-off values proposed by Inoue *et al.* for DAS28-CRP (10) support our finding that the DAS28-CRP values are, on average, 0.5 points lower than the DAS28-ESR values.

The second finding raises the question as to which index is best, as both have

their advantages and disadvantages. For clinical trials, we would expect to use an index that rapidly shows the effect of therapeutic agents. Considering the fast response of CRP to variations in disease activity, we may choose DAS28-CRP in this case. On the other hand, in daily clinical practice we would prefer an index that showed us how the patient was on average during the preceding period, and DAS28-ESR would probably be better in this respect due to its slower response to variations in disease activity when compared with

CRP. However, DAS28-ESR has additional problems as it is less sensitive to changes in long-term patients. In addition, women may be less frequently considered in remission when assessing disease activity with the DAS28-ESR ($\text{DAS28} < 2.6$).

On the other hand, regarding factors that might bias our results, we may consider that only about 60% of our patients fulfilled the ACR criteria for RA classification (15). However, this factor did not significantly account for the differences between DAS28 calculated with ESR or CRP. In addition, CRP levels may increase with age in men but not in women (16). Nevertheless, our results suggest that this effect is probably moderate and it is clearly less important than the enhanced ESR levels observed in females with a long-term disease. Furthermore, other factors such as race, smoking, increased blood pressure, diabetes, high body mass index or abdominal adiposity may also be associated with increased CRP levels (16, 17). In our analysis, we did not adjust for all these variables since this information was not collected, and therefore, we can not exclude that they may influence the final results. Thus, perhaps the indexes proposed to evaluate the disease activity in RA patients should be evaluated in different subsets of patients in order to establish how robust they are.

In summary, our data suggest that when the DAS28 is calculated with the CRP it may be more accurate to determine RA activity, especially in long-term female patients. However, specific cut-off points should be estimated for the DAS28-CRP since it produces lower values than DAS28-ESR (10, 11). In this regard, preliminary threshold values have been proposed for DAS28-CRP in Japanese patients (10) and our group is now involved in a study to estimate such cut-off points in our population. In addition, our data suggest that DAS28 might behave similarly when applied to RA or UA patients. In this regard, we believe that comparisons between different populations should provide additional information about the reliability and reproducibility of these indexes.

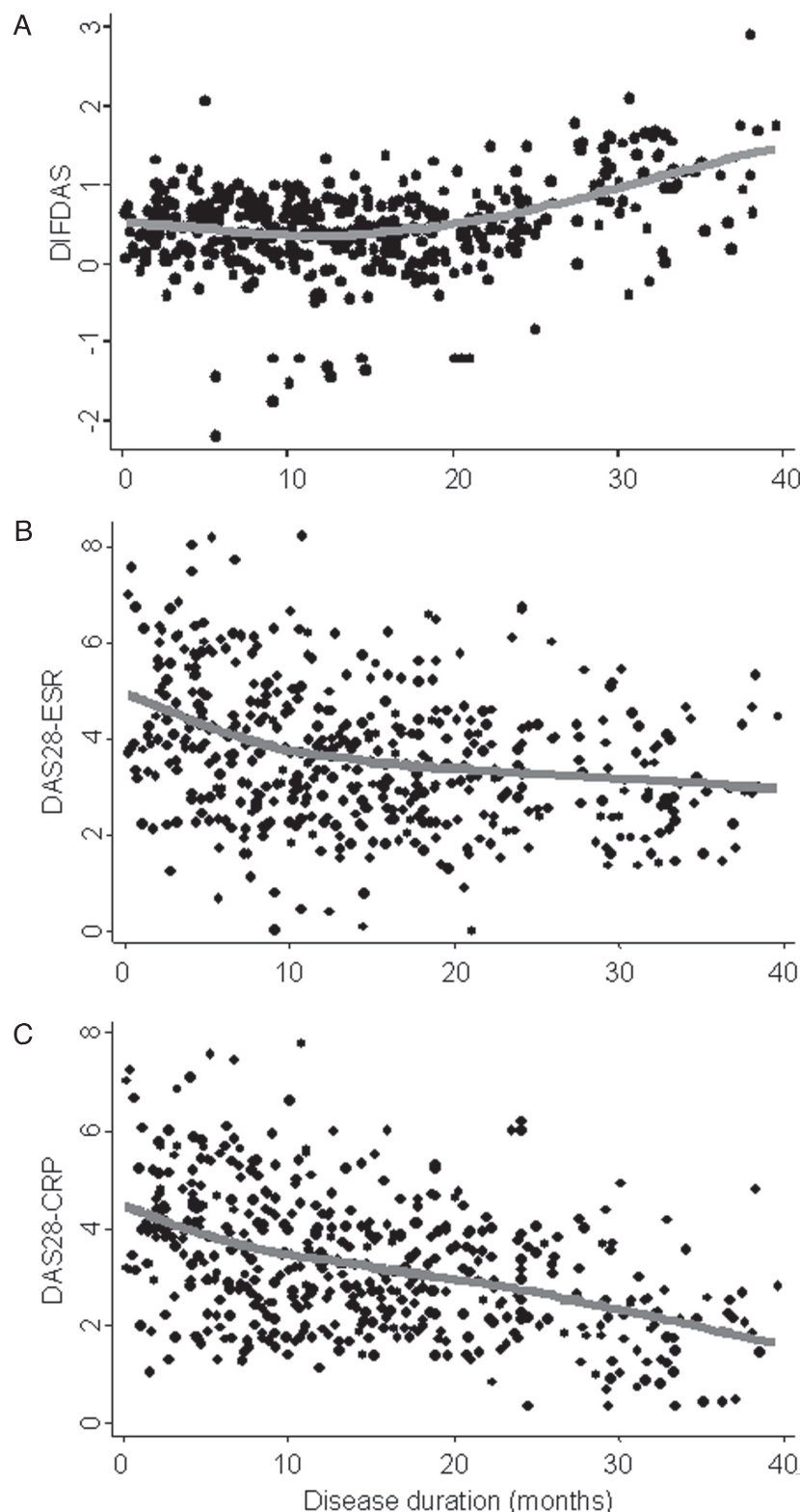


Fig. 3. Effect of disease duration on the evaluation of disease activity estimated with ESR or CPR. **A:** Distribution of the DIFDAS values (see *Materials and methods* for definition) over the disease duration of the patients in the cohort. **B:** Evolution of disease activity of the cohort estimated with DAS28-ESR. **C:** Evolution of disease activity of the cohort estimated with DAS28-CRP. Dots represent the values of each variable for each patient in the cohort at the different follow-up visits. The solid grey line represents the local (bandwidth 0.8) least-squares weighted regression of each variable (DIFDAS, DAS28-ESR or DAS28-CRP) with respect to disease duration estimated using the command `lowses` of Stata 9.2 for Windows.

Acknowledgements

The authors wish to recognize the influence of Dr Armando Laffon on our work, who instilled us with the eagerness to learn from the patient, both in the consultancy and in the laboratory, so that our findings might further improve the medical attention that we can offer them.

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