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RESEARCH

Disease activity and its correlation with anti-mutated citrullinated vimentin antibodies and other factors in rheumatoid arthritis

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ABSTRACT

Objectives: Our aim was to determine the disease activity (DAS28) and its correlation with anti- Mutated Citrullinated Vimentin antibody (anti-MCV) positivity and other factors in Rheumatoid Arthritis (RA) patients, Saudis and non-Saudis. And to compare Disease Activity measurements using ESR (DAS28-ESR) and CRP (DAS28-CRP).

Patients and methods: Retrospectively, data were obtained by files' reviewing, for a period of seven years (2007-2014), at king Abdulaziz university hospital (KAUH), Jeddah, Saudi Arabia. Disease Activity Scores were assessed by DAS28-ESR (104 patients), and together with DAS28-CRP (36 patients). One hundred and four (104) files had complete data for our objectives.

Results: DAS28-ESR was high [6 (SD=3)] among non-Saudi patients, moderate among Saudis [4.3 (SD=1.7)] and the total cohort [4.8(SD=2.3)]; with significant differences (P=0.000; R^2=11.3%) between Saudi and non-Saudi patients for DAS28. In a linear regression and by correlation analysis; the variables (Sex, age, age-group, anti-MCV positivity) showed no correlations with DAS28, neither for Saudis nor for non-Saudis. Eighty one (81) patients had data concerning presence of comorbid conditions; 34/81(42%) were with comorbid conditions. There was no significant correlation between presence of comorbid condition and disease activity neither for the total cohort (P=0.75) nor for Saudis (P=0.65) and non-Saudis (P=0.70).

Conclusion and recommendation: In both Saudi and non-Saudi RA-patients, disease activity can neither be assessed by anti-MCV positivity nor correlated with, comorbidity, sex, age and age groups. DAS28-ESR and DAS28-CRP were significantly correlated. A larger scale study is recommended.

keywords: Saudi Arabia, Anti-MCV antibodies, Saudi, Rheumatoid Arthritis, Rheumatoid factor, DAS28-CRP, DAS28-ESR, Disease activity, anti-mutated citrullinated vimentin antibody.

Abbreviations: DAS28-28 joint disease activity score; TJ- Tender Joint**;** SJ- *Swollen joint***;** DMARDs- Disease modifying antirheumatic drugs; VDD-vitamin D deficiency; HT-Hypertension ; SLE-Systemic lupus erythematosus; DM-Diabetes mellitus; RHD- Rheumatic Heart disease; OP-osteoporosis; Anti-MCV- Anti-mutated citrullinated vimentin; RA- Rheumatoid arthritis; *CRP-C-reactive protein; ESR-erythrocyte sedimentation rate;* FA- Folic acid; ANOVA- Analysis of variance; SPSS- statistical package for social science.

1. INTRODUCTION

Rheumatoid arthritis phenotypes can be either mild or high with more comorbidity and more joint destruction, thus, measuring disease activity is essential for adjusting therapy "treatment to target" (Smolen et al. 2010, Goldblatt et al 2005). Disease Activity Score (DAS), Disease Activity Score With 28-Joint Counts (DAS28) and several other measures of Disease Activity for Rheumatoid Arthritis have been described(Anderson et al 2011, Tamhane et al 2013). The DAS28 (which is analogous to the DAS) includes 28-joint counts for tenderness and swelling (Prevoo et al 1993, Prevoo et al 1995), and can be calculated using C-reactive protein (CRP) level as well as ESR measures (Anderson et al 2011). DAS and DAS28 were preceded by the Simple Disease Activity Index (SDAI) (Smolen J et al. 2003), and Clinical Disease Activity Index (CDAI) (Aletaha et al. 2005). Moreover, DAS28 was included in the recommendations of the American College of Rheumatology 2008 and 2012 for treatment decisions using disease-modifying anti-rheumatic drugs (DMARDs) (Saag et al. 2008, Anderson et al. 2012, Singh et al. 2012). DAS28-ESR was substituted by DAS28-CRP (Fransen et al 2004), for which Several studies have reported higher DAS28 - ESR than DAS28 – CRP (Bathon et al 2005, Soubrier et al 2006, Matsui et al 2007, Inoue et al 2007, Wells et al 2009). Thus, if compared with DAS28-ESR, DAS28-CRP may significantly underestimate disease activity and consequently overestimate the improvement in disease activity after treatment (Wells et al 2009). Gauloux-Viala summarized three reasons for DAS28-CRP to be an attractive alternative to DAS28-ESR (Gauloux-Viala et al 2013); "First, CRP is very sensitive to short-term changes in inflammation (Van Leeuwen and van Rijswijk 994), second, CRP is more accurate as an indicator of inflammation than ESR, the latter being influenced by a number of unrelated factors, such as age, sex, anemia, fibrinogen levels, hypergammaglobulinemia, and rheumatoid factor (Van Leeuwen and van Rijswijk 1994); third, CRP measurements are routinely used in clinical practice, and measurements can be standardized in a central laboratory for multicenter clinical trials".

Objectives

In this study, our aim was to determine disease activity (DAS28-ESR) and its correlation with anti mutated citrullinated vimentin antibodies (anti-MCV) and other factors in rheumatoid arthritis (RA) patients, both Saudis and non-Saudis. And to compare Disease Activity measurements using ESR (DAS28-ESR) and CRP (DAS28-CRP).

2. MATERIAL AND METHODS

Data were obtained by retrospective files' reviewing, for a period of seven years (2007-2014), since the anti-MCV test was available in the laboratories of KAUH. During this period, 310 RA patients met the American College of Rheumatology (ACR) 1978 classification criteria for RA. Files of 104 patients contained complete data for our study (including anti-MCV, age, sex, nationality and DAS28-ESR), thus they were recruited in this study; of them only 81 files had data concerning presence of comorbid conditions and 36 files had data for both DAS28-ESR and DAS28-CRP.

Anti-MCV was measured by ELISA (Alegria machine from Orgentec Diagnostika GmbH. Germany) and was considered positive when the concentration was > 20 IU/ml (normal value 0-20 IU/ml). Disease activity was assessed using the 28 joint disease activity score (DAS28) (Prevoo et al 1995) which was calculated according to TJ, SJ and ESR.

Patients were divided into three groups based on their age: group 1, patients younger than 45 years of age (<45); group 2, patients aged between 45 and 65 years of age (45-65); group 3, patients older than 65 years (>65).

Data concerning comorbid conditions was available for 81 patients only. The recorded conditions included the following conditions (as single and/or mixed): vitamin D deficiency (VDD), Hypertension (HT), Hypothyroidism, Systemic lupus erythematosus (SLE), Diabetes mellitus (DM), Rheumatic Heart disease (RHD), osteoporosis (OP); Epilepsy and others.

The collected data were part of retrospective review, thus informed consent was not obtained; however written ethical approval was obtained before commencing the study, ad was presented to the filing department before the retrospective review.

The following were used for checking references and prior related research: Entrez-PubMed "http://www.ncbi.nlm.nih.gov/entrez/query/static/citmatch.html", advanced search - PubMed - NCBI "http://www.ncbi.nlm.nih.gov/pubmed/advanced", and Saudi Digital Library (SDL) "http://www.sdl.edu.sa/SDLPortal/AR/Publishers.aspx".

Statistical Analysis

The data were analyzed using statistical package for social science (SPSS Inc), Version 14. Chicago. The results were illustrated in tabulated form and figures, showing comparisons and frequencies of variables. Results were considered significant if the p-value was less than 0.05. The predictive value of the various factors for disease activity (DAS28) was analyzed using the Linear Regression Analysis (Stepwise Model); with a

confidence interval 95%. Comparison among the three age groups was carried out by one-way analysis of variance (ANOVA) and to determine presence of any significant differences between the means of unrelated variables and for Means Plots. The assumption of Homogeneity of Variances was tested using Levene's test.

3. RESULTS

Demographic and clinical characteristics of RA patients (n=104), Saudis and non-Saudis, are shown in Table 1. Respectively, we investigated the disease activity and its correlation with anti-mutated citrullinated vimentin antibodies in 104 Rheumatoid Arthritis (RA) patients, Saudis (74) and non-Saudis (30). They were 95 (91.3%) female / 9 (8.7%) male; with a mean age of 46.05 years (SD=12.259). The 74 Saudi patients were 66(89.2%) female /8(10.8%) male, with a mean age of 44.47 years (SD=11.45). The 30 non-Saudi patients were 29(96.7%) female/1(3.3%) male, with a mean age of 49.96 years (SD=13.46). Prevalence of positive anti-mutative citriluuated vancomycine in this cohort was 42.3% (44/104); divided as 34/74 (46%) Saudis and 10/30 (33.3%) non-Saudis, with no significant difference between Saudis and non-Saudis (P=0.24). Disease Activity Score was assessed using ESR (DAS28-ESR), and was high [6 (SD=3)] among non-Saudi patient but moderate among the Saudi [4.3 (SD=1.7)] and the total cohort [4.8(SD=2.3]). In the total cohort; DAS28-ESR was low (< 3.2) in 22/104 (21%), moderate (3.2-5.1) in 44/104 (42.5%) and high (>5.1) in 38/104((36.5) %. In the Saudi patients; it was low in 19/74(26%), moderate in 31/74(42%) and high in 24/74(32%). In the non-Saudi patients; it was low in 3/30(10%), moderate in 13/30(43%) and high in 14/30(47%). There was significant differences (P=0.000; R^2=11.3%) between Saudi and non-Saudi patients for DAS28-ESR.

Table 2 illustrates the correlation analysis of DAS28-ESR with different factors. Correlation between DAS28 and anti-MCV positivity was significant (P=.04) in the total cohort, but not in Saudi (P=0.3) or non-Saudi patients (P=0.14); DAS28-ESR also showed significant correlation with both age (P=0.007) and age groups (P=0.011) only in the total cohort but not in Saudis and non-Saudis (Table 2). Sex had no significant correlation with DAS28 in total cohort (P=0.61), Saudis (P=0.93) and non-Saudis (P=0.74) (Table 2).). Comoridity had no significant correlation with DAS28-ESR in total cohort (P=0.75), Saudis (P=0.65) and non-Saudis (P=0.70) (Table 2).

We also examined the possible predictors of disease activity by linear regression (Table 3) using DAS28-ESR as the dependent variable; the following were included as independent variables: age, sex, age-groups, anti-MCV positivity and comorbidity; all of which were excluded from the regression model in both Saudis and no-Saudis, indicating no significant influence of these factors (as predictors) on disease activity, in these two groups of patients (Saudis and non-Saudis).

Illustration of the distribution of patients (Table 4) with their DAS28-means (Table 4 and Figure 1) according to age groups, by one way ANOVA. Among the total cohort, Saudis and non-Saudis, the disease activity was ascending by aging. Disease activity (as judged by the mean DAS28-ESR) was maximum among the age group > 65 years for Saudis, non-Saudis and total cohort The influence of age groups on DAS28-ESR was also evaluated by one way ANOVA (tables not illustrated); the assumption of homogeneity of variances was tested, and found tenable using Levene's test; F(2,101)=1.5,P=0.23 for the total cohort; F(2,71)=0.6,P=0.5 for Saudis; F(2,27)=1.3,P=0.28 for non Saudis. The ANOVA statistic was F(2,103)=3, P=0.056 for the total cohort; F(2,71)=1.3, P=0.26 for Saudis; F(2,27)=0.7, P=0.5 for non-Saudis. Thus, there was no significant difference of age groups with disease activity (DAS28-ESR), indicating no influence of age groups on DAS28-ESR, neither for the total cohort nor for Saudis and non-Saudis.

DAS28-CRP was recorded in 36 patients (Table 5); the mean of which was 4.23 (S.D=1.14). Table 5, also represents comparison between mean DAS28-ESR and mean DAS28-CRP; DAS28-ESR and DAS28-CRP were significantly correlated (P=.0.000) with correlation coefficient of DAS28-ESR versus DAS28-CRP equal to 0.836. In the scatter plot (Figure 2), DAS28-ESR is plotted against DAS28-CRP for 36 patients that had data for both DAS28-ESR and DAS28-CRP, to display a positive significant correlation (R^2 linear=70%).

Table 1

Demographic and clinical characteristics of RA patients (n=104); Saudi and non-Saudi

	Mean (SD) or Number (%)		
Variable	**Saudi and non-Saudi**	**Saudi**	**Non-Saudi**
Frequency of patients that have available data	104	74	30
Age	46.05(12.259)	44.47(11.45)	49.96 (13.46)
Sex (F/M)	95(91.3)/9(8.7)	66(89.2)/8(10.8)	29(96.7)/1(3.3)
Anti-MCV Positivity	44/104(42.3%	34/74(46%)	10/30(33.3%)
Disease activity (DAS28)	4.8(SD=2.3)	4.3(SD=1.7)	6(SD=3)
Low disease activity (DAS28<3.2)	22/104 (21.2%)	19/74(26%)	3/30(10%)
Moderate disease activity (DAS28=3.2 -5.1)	44/104 (42.3%)	31/74(42%)	13/30(43%)

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High disease activity (DAS28>5,1)	38/104((36.5)%	24/74(32%)	14/30(47%)

Table 2

Correlation of DAS28-ESR with different factors

		sex	age	Age-groups	Anti-MCV positivity	Comorbidity
Total cohort	P*	.61	**.007**	**.017**	**.04**	0.75
Saudi	P*	.928	.22	.15	.302	0.65
Non-Saudi	P*	.74	.10	.25	.141	0.70

*Significant correlation indicated by P values <0.05 (bold)

Table 3

Linear Regression Analysis (Stepwise Model) of factors (Sex, age, age-group, anti-MCV positivity, comorbidity) related to DAS28-ESR (dependent variable).

population	Model	Unstandardized Coefficients		Significance	Excluded factors	R^2
		B	Std. Error			
Total cohort (Saudis and non-Saudis)	Age Anti-MCV positivity	0.050 -0.93	0.018 0.44	0.006 0.035	Sex, Age-group, Comorbidity	11%
udis	All interred variables were removed					
Non-Saudis	All interred variables were removed					

Table 4

Distribution of patients with their DAS28-means (SD) according to age groups; among the total cohort, Saudis and non-Saudis^

Age- groups (years)	Total cohort (No=104)			Saudi (N0=74)			Non-Saudi (No=30)		
	DAS28 Mean	N	SD	DAS28 Mean	N	SD	DAS28 Mean	N	SD
<45	4.28	50	1.7	4.0	39	1.5	5.1	11	2.4
45-65	5.2	48	2.6	4.67	32	1.9	6.4	16	3.4
>65	**5.9**	6	3	**4.68**	3	1.6	**7.1**	3	3.9
Total	4.8	104	2.3	4.3	74	1.7	6.0	30	3.1
Between groups	Significant difference	P=.056		Significant difference	P=0.26		Significant difference	P=0.5	

^by one way ANOVA

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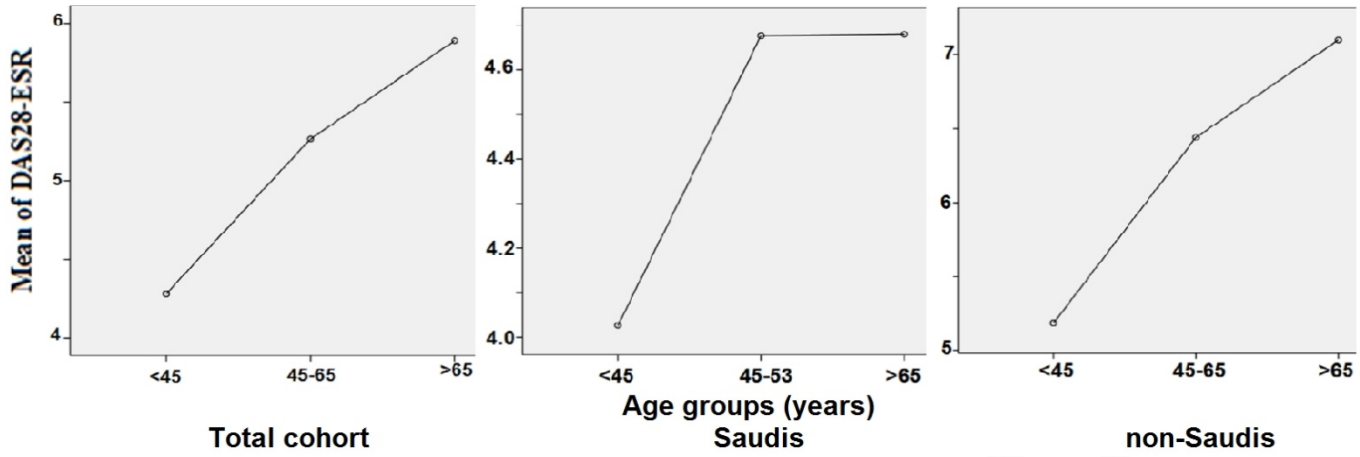

Figure 1

Comparison of means of DAS28-ESR according to age groups in total cohort, Saudis and non-Saudis

Table 5

Comparison between DAS28-ESR and DAS28-CRP among the total cohort*

	N	Minimum	Maximum	Mean	Std. Deviation
DAS28-CRP	36	2.22	6.60	4.2310	1.14588
DAS28-ESR	104	1.87	13.00	4.8284	2.32008

P=.0.000; correlation coefficient of DAS28-ESR versus DAS28-CRP (0.836)

***** Among the 104 patients with DAS28-ESR, 36 of them had data for DAS28-CRP

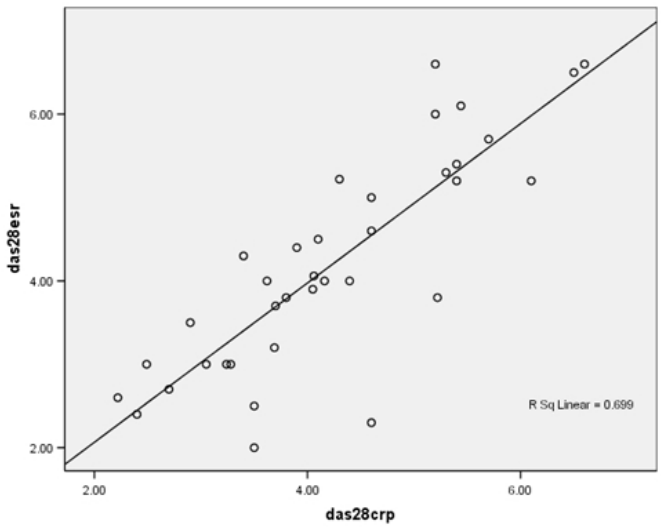

Figure 2

Scatter plot of DAS28-ESR versus DAS28-CRP values for the 36 patients that had data for both DAS28-ESR and DAS28-CRP

4. DISCUSSION

This study involved two groups of Rheumatoid Arthritis (RA) patients, Saudis (74) and non-Saudis (30). They were 95 (91.3%) female / 9 (8.7%) male; with a mean age of 46.05 years (SD=12.259); among these two groups, our aim was to determine DAS28 and its relation to anti-MCV positivity and comorbidity. With this in mind, the Disease Activity Scores were assessed using ESR (DAS28-ESR), and was higher among non-Saudis [6(SD=3)] than Saudis [4.3 (SD=1.7)].. Mean DAS28 was 4.3 (SD=1.7) among the 74 Saudis, which was lower than that was previously reported [(SD=0.87)] in 200 Saudi RF-ve RA patients (Safi et al 2012). In the current study, DAS28-ESR among the non- Saudis was 6 (SD=3), which fits within the ranges (3.1-6.0) among other 25 countries (Sokka et al 2009); thus disease activity in Saudis (as judged by Das28-ESR) shows discrepancies between different studies.

In this study, the RA patients both Saudis (P=0.065) and non-Saudis (P=0.07) showed no significant correlation between DAS28-ESR and anti-MCV positivity, indicating that presence of anti-MCV antibodies is not useful in predicting disuse activity. Two studies from Egypt showed contradictory results in this respect; Alshazly et al (El Shazly et al 2014) reported no significant difference between anti-MCV positive and negative RA patients as regards to DAS28; in contrast, Mansour et al reported that anti-MCV positive RA patients had significantly higher DAS28 than anti-MCV negative patients (Mansour et al 2010); likewise, Innala et al also concluded that anti-MCV titer was significantly correlated with DAS28 (Innala et al. 2008). However, to the best of our knowledge, there were no reports from Saudi Arabia, in this concern, to compare our results with it. Presence of significant discordance between the ESR-based and CRP-based DAS28 is a situation that might affect clinical treatment decisions (Matsui et al 2007); with this in mind, we made a comparison between DAS28-ESR and DAS28-CRP. Among the 104 patients with DAS28-ESR, 36 of them had data for DAS28-CRP, with mean [4.23 (S.D=1.14)] that was significantly lower (P< 0.0001) than that for DAS28-ESR for the 104 patients [4.8 (SD=2.3)], with significant correlation coefficient of DAS28-ESR versus DAS28-CRP equal to 0.836, reflecting a strong linear relationship between DAS28-ESR and DAS28-CRP values ,which was also confirmed by a positive scatter plot with R^2 linear =70% . In this respect, we were in concordance with other previous studies in other populations who reported significant ($p < 0.0001$) higher mean DAS28 - ESR (4.31, SD 1.32) than mean value of DAS28-CRP (3.59, SD 1.25) (Matsui et al 2007), and significant correlation coefficient (0.946) of DAS28-ESR versus DAS28-CRP (Inoue et al 2007).

The Saudi patients in this cohort [24/74 **(**32%)] that had high DAS28 scores (>5.1), was lower than [160/200 (80%)] that was previously reported in Saudi RF-ve patients (Safi et al 2012); this patients group that showed high rate of high DAS28-ESR scores (>5.1) was from a private centre for Rheumatism & Physiotherapy and Acupuncture, while the other patients group of this study, with lower rate of high DAS28-ESR scores, was from a university hospital; indicating that patients with high disease activity usually consult private centers , and thus would be the reason for this difference.

Correlation between DAS28-ESR and age was found non significant by linear regression and by correlation analysis, for both Saudis (P=0.22) and non-Saudis (P=0.10), indicating no influence of age on DAS28-ESR. Correlation of age groups on DAS28-ESR was also found non significant by linear regression and by correlation analysis, for both Saudis (P=0.15) and non-Saudis (P=0.25), The influence of age groups on DAS28-ESR was also evaluated by one way ANOVA that revealed no influence of age groups on DAS28-ESR, neither for the total cohort nor for Saudis and non-Saudis. In this respect, Radovits BJ et al 2008 found that if the DAS28 was more than.3.2, age does not have a significant effect on any components of the DAS28.and that DAS28(CRP) was not influenced by age.

Likewise, the linear regression analysis using DAS28-ESR as the dependent variable, revealed no correlation between DAS28-ESR with sex, and comorbidity; the same results were found by correlation analysis, for both Saudis and non-Saudis; this was in concordance with another previous report among Saudi Rf-ve RA patients; (Safi et al 2012), indicating, that none of these factors had influence on disease activity, and thus none could act as predictor for disease activity. Radovits BJ et al 2008 also found no significant effect of gender on any components of the moderate and high DAS28 scores.

5. CONCLUSION

In both Saudi and non-Saudi RA-patients of this study, disease activity cannot be assessed by anti-MCV positivity; the non predicting agents for disease activity included, age, comorbidity, sex, and age groups; disease activity (as judged by the mean DAS28-ESR) was maximum among the age group > 65 years. DAS28-ESR and DAS28-CRP were significantly correlated for disease activity. Larger scale study is recommended.

DISCLOSURES

The work was not supported or funded by any funding agency or any drug company.Ethical approval was obtained before commencing the study. All authors have read and approve this manuscript. The authors declare no conflict of interests that exist.

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