RHEUMATOLOGY

Rheumatology 2020;59:1622–1625
doi:10.1093/rheumatology/kez490
Advance Access publication 26 October 2019

Concise report

What do we measure with 28-joint DAS in elderly patients? An explorative analysis in the NOR-DMARD study

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Abstract

Objective. Insight into the influence of ageing on disease outcomes is limited. The objective of this study was to examine the potential effect of age on disease activity using the 28-joint DAS (DAS28) and its components in patients with RA.

Methods. Baseline data of DMARD-naïve patients with RA from the Norwegian Register of DMARDs were used. Linear regression explored the strength of the association between age (<45, 45–65 and >65 years) and each DAS28 component while accounting for education and gender. Adjusted predicted scores for DAS28 components and total DAS28 score were calculated for each age category.

Results. Baseline data from 2037 patients [mean age 55.2 years (S.D. 14.0), 68% females] were available. Regression models had to be stratified for gender (*P* for interaction <0.001); education was a significant covariate. Males >65 years of age with an intermediate level of education have a 56% higher ESR and 25% higher 28-joint swollen joint count as compared with their younger counterparts (<45 years). For females, corresponding differences were 51% and 27%, respectively. The age effect on the 28-joint tender joint count and patient global assessment was negligible. In patients with an intermediate education level, DAS28 was 5.0 *vs* 5.5 (10% increase) in the youngest *vs* oldest age groups, independent of gender.

Conclusion. The age-related increase in ESR and 28-joint swollen joint count scores without a relevant corresponding increase in 28-joint tender joint count and patient global assessment might imply that age-related processes (e.g. soft tissue changes, physiological ESR increase) contribute to a higher DAS28 in elderly patients.

Key words: rheumatoid arthritis, elderly, 28-joint Disease Activity Score (DAS28)

CLINICAL SCIENCE

Rheumatology key messages

- Elderly patients show increasing ESR and 28-joint swollen joint count scores without an increase in 28-joint tender joint count and patient global assessment.
- Age-related processes (e.g. osteoarthritis) might drive the DAS28 in elderly patients.

Introduction

Worldwide, the rate of population ageing will double in the next 3 decades [1]. As a result, the number of patients with inflammatory arthritis, including those with RA, will continue to increase [2]. The evolving demographic transition of the population living with RA makes it necessary to critically review the impact of ageing on disease activity, as this steers our treatment decisions.

The 28-joint DAS (DAS28) is commonly used to measure disease activity. The DAS28 was originally developed in a study population with a median age of 55 years, but it is conceivable that the DAS28 behaves differently in the elderly patient population [3]. Limited evidence suggests that OA and age-related changes in soft tissue have a negative impact on pain and remission criteria. For instance, researchers concluded that only 15% of the general population >50 years of age fulfil all four ACR remission criteria for RA [4, 5]. In addition, it is commonly known that ESR levels increase

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Submitted 7 June 2019; accepted 19 September 2019

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with age [6]. These findings suggest it might be important to take age into account when interpreting the DAS28-ESR. The objective of the current study was to explore a possible effect of age on the (components of the) DAS28-ESR in patients with RA.

Methods

Study design and data collection

Baseline data of patients enrolled between 2000 and 2012 into the Norwegian Register of DMARDs (NOR-DMARD) longitudinal cohort study and starting their first conventional synthetic DMARD (csDMARD) were used [7]. The NOR-DMARD was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee of Eastern Norway [7]. Written informed consent was obtained before inclusion. For the current study, additional ethical approval was not needed.

Study variables

Data on age, gender, level of education, disease duration, RF, 28-joint tender joint count (28-TJC), 28-joint swollen joint count (28-SJC), patient global assessment (PGA), ESR and CRP were used. Patients were categorized into three age groups: group 1, patients <45 years; group 2, patients 45–65 years; group 3, patients >65 years. Education level was categorized in three categories: low, ≤ 7 years of primary school to middle school/junior high school; intermediate, 1 year of high school to high school degree; high, 1 year of college/university to college/university degree.

Statistical analysis

Descriptive statistics were used to present the total DAS28-ESR and its components across age groups. Differences across groups were tested by one-way analyses of variance.

Regression analyses were performed to assess a possible age effect on DAS28-ESR and its components, adjusted for relevant confounders (i.e. gender, education, disease duration). Robust regression was performed next to conventional linear regression to understand whether the conventional linear regression was robust against deviations from normality assumptions. Potential interactions between age and confounders in the model were tested.

Next, to illustrate the magnitude of the (adjusted) effect of age on the absolute score, predicted values for DAS28 components (28-TJC, 28-SJC, PGA and ESR) across age categories were computed. Using the results of the regressions, and after stratification in case of relevant interactions, the total adjusted predicted DAS28-ESR was calculated by incorporating all the predicted DAS28 components into the DAS28 formula (see supplementary material, available at *Rheumatology* online) [3]. The model was kept as simple as possible, to remain close to clinical practice.

Analyses were done in patients with complete baseline data. SPSS version 22.0 (IBM, Armonk, NY, USA) and Stata version 12 (StataCorp, College Station, TX, USA) were used.

Results

Patient characteristics

In total, baseline data from 2037 patients [68% female, mean age 55.2 years (S.D. 14.0), 25.4% ≥ 65 years of age, 59.5% RF positive] were available. Only 40 (8.8%) of 465 patients <45 years had a low level of education. In patients >65 years of age, this proportion increased to 293 of 510 patients (57.5%) (Table 1). The 28-SJC and ESR were higher in older patients ($P < 0.001$), while no differences by age category were observed for the 28-TJC and PGA (Table 1).

Effect of age on components of the DAS28-ESR

Robust regression showed that conventional linear regression was robust to violation of normality assumptions (data not shown), and linear regression was therefore used for the analyses. Table 2 shows the effect of age on individual DAS components for patients with an intermediate education level. A significant interaction was found between age and gender for the 28-TJC, PGA and ESR ($P < 0.001$) and thus analyses were stratified by gender. Furthermore, as education was a significant covariate in all regression analyses, predicted scores across age groups were calculated for the different education levels. Disease duration was not a significant confounder and therefore was not included in the model.

Male patients >65 years of age with an intermediate level of education had 56% higher ESR and 25% higher 28-SJC than the youngest age group. For females, these percentages were 51% and 27%, respectively. With regard to the 28-TJC and PGA, the differences were negligible (males: 28-TJC 3% and PGA 1%; females: 28-TJC 1% and PGA 2%). The difference between the youngest and oldest age group for the total DAS28-ESR was 10% for both males and females. In absolute values, the DAS28 for males and females was 5.5 in the oldest group compared with 5.0 in the youngest age group (Table 2). While education did not modify the relation between age and DAS components, education had a small independent influence on all DAS components. In general, the higher the education level, the lower each of the DAS28 components and the total DAS28 score (Supplementary Tables S1 and S2, available at *Rheumatology* online).

Discussion

The present study explores the effect of age on DAS28-ESR and its components while accounting for the confounding effects of gender and education. We found that the ESR and 28-SJC were higher in patients

Table 1 Demographic and disease characteristics according to the three age groups

Characteristics	Age group 1 (<45 years)	Age group 2 (45–65 years)	Age group 3 (>65 years)	*P*-value
Number of patients	460	1059	518	NA
Age, years, mean (S.D.)	34.9 (7.3)	55.9 (5.4)	71.9 (4.9)	NA
Disease duration, years, mean (S.D.)	1.0 (2.7)	1.6 (5.0)	2.4 (6.5)	<0.001
Males, *n* (%)	144 (24.8)	368 (34.7)	174 (33.6)	<0.001
Education level, *n* (%)[a]				<0.001
Low	40 (8.8)	318 (30.4)	293 (57.5)	
Intermediate	181 (39.7)	419 (40.0)	123 (24.1)	
High	235 (51.5)	310 (29.6)	94 (18.4)	
RF positive, *n* (%)[b]	270 (59.7)	627 (59.1)	286 (55.0)	0.38
28-TJC, mean (S.D.)	7.4 (6.8)	7.8 (6.7)	8.1 (7.1)	0.37
28-SJC, mean (S.D.)	6.0 (5.6)	6.6 (5.6)	7.8 (5.9)	<0.001
PGA, mean (S.D.)	45.2 (25.7)	46.7 (24.2)	47.6 (23.9)	0.31
ESR, mean (S.D.)	23.3 (20.0)	27.7 (22.2)	34.7 (23.8)	<0.001
CRP, mean (S.D.)	16.8 (24.1)	21.8 (29.5)	27.7 (31.2)	<0.001
DAS28-ESR, mean (S.D.)[c]	4.6 (1.5)	4.8 (1.3)	5.1 (1.4)	<0.001

[a]Education level was unknown in 24 patients (1%).
[b]RF status was unknown in 50 patients (2%).
[c]Data to calculate the DAS28-ESR were incomplete in 219 patients (11%). One-way analysis of variance was used to analyse differences among group means.
NA, not applicable.

Table 2 Predicted individual components and total DAS28-ESR for patients with an intermediate education level

Component	< 45 years (reference) *n* = 181 (25%)	>45–65 years n = 419 (58%)	> 65 years *n* = 123 (17%)	Difference between highest and lowest age group, %
	Predicted component (DAS28 value of component)[a]			
Males				
28-TJC	7.6 (1.5)	7.4 (1.5)	7.8 (1.6)	3
28-SJC	6.5 (0.7)	7.0 (0.7)	8.1 (0.8)	25[b]
PGA	40.1 (0.6)	41.5 (0.6)	40.7 (0.6)	1
ESR	22.5 (2.2)	26.9 (2.3)	35.2 (2.5)	56[b]
Total DAS28-ESR score	5.0	5.1	5.5	10
Females				
28-TJC	7.2 (1.5)	7.7 (1.6)	7.3 (1.5)	1
28-SJC	5.6 (0.7)	6.1 (0.7)	7.1 (0.8)	27[b]
PGA	47.8 (0.6)	48.8 (0.7)	48.7 (0.7)	2
ESR	23.8 (2.2)	28.8 (2.4)	36.0 (2.5)	51[b]
Total DAS28-ESR score	5.0	5.4	5.5	10

[a]Linear regression was used to compute predicted values for each component across age categories and education levels. The total predicted DAS28-ESR was calculated by incorporating all the predicted components into the DAS28 formula. As an example, for the 28-TJC in males <45 years of age, the predicted 28-TJC score is 7.6 tender joints. After incorporating this number in the DAS28-ESR formula, the DAS28-TJC component is 1.5.
[b]Difference in scores is significant ($P < 0.05$).

>65 years of age with an intermediate education level as compared with patients <45 years of age. This effect was not observed for the 28-TJC and PGA. After incorporating the four individual components in the DAS28-ESR formula, the effect of age on the DAS28-ESR score was attenuated to 10%, mainly because of the logarithmic transformation of the ESR [3]. The observed age-related increase in ESR and 28-SJC without a simultaneous increase in 28-TJC and PGA might imply that age-related processes (e.g. soft tissue changes and a physiological increase in ESR), rather than the presence of joint inflammation, drive the DAS28 score in older patients.

When considering the inconsistent changes with age between ESR and 28-SJC compared with 28-TJC and PGA, we should realize that, except for ESR, our current measures for disease activity in RA are not benchmarked against the effect of ageing in population subjects. It therefore remains unknown whether the human ageing process and not 'true' joint inflammation is

indeed the driving factor behind the increased DAS28-ESR in older patients. However, higher levels of illness acceptance, less nociception and lower expectations might then be responsible for a negligible increase in TJC and PGA scores [8]. Previous research suggests that neural changes accompany ageing and may lead to changes in nociceptive processing, resulting in an increased pain threshold [9].

In contrast, several studies suggest that ageing and emerging comorbidity by itself may independently alter commonly used RA-specific outcome measures, including joint scores, remission criteria and functional disability assessments [4–6, 10]. As an example, in a study by Radner *et al.* [10], physical disability as measured by the HAQ became worse with increasing levels of comorbidity, and this effect was irrespective of RA disease activity.

If factors such as alterations in bone and peri-articular soft tissues or a physiological increase in ESR indeed drive the DAS28-ESR as patients age, this may have unfavourable consequences for management of RA in elderly patients. In this case rheumatologists might 'upgrade' or 'downgrade' the result of the DAS28-ESR, resulting in over- or undertreatment of patients with RA. A potential negative effect of this 'downgrading' might be later referral or later start of the first DMARD, as suggested by the longer disease duration in patients >65 years of age.

In this study, patients with a low level of education had a higher DAS28-ESR than patients with a intermediate or high level of education. The negative impact of a low education level has been described previously [11]. In a study by Putrik *et al.* [11], also performed in the NOR-DMARD registry, less-educated patients had reduced access to biologic DMARDs. Again, the question remains whether factors such as an implicit adjustment for the DAS28 or 'true' disease activity are responsible for these effects.

This study also has limitations. First, we used baseline data from DMARD-naïve patients entering the NOR-DMARD registry. We chose to use the baseline data since follow-up data might be influenced by possible differences in treatment effects across age categories influencing access to biologic DMARDs or an altered disease course because of comorbidities. Next, our results suggest a 'pure' age effect on disease activity. However, in line with the discussion above, it should be further explored whether RA disease activity is truly higher in elderly patients, due to, for instance, a referral delay or different disease presentation.

In conclusion, the present study indicates that age has a significant positive relationship with the DAS28-ESR, with the ESR and 28-SJC driving the increase. Validation of disease activity measures in elderly RA patients should be performed in future studies where the influence of comorbidity and physiological ageing is studied. The age effect on DAS28 might be relevant in a treat-to-target strategy, but longitudinal data are needed to further explore this.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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