Resumo dos resultados, conclusões e implicações

O estudo teve como principal objetivo determinar os fatores que afetam a felicidade e a qualidade de vida em pessoas com artrite reumatoide.

Os resultados apontaram que a felicidade está relacionada de forma positiva com os traços de personalidade, e negativa com o impacto da doença. Por outro lado, o impacto da doença encontra-se relacionado de modo positivo com a atividade da doença e negativo com os traços de personalidade. Os efeitos da doença têm uma relação mais forte com a qualidade de vida do que com a felicidade. Para além disso, a felicidade atenuou o efeito negativo do impacto da doença sobre a qualidade de vida.

Em conjunto, estes achados têm implicações clínicas muito relevantes. Ao aceitar que a diminuição da atividade inflamatória da doença constitui o alvo essencial de tratamento, os profissionais de saúde também devem considerar os traços de personalidade, já que estes parecem desempenhar um relevante papel mediador na forma com os doentes sentem a doença (impacto). Nesse sentido, a otimização da qualidade de vida e da felicidade não exige apenas o controlo efetivo do processo da doença, mas também uma redução efetiva do impacto. Para isso, é necessária uma aplicação personalizada e dirigida de outras intervenções, além da imunossupressão, e exigindo uma intervenção multidisciplinar.

Especificação do Prémio

O artigo "Determinants of happiness and quality of life in patients with rheumatoid arthritis: a structural equation modelling approach" publicado no Annals of the Rheumatic Diseases (revista n.º 1 da área da Reumatologia e que conta com um fator de impacto de 12.811) ganhou o prémio “EMEUNET Paper of the Month”.

Anteriormente foi selecionado para apresentação oral no Congresso Europeu da Liga Europeia contra as Doenças Reumáticas (EULAR) em Amesterdão, com atribuição de bolsa de mérito (350€) e mais recentemente para Lay Summary (resumo do artigo escrito para doentes e não-clínicos).

EMEUNET

A Emerging EULAR NETwork (EMEUNET) é um grupo de trabalho da EULAR constituída por clínicos e investigadores na área da reumatologia cujos principais objetivos são melhorar a qualidade da educação, promover a investigação e criar colaborações entre os jovens reumatologistas e investigadores.

EXTENDED REPORT

Determinants of happiness and quality of life in patients with rheumatoid arthritis: a structural equation modelling approach

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ABSTRACT

Objectives Besides increasing longevity, the ultimate goal of medical care is to improve patients' enjoyment of life, a concept akin to happiness. This study examined the determinants of happiness and quality of life (QoL) in patients with rheumatoid arthritis (RA).

Methods In this observational, cross-sectional study, patients were assessed on disease activity, disease impact, personality, QoL and happiness. Structural equation modelling estimation was used to analyse the associations between these dimensions, pursuing three hypotheses: H_1—disease activity and perceived impact of disease are negatively associated with overall QoL and happiness in patients with RA; H_2—'positive' personality traits are related to happiness both directly and indirectly through perceived disease impact; H_3—happiness has a mediating effect in the relation between impact of disease and QoL.

Results Data from 213 patients were analysed. Results supported all driving hypotheses. Happiness was positively related to 'positive' personality and, to a lesser extent, negatively related to impact of disease. Impact of disease, in turn, was positively related to disease activity and mitigated by 'positive' personality traits. Impact of disease had a much stronger relation with QoL than with happiness. Happiness mitigated the negative effect of disease impact on QoL.

Conclusion Optimisation of QoL and happiness of people with RA requires effective control of the disease process and also improvement of the disease impact domains. Personality seems to play a pivotal mediating role in these relations.

INTRODUCTION

The current paradigm for the management of rheumatoid arthritis (RA), in both clinical and research settings, is epitomised by the treat-to-target strategy[1 2] which establishes that the target of remission, or at least low disease activity, should be pursued and achieved as early and consistently as possible. This target is defined essentially by measures designed to gauge the disease process: number of tender and swollen joints and acute phase reactants supplemented by the patient's and physician's global impression of disease activity.[3] The incorporation of patient-reported outcomes (PROs), designed to provide the patient's perspective of the disease[4–9] into clinical practice and research, is widely supported by international organisations and professional groups.[2 4 10]

Many studies have shown that the control of inflammation through immunosuppressive therapy has a markedly positive impact on PROs: controlling the disease process is, undoubtedly, as important to prevent long-term damage as to improve patients' quality of life (QoL).[2 4–6 11 12] Despite this, a sizeable proportion of patients with RA who are in remission still describe a high impact of disease[13 14] and reduced QoL.[15]

Our group has recently highlighted this view by proposing that the management of RA should pursue two different targets: disease process remission and disease impact control.[13 14] Controlling the disease impact, in terms of quality and duration of life, are the final objectives of disease management, while controlling the disease process should be seen as an important means to that end, but not a guarantee.

Within this perspective, the concept of overall subjective well-being, equivalent to 'happiness', emerges as a decisive goal as well ('the ultimate currency').[16–18] All healthcare professionals know patients who lead a reasonably happy and fulfilling life despite aggressive disease, while others seem to succumb to the diagnosis. Understanding the main determinants of happiness in patients with rheumatic diseases and exploring the potential avenues to maximise it is, in this light, an ethical obligation. Curing or controlling disease is, certainly, an essential contribution, but we need to understand how far disease control can go towards happiness and whether health professionals may contribute to that goal beyond disease control.

Happiness includes different aspects of life such as life satisfaction, healthy interpersonal relationships, personal growth and appreciation of nature, beauty and other people, resulting in a global predominance of positive emotions over negative ones.[16 17] QoL is more focused on physical functioning and negative mental aspects, such as depressed mood and anxiety.[18 19] Happiness is, therefore, a broader concept than QoL, as it goes beyond the ability to do things and incorporates the satisfaction of doing them, that is, the enjoyment of life as a whole.[18 19] Personality is recognised as a key factor in predicting happiness,[16 20 21] as it provides the context in which the roots of happiness operate.[22] Although happiness levels may be

negatively influenced by the experience of living with a disease, especially if it has a chronic course and causes a marked impairment in daily functioning, several studies in this area have also demonstrated that happiness may have a positive impact on physical health and longevity. This has been mostly attributed to its effect on the perception of impact disease and on the engagement in health-related behaviours.[18]

Based on the previous literature, this study was designed to address the following hypotheses in patients with RA:

- H_1—Disease activity and perceived impact of disease are negatively associated to overall QoL and happiness;
- H_2—'Positive' personality traits are related with happiness, both directly and indirectly through perceived disease impact;
- H_3—Happiness has a mediating effect in the relation between impact of disease and QoL.

METHODS

Participants and study design

We used data from an observational, cross-sectional study, performed in a single rheumatology outpatient department,[14] that aimed at exploring the determinants of patient global assessment. The study included consecutive adult patients with RA[23 24] who (1) were followed and treated according to standard guidelines, (2) had the ability to read and interpret the questionnaires applied, and (3) agreed to participate. The current analysis included data from patients who answered all measurements required.

All participants provided informed written consent before the start of study procedures, and the ethical approval was granted by the University of Coimbra's Faculty of Medicine Ethics Committee (CEU 037/2015).

Measures/instruments

Data collection included the Rheumatoid Arthritis Impact of Disease score,[25 26] which is composed of seven items rated on a 10-point numeric rating scale. A higher score indicates greater impact of the disease. Happiness was assessed through the Subjective Happiness Scale (SHS),[27] a four-item measure (seven-point Likert scale). A higher mean score indicates more intense perception of a 'happy life'. Personality was assessed by the Ten-Item Personality Inventory (TIPI),[28] a brief measure of the Big-Five personality dimensions, each being scored as the mean of two items (seven-point Likert scale) addressing extraversion, agreeableness, conscientiousness, emotional stability and openness to experience. Higher scores indicate a stronger expression of the respective trait. We designated the latent higher order factor derived from TIPI as 'Positive' personality to represent the predominantly adaptive nature of the represented dimensions. We recognise that the term 'positive' is questionable especially in the extremes of expression of certain traits, such as conscientiousness. Health-related QoL was accessed by the EuroQOL (EQ-5D) questionnaire, which includes five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three levels: no problems, some problems and extreme problems. The combination of the five scores leads to an index score between −0.59 and 1.00.[29] Higher scores indicate a best perceived health status and QoL.

Disease activity was measured with the Disease Activity Score 28 joints (DAS28), in its three variables (3v) and C reactive protein (CRP) variant—DAS28CRP(3v).[30]

For patient's characterisation, demographic data, disease characteristics, comorbidities and current treatment were collected.

Data analysis

Descriptive and correlational analyses were performed with SPSS V.23 (IBM). Pearson correlation analyses were conducted to examine the associations between disease activity, measures of disease impact, personality traits, QoL and happiness and interpreted as small (0.10 to 0.30), moderate (0.30 to 0.50) or large (>0.50).[31]

Structural equation modelling (SEM, latent variable structural model) was used to estimate the association between the variables under analysis in the theoretical model and performed with AMOS V.24.0 (IBM SPSS, Chicago, Illinois, USA), using a maximum-likelihood estimation. SEM defines latent variables (summary constructs) from one or more observed variables and examines in a structured way models specifying relationships between these latent variables.

Prior to this analysis, the assumptions of normality and multicollinearity were confirmed. Skewness values ranged from −0.93 to 0.98, while values of kurtosis ranged from –1.1 to 1.29, indicating no violation of univariate and multivariate normality.[32] Variance inflation factor values were below 5 for all variables included in the model, excluding multicollinearity as an issue.

As recommended, different goodness-of-fit indices were used to estimate the model fit, namely (1) the χ^2, (2) the Comparative-of-Fit Index (CFI), (3) the Goodness-of-Fit Index (GFI), (4) the Tucker-Lewis Index (TLI) and (5) the root mean square error of approximation (RMSEA). A good fit of the models was assumed when the ratio of χ^2 to its df was less than 3.0 and CFI, GFI and TLI were larger than 0.90[33]; RMSEA values <0.06 were considered ideal and values between 0.08 and 0.10 were considered acceptable.[34]

Four covariances were entered in the measurement model following modification indices examination/analysis.

The examination of the structural model included a test of the overall model fit as well as individual tests of the relationships among latent constructs. Statistically significant effects were assumed for $P < 0.05$. Other paths with theoretical and clinical plausibility were also tested (DAS28CRP3v→happiness; 'positive' personality→QoL). Non-significant paths were excluded, and the initially proposed model was readjusted accordingly. Furthermore, the bootstrap resampling method, with 700 bootstrap samples and 95% bias-corrected CIs around the standardised estimates of total, direct and indirect effects, was used to test the significance of the mediational path.[35]

To address the potential bias due to missing data, we tested a model-based missing data method (full information maximum-likelihood), which did not show significant differences. In the end, we preferred to use only truly obtained data.

RESULTS

Patient characteristics

This study included 213 of the original sample of 309 patients with RA due to missing data. Baseline demographic and clinical characteristics of patients are presented in table 1. Participants were aged between 27 and 88 (M=57.8) years and had a mean disease duration of 11.8 years. Around one-third (n=69, 32.4%) of patients had no identified comorbidities. The mean DAS28CRP3v was 2.48, with 59.6% (n=127) of patients being in remission according to this index.

Table 1 Demographic and clinical characteristics of 213 patients with RA

Variables	Scores
Age, years, mean (SD)	57.8 (13.2)
Female gender, n (%)	172 (80.8)
Disease duration, years, mean (SD)	11.8 (8.9)
Rheumatoid factor positive, n (%)*	154 (72.3)
Anticitrullinated antibody positive, n (%)*	101 (70.6)
Comorbidities, yes, n (%)	
Fibromyalgia*	35 (16.4)
Depression*	38 (17.8)
Low back pain*	40 (18.8)
Osteoporotic fractures*	16 (7.5)
Osteoarthritis*	108 (50.7)
Stroke*	4 (1.9)
Current treatment with biologic agents, n (%)	66 (31)
Tender joint counts using 28 joints (0–28), mean (SD)	1.52 (3.2)
Swollen joint counts using 28 joints (0–28), mean (SD)	1.46 (2.7)
C reactive protein, CRP (mg/dL), mean (SD)	0.81 (1.4)
Disease Activity, DAS28CRP3v (0–9.4), mean (SD)	2.48 (0.93)
Remission, n (%)	127 (59.6)
Low, n (%)	49 (23)
Moderate, n (%)	34 (16)
High, n (%)	3 (1.4)
Physician global assessment (VAS, 0–100), mean (SD)	14.2 (15. 9)
Patient global assessment (VAS, 0–100), mean (SD)	47.5 (28.6)
Rheumatoid Arthritis Impact of Disease (0–10), mean (SD)	
Pain	4.8 (2.5)
Functional disability	4.9 (2.6)
Fatigue	5.1 (2.7)
Emotional well-being	4.6 (2.7)
Sleep	4.4 (2.9)
Coping	4.2 (2.7)
Physical well-being	4.9 (2.5)
EuroQOL five dimensions (−0.59 to 1), mean (SD)	0.43 (0.26)
Subjective Happiness Scale (1–7), mean (SD)	4.8 (1.3)
Ten-Item Personality Inventory (1–7), mean (SD)	
Extraversion	4.1 (1.5)
Agreeableness	5.7 (1.3)
Conscientiousness	5.6 (1.3)
Emotional stability	3.7 (1.5)
Openness to experience	4.4 (1.5)

*Percentages of patients with missing data were <2.8%, except for ACPA (32.8%) and erosions (18.8%), fibromyalgia (7%), depression (7.5%), low back pain (10.3%), osteoporotic fractures (19.7%), osteoarthritis (8.9%) and stroke (8.5%).

Correlation coefficients

Pearson correlation coefficients for the measured variables are presented in table 2.

As expected, QoL was found to be strongly and inversely correlated with impact of disease.

The personality traits extraversion, emotional stability and openness to experience were associated, with low correlations, with QoL and with virtually all aspects of impact of disease. Openness to experience was not associated with sleep. All happiness items except item 4 presented moderate positive correlations, with QoL; low to moderate positive correlations with all personality traits, except for agreeableness (not significant at SHS 1 and 3); and negative correlations, with impact of disease. Finally, DAS28CRP3v showed moderate associations with impact of disease (positive correlation) and QoL (negative correlations), low correlations with happiness and no significant correlations with each personality trait.

The fourth question of SHS (which was a complex item with a negative formulation and reversed scoring) showed a totally discordant profile vis-a-vis the other three (ie, harming internal consistency of the SHS). For this reason, this question was not included in the happiness construct when we performed the structural equations model, as technically recommended.[34]

Structural equation modelling

The overall fit of the final measurement model was good, thus permitting the examination of the structural model ($\chi^2_{(111)}$=154.22, χ^2/df=1.38, P=0.004; CFI=0.98; GFI=0.92; TLI=0.97; RMSEA=0.04, 95% CI 0.02 to 0.05). Although the χ^2 statistic was significant (P<0.05), its ratio regarding the df was within the accepted range (χ^2/df <3).[33]

The direct path coefficients for the model are shown in table 3 and figure 1. The bootstrap indirect effects are shown in table 4.

H_1—*Disease activity and perceived impact of disease are negatively associated to overall QoL and happiness in patients with RA.*

Impact of disease showed a significant negative direct relation with QoL (β=−0.70; P<0.001) and happiness (β=−0.17; P=0.02). Impact of disease was higher with higher disease activity (DAS28CRP3v) (β=0.36; P<0.001) (table 3 and figure 1).

Moreover, disease activity had also a negative indirect effect of −0.26 (P=0.003) on QoL, through the perception of impact of disease (table 4).

H_2—*'Positive' personality traits are related with happiness, both directly and indirectly through perceived disease impact.*

'Positive' personality traits had a total effect of 0.56 on happiness, being a direct effect of β=0.50 (P<0.001) and an indirect effect of β=0.06 (P=0.03) through impact of disease.

'Positive' personality traits showed also a negative direct relation with impact of disease (β=−0.37; P<0.001), and an indirect effect of β=0.33 (P=0.004) on QoL, through the impact of disease (tables 3 and 4 and figure 1).

'Positive' personality and disease activity explained 27% of the variance of impact of disease (R^2=0.27) (figure 1).

H_3—*Happiness has a mediating effect in the relation between impact of disease and QoL.*

Impact of disease had a total effect of 0.72 on QoL, of which β=−0.02 (P=0.04) was an indirect effect through happiness, indicating a mediating influence between this relationship. Furthermore, there was a significant direct association between happiness and QoL (β=0.13; P=0.01) (tables 3 and 4 and figure 1).

Disease activity had a negative indirect effect of β=−0.06 (P=0.04) on happiness, through the perception of impact of disease (table 4).

Altogether, happiness and impact of disease explained 57% of the variance of QoL (R^2=0.57), and 35% of the variance of happiness (R^2=0.35) was explained by impact of disease and personality traits (figure 1).

DISCUSSION

This study provides a comprehensive model that illustrates the relationships between disease activity, impact of disease, personality traits, QoL and happiness in people with RA. Overall, the results show that happiness is related to a 'positive' personality and, to a small extent, to the perception of impact of disease. The latter was, in turn, positively related to disease activity and

Table 2 Pearson correlation coefficients among variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Impact of disease																				
Pain (1)	1.00																			
Functional disability (2)	0.82**	1.00																		
Fatigue (3)	0.76**	0.82**	1.00																	
Sleep (4)	0.66**	0.69**	0.71**	1.00																
Physical well-being (5)	0.75**	0.82**	0.84**	0.73**	1.00															
Emotional well-being (6)	0.71**	0.72**	0.77**	0.75**	0.85**	1.00														
Coping (7)	0.72**	0.74**	0.79**	0.70**	0.81**	0.80**	1.00													
RAID score (8)	0.89**	0.91**	0.91**	0.83**	0.92**	0.89**	0.89**	1.00												
Quality of life (9)	−0.60**	−0.69**	−0.68**	−0.59**	−0.69**	−0.64**	−0.63**	−0.73**	1.00											
Positive personality																				
Extraversion (10)	−0.18**	−0.20**	−0.23**	−0.20**	−0.21**	−0.19**	−0.24**	−0.23**	0.23**	1.00										
Agreeableness (11)	−0.03	−0.01	−0.03	−0.10	−0.03	−0.14*	−0.10	−0.07	0.04	0.04	1.00									
Conscientiousness (12)	−0.01	−0.06	−0.08	−0.15*	−0.07	−0.15*	−0.12	−0.1	0.10	0.28**	0.40**	1.00								
Emotional stability (13)	−0.21**	−0.26**	−0.29**	−0.29**	−0.29**	−0.35**	−0.25**	−0.31**	0.25**	0.32**	0.20**	0.21**	1.00							
Openness to experience (14)	−0.16*	−0.21**	−0.27**	−0.11	−0.21**	−0.18**	−0.24**	−0.23**	0.15*	0.39**	0.18**	0.28**	0.21**	1.00						
Happiness																				
SHS 1 (15)	−0.22**	−0.21**	−0.28**	−0.29**	−0.25**	−0.32**	−0.29**	−30**	0.31**	0.36**	0.12	0.24**	0.32**	0.17*	1.00					
SHS 2 (16)	−0.26**	−0.23**	−0.31**	−0.30**	−0.30**	−0.33**	−0.32**	−0.33**	0.36**	0.33**	0.17*	0.28**	0.31**	0.23**	0.82**	1.00				
SHS 3 (17)	−0.26**	−0.18**	−0.28**	−0.25**	−0.29**	−0.31**	−0.32**	−0.30**	0.33**	0.39**	0.10	0.23**	0.31**	0.25**	0.58**	0.60**	1.00			
SHS 4 (18)	0.04	0.09	0.05	0.04	0.08	0.07	0.09	0.08	−0.07	−0.02	0.03	−0.01	−0.04	−0.05	0.04	0.02	0.09	1.00		
SHS three-item score (19)	−0.28**	−0.24**	−0.33**	−0.32**	−0.33**	−0.37**	−0.36**	−0.35**	0.38**	0.41**	0.15*	0.29**	0.36**	0.25**	0.90**	0.91**	0.84**	0.07	1.00	
DAS28CRP3v (20)	0.34**	0.35**	0.31**	0.32**	0.35**	0.30**	0.32**	0.37**	−0.34**	−0.001	−0.05	0.01	−0.11	0.01	−0.15*	−0.21**	−0.15*	0.09	−0.20**	1.00

DAS28CRP3v, DiseaseActivity Score using 28 joints and C reactive protein and three variables; RAID, Rheumatoid Arthritis Impact of Disease; SHS, Subjective Happiness Scale.
*P<0.05, ** P<0.001.

Table 3 Regression weights between structural parameters

	Unstandardised direct effects	Standardised direct effects	SE	Critical ratio	Significance level
Impact of disease←positive personality	−0.84	−0.37	0.19	−4.30	<0.001
Impact of disease←DAS28CRP3v	0.91	0.36	0.16	5.66	<0.001
Happiness←positive personality	0.59	0.50	0.12	4.81	<0.001
Happiness←impact of disease	−0.09	−0.17	0.03	−2.31	0.02
Coping←impact of disease	1.00	0.87			
Emotional well-being←impact of disease	1.01	0.90	0.05	18.99	<0.001
Physical well-being←impact of disease	1.00	0.94	0.04	21.09	<0.001
Sleep←impact of disease	0.98	0.80	0.06	15.23	<0.001
Fatigue←impact of disease	1.02	0.90	0.05	19.05	<0.001
Function disability←impact of disease	0.98	0.89	0.05	18.51	<0.001
Pain←impact of disease	0.88	0.82	0.05	15.84	<0.001
Extraversion←positive personality	1.00	0.67			
Agreeableness←positive personality	0.38	0.32	0.11	3.20	0.001
Conscientiousness←positive personality	0.55	0.46	0.11	5.02	<0.001
Emotional stability←positive personality	0.76	0.52	0.13	5.57	<0.001
Openness to experience←positive personality	0.77	0.54	0.13	5.68	<0.001
SHS 1←happiness	1.00	0.89			
SHS 2←happiness	1.08	0.92	0.06	15.95	<0.001
SHS 3←happiness	0.88	0.67	0.08	10.95	<0.001
Quality of life←impact of disease	−0.08	−0.70	0.01	−12.20	<0.001
Quality of life←happiness	0.03	0.13	0.01	2.44	0.014

Unstandardised direct effects come directly out of the estimation procedure. Due to the metric differences of the instruments, in this case, standardised direct effects should be preferred to indicate the strength of the associations (magnitude between −1 and +1). Higher absolute values indicate a stronger (positive or negative) association. An absolute critical ratio >1.96 reflects that path coefficients are significant at the 0.05 level.
DAS28CRP3v, Disease Activity Score using 28 joints and C reactive protein and three variables; SHS, Subjective Happiness Scale.

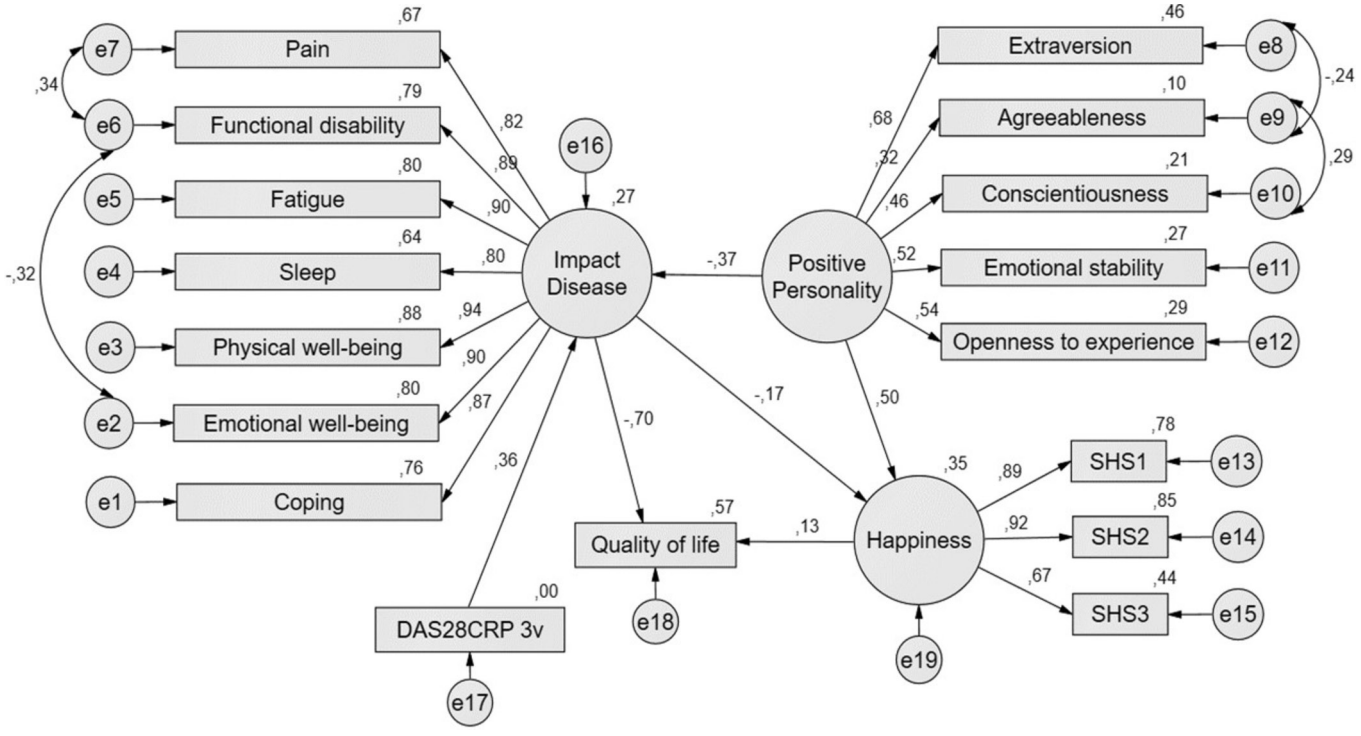

Figure 1 Estimated standardised direct effects for the proposed model. Circles represent latent factors. Squares represent measured variables (the scale scores). Arrows connecting circles and rectangles in one direction show a hypothesized direct relationship between the two variables. Curved lines with an arrow in both directions demonstrate a bi-directional relationship (covariance). Circles with the letter "e" written in it represent the associated error. DAS28CRP3v, Disease Activity Score using 28 joints and C-reactive protein and three variables; SHS, Subjective Happiness Scale.

Table 4 Bootstrap results for indirect effects between structural parameters

	Quality of life		Happiness	
	Estimates, SE	95% CI, significance level	Estimates, SE	95% CI, significance level
DAS28CRP3v	β=−0.26, 0.05	(−0.36 to −0.16), 0.003	β=−0.06, 0.03	(−0.13 to −0.01), 0.04
Positive personality	β=0.33, 0.06	(0.21 to 0.45), 0.004	β=0.06, 0.03	(0.01 to 0.14), 0.03
Impact of disease	β=−0.02, 0.01	(−0.06 to −0.001), 0.04	–	

Standardised indirect effects indicate the strength of the associations (magnitude between −1 and +1). Higher absolute values indicate a stronger (positive or negative) association.
DAS28CRP3v, Disease Activity Score using 28 joints and C reactive protein and three variables.

mitigated by 'positive' personality with very similar weights. Our findings also show that happiness mediates (and mitigates) the association between impact of disease and QoL. Impact of disease has a stronger relation with QoL than with happiness, further supporting the distinct nature of the latter two concepts.

Taken together, these findings imply important clinical implications. Assuming that the perceived impact of disease is, in itself, a valuable treatment target, the model suggests that healthcare professionals should consider personality traits while making the best efforts to control the disease process. In fact, disease activity and personality explained around 27% of the variance in perceived impact, with similar weights for each.

If quality of life is elected as a high-priority treatment objective,[8] the perceived impact of disease should be acknowledged as major determinant,[36 37] but, to a lesser extent, happiness should be considered an ameliorating factor as well. Happiness has been shown to be related to QoL[38 39] and to a variety of better health outcomes, also in a prospective study.[39]

If happiness is taken as the ultimate goal of disease management, the model suggests that personality traits are the most important determinants, with small influences of perceived impact of disease and QoL. The relationship between personality traits, most clearly extraversion, and happiness is well established in the literature.[16 20 21] Our results highlight that this association persists even in the presence of a severely impacting disease, such as RA. Four personality domains seem particularly important in this association: extraversion, emotional stability, conscientiousness and openness to experience. Multiple potential mechanisms may explain these associations: the ability to establish positive personal relationships,[40] to adopt positive attitudes in life's challenging events[41 42] and to accept novel attitudes and unaccustomed values[16] have all been shown to be important ingredients of happiness. It is easy to conceive that they become even more important when facing such a challenging health condition. According to our model, the disease activity control on happiness is indirect, through perceived disease impact, and accounts only for ∼6% of its variance.

Our results should be interpreted while taking into account some limitations. First, although the sample size and the diversity of patients' characteristics were satisfactory, the recruitment was performed in a single centre, which advises caution in results' generalisation. Second, this was a cross-sectional design, not allowing testing causal relationships: longitudinal studies are thus indispensable to further assess the associations suggested here. Third, although we have accessed the presence of some comorbidities, we did not use a validated index for that purpose. This precluded the inclusion of this variable in the statistical analyses, despite its potential confounder effect. Fourth, all variables of this study are also influenced by other factors, such as material wealth, occupation and loneliness, which were not accounted for in the present study, as it was focused on exploring the relevance of disease activity. Finally, the reader should take into account that the concepts of happiness and QoL herein should be interpreted according to the instruments used to define them.

In summary, our results indicate, in line with a substantial literature, that personality traits have a considerable influence on how impactful/disrupting patients perceive their disease to be, with decisive consequences on their QoL, and also on how happy they feel towards life. Taken together, our observations indicate that treatment strategies focused solely on the control of disease activity can be expected to have only a limited impact on QoL and a probably minor effect on happiness. Personality traits represent another realm of potential intervention towards minimising the effects of disease on patients' lives. They seem to be as important as disease control regarding QoL and more important than the disease process if happiness is taken as the ultimate goal. Fully gauging these dimensions would require a more detailed evaluation of patients and a wider scope of interventions than usually done in rheumatology practice.

This can only be attained by multidisciplinary teams working to optimise RA management through tight control of the disease process and also by exploring the full potential of interventions beyond immunosuppression. Within this context, appropriate pain control and non-pharmacological interventions, such as patient education, counselling and support[43 44] and occupational therapy,[45] deserve additional consideration. Interventions in the scope of the positive psychology movement, including 'third wave' cognitive–behavioural therapies designed to boost resilience factors such as acceptance, mindfulness, positive affect and happiness,[46 47] may be of paramount importance for the individual patient's global health and enjoyment of life.

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Contributors EJFS performed the statistical analyses (assisted by RJOF and AMP) and wrote the manuscript. CD, RJOF and JAPdS designed the study. AMP and RG revised the final manuscript from their respective specialist perspective. JAPdS supervised and contributed to all steps of the work. All members of the 'Promoting Happiness Through Excellence of Care ' contributed through inspiring discussions on the topic of happiness and medical care, through examining and interviewing patients and revising the manuscript. Co-authors: "Promoting Happiness Through Excellence of Care" is the registered moto of the Rheumatology Department at the Faculty of Medicine and University Hospital of Coimbra. Additional members of this group: Alexandra Daniel, Ana Pinto, Anabela Silva, Andréa Marques, Armando Malcata, Carlos Costa, Cristiana Silva, Diogo Jesus, Flávio Costa, Gisela Eugénio, João Freitas, João Rovisco, Jorge Silva, José Laranjeiro, Luísa Brites, Margarida Coutinho, Maria Salvador, Mariana Luís, Mariana Santiago, Marília Rodrigues, Mary Marques, Pedro Carvalho, Pedro Freitas, Sara Serra, Tânia Santiago.

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PRESS REVIEW AND JOURNAL CLUB

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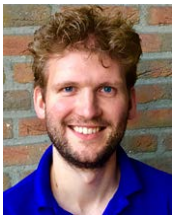


DIRECTORY

Dear Reader,

We are happy to present the fourth issue of the ‘Press Review and Journal Club’ newsletter that is part of a EULAR School of Rheumatology educational initiative, the EULAR-EMEUNET Journal Club. This newsletter includes an overview of relevant articles published both in top rheumatology journals and in major internal medicine journals during the previous 4 months. The article selection includes translational and clinical research papers; in case you want to read the article in more detail, a hyperlink will redirect you to the respective journal. Among the selected articles, one has been chosen by the School of Rheumatology faculty to be discussed in a few weeks in an online Twitter Journal Club. Another article, the ‘EMEUNET Paper of the Month’ has been selected by popular vote through a survey circulated among the rheumatology community. For the latter, a video interview with the first author explaining the main findings of the paper is available on our YouTube channel.

The Journal Club aims to bring together rheumatologists, clinical researchers, basic scientists, and anyone else who might be interested in the topic, to participate in an online, lively discussion. These 'meetings' take place on Twitter at pre-specified times and dates; the next is planned **on September 26 at 8:30 PM GMT (9:30PM CET)**. 'Save the date' reminders will be sent in advance. Where possible, key authors involved in selected articles will be invited to participate. The selected article will be freely accessible for a limited period of time on the journal website. Details of the article selected and of the Journal Club are included on pages 3 and 4 of this issue.

We hope that you will enjoy reading this newsletter and look forward to 'seeing' you soon at our Twitter JC meeting!

Paul Studenic, Richard Conway, Alessia Alunno, Elena Nikiphorou, Antonis Fanouriakis, Gonçalo Boleto, Diederik De Cock, Deshire Alpizar, George Fragoulis and Casper Webers, on behalf of the EULAR EMEUNET Journal Club team

FACULTY CHOICE FOR THE JOURNAL CLUB

Tadej Avčin
Ljubljana University
Slovenia

Xenofon Baraliakos
Ruhr-University Bochum
Germany

Christopher Edwards
University Hospital Southampton
United Kingdom

Annamaria Iagnocco
University of Turin
Italy

Nikiphorou E, Norton S, Young A, Dixey J, Walsh D, Helliwell H, Kiely P, Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network

The association of obesity with disease activity, functional ability and quality of life in early rheumatoid arthritis: data from the Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network UK prospective cohorts

Rheumatology (Oxford). 2018 Jul; 57(7):1194-1202 (**FREE FULL TEXT HERE**)

Obesity has been implicated as a risk factor for developing rheumatoid arthritis (RA) and is an increasingly prevalent comorbidity in RA patients. The authors used data from two prospective inception cohorts (2386 newly diagnosed patients in total) to explore the association between body mass index (BMI) and various disease outcomes over time. They found that RA patients tend to increase their BMI in their first years post-diagnosis. Moreover, obesity at baseline was associated with a significantly lower probability to achieve a low DAS28 at 2 years (OR 0.52), as well as worse outcomes in terms of functional ability and quality of life (QoL) at the same time point. Being obese at 2 years was also associated with significantly higher HAQ and QoL scores, although not with increased disease activity, 3 years later. These data suggest that obesity has a negative impact on the outcome of RA and that obesity management needs to become central within treatment strategies of RA.

The online Journal Club will take place on:

Wednesday 26th September 2018 at 8:30PM GMT (9:30PM CET)

-duration 1 hour-

Follow the accounts **@EULAR_JC**, **@eular_org** and **@EMEUNET**

Use the hashtag **#EULARJC** to follow and join the discussion

EMEUNET PAPER OF THE MONTH

Santos EJF, Duarte C, Ferreira RCO, Pinto AM, Geenen R, da Silva JAP, "Promoting Happiness through Excellence of Care Group"

Determinants of happiness and quality of life in patients with rheumatoid arthritis: a structural equation modelling approach

Ann Rheum Dis. 2018 Aug; 77(8):1118-1124. (full text here)

An ultimate goal of medical care is to improve patients' enjoyment of life, a concept akin to happiness. The authors performed an observational, cross-sectional study, to examine the determinants of happiness and quality of life (QoL) in patients with rheumatoid arthritis (RA). They followed a structured equation modelling approach to assess the relationships between disease activity, disease impact, personality, QoL and happiness, in 213 patients with RA. Results showed that happiness was positively related to 'positive' personality and the impact of disease, albeit positively related to disease activity, was mitigated by 'positive' personality traits. Impact of disease had a much stronger relation with QoL than with happiness. Thus, optimisation of QoL and happiness of people with RA requires control of the disease process, but also improvement of the disease impact domains. Patient personality seems to play a pivotal mediating role in these relations.

Eduardo JF Santos
MSc, PhD (cand.)

Explore this paper in greater detail through an exclusive interview with study first author ...

Interview available here

The EMEUNET Paper of the Month is selected by an online vote of selected articles from each of the rheumatology journal contributions.

Watch out for our next poll!

ANNALS OF THE RHEUMATIC DISEASES

Volume 77 Issues 5-9

Diederik De Cock and Deshire Alpizar-Rodriguez

Diederik is an epidemiologist working either in Manchester, UK or Leuven, Belgium. Aside from his full time job of being a father and professional sport enthusiast, he is analyzing investigator-initiated trials in early rheumatoid arthritis, investigating unmet needs for patients with early rheumatoid arthritis and analyzing the safety of biologic treatment in established rheumatoid arthritis and juvenile idiopathic arthritis. Diederik is the co-leader of the Social Media Subgroup.

Deshiré is an internal medicine physician and rheumatologist. Her major research interests include female reproductive factors and rheumatic diseases, particularly rheumatoid arthritis and systemic lupus erythematosus. She is currently completing a MD-PhD in clinical research at the University of Geneva, Switzerland. Deshire is a member of the Social Media Subgroup.

An important clinical question is how we adapt drug combinations in an age where a holistic approach, necessitated by high rates of comorbidities, is becoming more and more important. Park et al. (pp 898-904) tried to address this issue. Their study tried to address the question of whether methotrexate (MTX) discontinuation is beneficial when vaccinating patients with **rheumatoid arthritis** (RA) for seasonal influenza. This prospective randomised parallel-group multicentre trial included patients with RA on stable dose of MTX that were randomly assigned at a ratio of 1:1 to continue MTX or to hold MTX for 2 weeks after seasonal influenza vaccine containing H1N1, H3N2, B-Yamagata and B-Victoria. Significantly more patients in the “MTX-hold” group achieved a satisfactory vaccine response, defined as greater than or equal to fourfold increase of haemagglutination inhibition antibody titres at 4 weeks after vaccination against ≥2 of four vaccine strains as compared to the “MTX-continue” group (75.5% vs 54.5%, p<0.001). Hence, MTX discontinuation seems to improve overall vaccination responses, but the patients included in this trial displayed a stable and low disease activity which could raise questions for the generalisability of these results.

In systemic lupus erythematosus (SLE), Barrera Vargas et al (pp 944-950) found ubiquitinated proteins in neutrophil extracellular traps (NETs), with a lower expression of polyubiquitinated proteins in lupus patients compared to healthy controls. Patients with SLE seem to develop antiubiquitinated myeloperoxidase antibodies and the authors showed a positive correlation between antibody titres and SLEDAI score. The distinct differences observed in ubiquitin profile in NETs may contribute to dampened anti-inflammatory responses observed in SLE.

In **juvenile idiopathic arthritis** (JIA), Klotsche et al (pp 996-1002) discussed the issues of MTX usage in 1514 young patients with JIA. They tried to determine the reasons of MTX discontinuation as well as frequency of adverse events (AE) and whether the duration of inactive disease before MTX withdrawal disease is associated with the risk of disease flare. The most common reasons to discontinue MTX were ineffectiveness (36.9%) and achievement of inactive disease state (32.1%). However, patients who spent at least 12 months in inactive disease before MTX discontinuation had a significantly lower flare rate. This study highlights how challenging it is for clinicians to deal with MTX treatment in patients with JIA.

ANNALS OF THE RHEUMATIC DISEASES

Volume 77 Issues 5-9

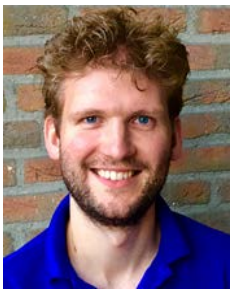
Diederik De Cock and Deshire Alpizar-Rodriguez

Santos et al (pp 1118-1124) went back to the basics of patient care: improving patient quality of life (QoL). They called this improved state, happiness. In their study, the determinants of happiness and QoL in patients with **rheumatoid arthritis** (RA) were explored. 213 patients from a single hospital were assessed regarding disease activity, disease impact, personality, QoL and happiness. Happiness was positively related to a 'positive' personality and, to a lesser extent, negatively related to impact of disease. Impact of disease, in turn, was positively related to disease activity and mitigated by 'positive' personality traits. Impact of disease had a much stronger relation with QoL than with happiness. Happiness mitigated the negative effect of disease impact on QoL. Hence, controlling the disease process is crucial as it improves QoL and happiness, and other disease impact domains. Personality seems to play a pivotal mediating role in happiness and QoL in patients with RA. Dubreuil et al (pp 1137-1142) sought to describe myocardial infarction (MI) risk among patients with **spondyloarthritis** (SpA) who were prescribed NSAIDs, since these drugs may influence the underlying cardiovascular mechanics. The authors compared the risk in SpA with that in osteoarthritis (OA). The Health Improvement Network (THIN) cohort was used including the SpA cohort of 8,140 and the OA cohort of 244,339 with 115 and 6287 MI cases. Diclofenac use in SpA was associated with a significant increase of MI (adjusted OR 3.32, 95% CI 1.57 to 7.03). On the other hand, naproxen was not associated with a significant increase of MI (adjusted OR 1.19, 95% CI 0.53 to 2.68). A ratio of ORs for SpA/diclofenac relative to OA/diclofenac was 2.64 (95% CI 1.24 to 5.58). Hence, this study shows that diclofenac use, but not naproxen use, is associated with an elevated risk of MI risk in SpA. Finally, Terrier et al (pp 1150-1156) compared the long-term efficacy of remission-maintenance regimens in patients with newly diagnosed or relapsing **antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides** in the context of the Systemic ANCA-associated Vasculitis trial. This trial compared rituximab versus azathioprine to maintain remission in patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis or renal-limited ANCA-associated vasculitis. For the rituximab and azathioprine-treated groups, respectively, at month 60, the major relapse-free survival rates were 71.9% and 49.4% (p=0.003). Therefore, this study shows remission rates to be higher in ANCA-associated vasculitides patients using rituximab-based maintenance regimens, with better overall survival.

ARTHRITIS AND RHEUMATOLOGY

Volume 70 Issues 5-8

George Fragoulis and Casper Webers



George is a rheumatology registrar at "NIMTS" hospital, Athens, Greece. His main research interests include rheumatoid and psoriatic arthritis, Sjögren's syndrome and IgG4-related disease. His PhD thesis related to phagocytosis and the role of cell-death in Sjögren's syndrome. He holds an honorary research fellow position at the University of Glasgow, UK, carrying out research focused on inflammatory arthritis. George is member of the Newsletter Subgroup.

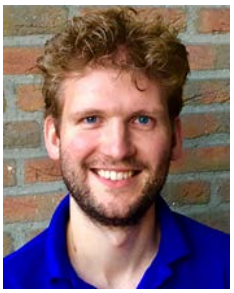
Casper is a PhD candidate at the Maastricht University Medical Center, The Netherlands. His major research focus is on axial spondyloarthritis (axSpA). His past work involved gender attributable differences in radiographic axSpA and willingness-to-pay for biologics. Currently, he is researching socioeconomic outcomes, such as employment and sick leave, and economic evaluations of axSpA. He is also involved in a Dutch registry for SpA. In 2019 he will commence specialist training in rheumatology. Casper is a member of the Newsletter Subgroup.

Mortality rates in **systemic lupus erythematosus** (SLE) are increased, with the majority of deaths occurring in females. Yen et al (pp 1251-1255) investigated the relative burden of cause-specific mortality by ranking causes of death in the US, and found that SLE was among the top-20 causes of death among females aged 5-64 years. Among black and Hispanic females, SLE ranked higher. As SLE might be underreported as cause of death, the true burden of SLE mortality could be even higher. Epigenetic changes play an important role into SLE pathogenesis. Ulff-Møller et al (pp 878-890) examined the genome-wide DNA methylation status of white blood cells in twins (thus ruling-out genetic variabilities) with at least one having SLE. They found promoters of interferon-regulated genes to be hypomethylated in all cell types and that promoters were predominantly hypermethylated in B-cells. Much controversy surrounds the contribution of uric acid, an important risk factor for **gout**, to cardiovascular disease (CVD), cancer and all-cause mortality. Cho et al (pp 1122-1132) demonstrated a U-shaped association between uric acid and mortality. Low uric acids levels were independently associated with increased all-cause mortality (males and females), CVD mortality (females) and cancer mortality (males). The antioxidant role of uric acid could possibly explain these findings. Yang et al (pp 855-867) highlighted the importance of IL-23/-17 axis, in **psoriatic arthritis** (PSA) characterizing a PsA animal model. These mice present a Th17-response, driven by T-cell specific STAT3C overexpression and develop clinical features of PsA. Abolishment of IL-17 and IL-22 led to disease improvement in these mice. Synovial tissue histopathology has been evaluated as a tool for optimizing treatment strategies in **rheumatoid arthritis** (RA). Orange et al (pp 690-701) explored the histopathology of synovial membrane using gene expression as a guide. Consensus clustering of the top-500 genes identified 3 subtypes: high-inflammatory, low-inflammatory and mixed-subtype. High-inflammatory group displayed higher systemic inflammation markers. The latter were dissociated from pain scores in the low-inflammatory group, possibly suggesting diverse pain pathways. **Fibromyalgia** sometimes coexists with RA. Basu et al (pp 1000-1007) used functional connectivity MRI to examine temporal correlations between networks and regions of the brain in RA patients with fibromyalgia features (measured by the "fibromyalgia-ness" score). A significant correlation was found between the default mode network connectivity to the left mid/posterior insula (characteristic in "primary" fibromyalgia patients) and the fibromyalgia-ness scores in RA patients.

ARTHRITIS CARE AND RESEARCH

Volume 70 Issues 5-8

George Fragoulis and Casper Webers



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Knowledge about longitudinal disease trajectories in **childhood-onset systemic lupus erythematosus** (cSLE) could help tailor management strategies for these patients. Using an inception cohort, Lim et al (pp 750-757) identified five classes of disease activity trajectories. Baseline major organ involvement and age at diagnosis predicted memberships in different classes. During 10 years after diagnosis, patients with relapsing/disease-transforming disease accumulated most damage and at the fastest rate, compared to other trajectories. Colliard et al (pp 1263-1268), examined, in a **systemic lupus erythematosus** (SLE) cohort, the presence of anti-ficolin-2 autoantibodies and its possible association with disease features. Ficolin-2 is a protein involved in the clearance of apoptotic cells which has been implicated in the pathogenesis of SLE. Serum levels of this protein were found to be decreased in SLE patients. In this study, anti-ficolin-2 antibodies were found in about one third of SLE patients, being associated with the presence of active lupus nephritis. Combination of anti-ficolin-2, anti-ficolin-3 and anti-c1q antibodies gave a sensitivity of 48% and a specificity of 98% for the diagnosis of SLE nephritis. Behavioral factors (diet, exercise, smoking, dental health) contribute to developing **rheumatoid arthritis** (RA), and behavioral change might reduce risk of RA. Sparks et al (pp 823-833) observed in a randomized-controlled trial that disclosure of personalized RA risk to first-degree relatives of RA patients led to increased motivation to improve risk-related behavior as compared to receiving standard, non-personalized information. ACPA-positive RA has always been considered as a more severe RA subset. Using a population-based inception cohort, Boer et al (pp 987-996) demonstrated that ACPA-negative and ACPA-positive patients have similar levels of pain, disease activity, functional disability and restrictions in household work over time. The authors concluded that both RA subsets have similar disease burden. In another study, Wysham et al (pp 961-969) showed that anti-CCP high positivity was associated, after controlling for other variables, with lower femoral neck bone mineral density (BMD) in patients with RA. Even more, anti-CCP levels were negatively associated with BMD amongst high anti-CCP positive individuals. In **psoriatic arthritis** (PsA), Ballegaard et al (pp 1206-1217) explored whether trial characteristics (considered contextual factors) act as effect modifiers in RCTs of targeted therapies. Results showed that drug retention was higher in patients with PsA compared to psoriasis, and that several trial eligibility criteria (related to treatment history, disease duration and rheumatoid factor) modified the probability of achieving treatment response in PsA.

ARTHRITIS RESEARCH AND THERAPY

Volume 20 Issues May-August

Diederik De Cock and Deshire Alpizar-Rodriguez

Diederik is an epidemiologist working either in Manchester, UK or Leuven, Belgium. Aside from his full time job of being a father and professional sport enthusiast, he is analyzing investigator-initiated trials in early rheumatoid arthritis, investigating unmet needs for patients with early rheumatoid arthritis and analyzing the safety of biologic treatment in established rheumatoid arthritis and juvenile idiopathic arthritis. Diederik is the co-leader of the Social Media Subgroup.

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Rheumatoid arthritis (RA) is more prevalent in women than in men, with a peak incidence in the post-menopausal period. Engdahl et al (20:84) reported that estrogens prompt anti-inflammatory effector functions in IgG by inducing ST6Gal1 expression in mouse and human antibody-producing cells and by increasing Fc sialylation. This finding provides a potential mechanistic explanation for the increased risk of RA in post-menopausal women. Further in pathogenesis, Aldridge et al (20:150) showed gender-based differences in the association between T cell subsets and disease activity in untreated early RA patients, such as a positive association of Th2 cells with disease activity in male, but not in female patients. Strand et al (20:129) observed in a follow-up of a phase III trial that RA patients under sarilumab monotherapy had greater improvements across multiple patient-reported outcomes (PROs) than adalimumab monotherapy. In **systemic lupus erythematosus** (SLE), Ceccarelli et al (20:126) identified erosive arthritis in 26% of 152 patients, of which 44% were positive to anti-carbamylated protein antibodies (antiCarp) and 26% to anti-citrullinated peptide antibodies (ACPA). Crohn's disease (CD), ulcerative colitis (UC) and **spondyloarthritis** (SpA) are characterized by dysbiosis. Regner et al (20:149) evaluated intraepithelial lymphocytes (IEL) from colon biopsies of patients with CD, UC and SpA and found increased IL-1β in patients with UC, increased IL-17A and IFN-γ in patients with CD, and increased TNF-α in patients with CD and SpA, compared to controls. IEL-produced cytokines negatively correlated with the relative abundance of multiple bacterial taxa which may be relevant to the pathogenesis of these conditions. Little is known about the effect of IL-17A blockade on local inflammatory and structural changes in the joints in **psoriatic arthritis** (PsA). Kapmpylafka et al (20:153) found that IL-17 inhibition by secukinumab over 24 weeks led to a significant decrease of synovial inflammation and no progression of catabolic or anabolic bone changes in the joints of patients with PsA. McInnes et al (20:113) reported that secukinumab provides rapid and sustained pain relief in PsA over 2 years of treatment when compared to placebo. Raouf J et al (20:83). analysed the lipidomic profile of patients with **polymyositis and dermatomyositis** and found a disproportionate level of saturated and polyunsaturated fatty acids, which might have negative effects on muscle performance. **Systemic sclerosis** (SSc) is characterized by vasculopathy and progressive fibrosis. Cutolo et al (20:157), found that CTLA4-Ig (abatacept) treatment downregulates circulating fibrocytes but not skin fibroblasts isolated from SSc patients.

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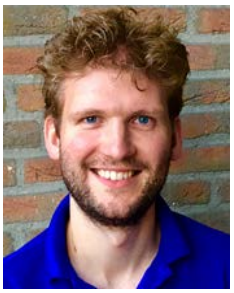
RHEUMATOLOGY (OXFORD)

Volume 57 Issues 5-8

George Fragoulis and Casper Webers



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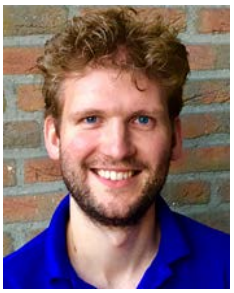
Several biomarkers of disease activity for **Sjögren's syndrome** (SS) have been proposed, including B-cell biomarkers such as B-cell activating factor, beta-2 microglobulin and free-light chains. James et al (pp 1222-1227) observed that, while these three biomarkers were all associated with total disease activity scores, they had distinct disease domain associations and could thus be considered complementary. Type I and type II Interferons (IFN) are also implicated in SS pathogenesis. Some authors suggest that different expression patterns are associated with distinct phenotypes. Bodewes et al (pp 921-930) examined, via RT-PCR, the expression of IFN-related genes. Three groups were identified: IFN-negative, IFN-I-activation and IFN-I/IFN-II combined activation. Although IFN activation did not correlate with disease activity, the frequency of SS patients positive for the biological domain was higher in patients with IFN activation. The latter was also associated with higher IgG levels and autoantibody presence. The impact of **giant cell arteritis** (GCA) on mortality is unclear. Aouba et al (pp 1047-1055) investigated cause-specific mortality associated with GCA, and found that age of death was not decreased in GCA compared to the general population. Mortality rates due to aortic aneurysms, dissections and hypertension were increased in GCA, while cancer-mortality was decreased. The underlying mechanisms of these associations remain unknown. Temporal artery biopsy (TAB) is the gold-standard for GCA diagnosis, it can be, however, negative in a substantial number of patients. Ciccia et al (pp 1377-1380) suggest a simple procedure to increase the diagnostic accuracy of this test. They showed that CD3 staining in TAB, increased the sensitivity and specificity to 89.5% and 95.0%, respectively, with positive and negative predictive values reaching 97.0% and 79.8%. Recent research indicates that obesity affects outcome in **rheumatoid arthritis** (RA). An analysis of two consecutive inception cohorts by Nikiphorou et al (pp 1194-1202) revealed that obesity is an increasingly prevalent comorbidity in early RA, having negative impact on disease activity, functioning and quality of life in the short-term. These findings support a central role for screening and management of obesity in RA. JAK-inhibitors are emerging therapeutic modalities in **inflammatory arthritis**. Vidal et al (pp 1461-1471), using a rat model of adjuvant-induced-arthritis, showed that tofacitinib decreased articular inflammation, preventing bone erosions and cartilage damage and reducing bone remodeling. Despite being able to restore bone hardness, this was not the case for cortical and trabecular bone structure. Also, mechanical features tested were not improved after treatment with tofacitinib.

THE JOURNAL OF RHEUMATOLOGY

Volume 45 Issues 5-8

George Fragoulis and Casper Webers



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In **systemic lupus erythematosus** (SLE), repeated testing of antibodies is common. Raissi et al (pp 827-834) using data from a SLE registry showed that, over time, anti-ENA antibody status rarely changed over time and costs to detect change in anti-ENA status were high. The authors argued that, in general, repeat testing of anti-ENA in SLE is likely not necessary. Depression might be the most prevalent comorbidity in **rheumatoid arthritis** (RA). In a prospective cohort of early RA patients, Kuriya et al (pp 1101-1108) observed that one fourth of patients experienced persistent depression over a two-year period. High disease activity was associated with persistent depression, particularly in females. Future studies are necessary to investigate whether early treatment of RA reduces the risk of adverse mental health outcomes. The association between disease activity and health-related quality of life (HRQoL) in patients with early axial **spondyloarthritis** (SpA) was investigated by van Lunteren et al (pp 779-784). Physical (but not mental) HRQoL was decreased compared to general population. An increase in ASDAS during follow-up was independently associated with a decrease in physical HRQoL, especially in males and blue-collar workers. These findings support the choice of disease activity as the treatment-target in axial SpA. SpA is not rare in the context of inflammatory bowel disease (IBD). However, biomarkers for its diagnosis with acceptable accuracy are lacking. Sclerostin (SOST), a protein that inhibits the Wnt signaling pathway leading to decreased bone formation, has been found to be low in patients with SpA, while anti-SOST antibodies have been associated with low SOST levels. Luchetti et al (pp 630-637) assessed SOST and SOST-antibodies in patients with IBD (with or without SpA – axial or peripheral), having as control groups patients with ankylosing spondylitis, RA and healthy individuals. SOST levels and SOST-antibodies were lower and higher, respectively, in patients with IBD and axial SpA compared to those with peripheral SpA, IBD, RA or healthy subjects. In **systemic sclerosis** (SSc), interstitial lung disease (ILD) has been recognized as a significant cause of morbidity and mortality. KL-6 and CCL-18 are two of the so-called pneumoproteins (serum proteins mainly synthesized in the lung) and have been associated with lung injury. In their study, Salazar et al (pp 1153-1158) sought to investigate whether these could serve as predictors of ILD progression in early SSc patients. It was found that KL-6, but not CCL-18 could predict the decrease of FVC% in both univariate and multivariate models.

RMD OPEN

Volume 4 Issue 2

Diederik De Cock and Deshire Alpizar-Rodriguez

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Ide et al (e000661) tried to find the relevance of classical markers of rheumatoid arthritis (RA) disease in **idiopathic inflammatory myositis** (IMM). Rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) are immunological hallmarks of RA, and presence of these antibodies is associated with higher disease activity and increased risk of joint destruction. However, little is known about the prevalence of RF and ACPA in IIM. In this study, the authors found that RF was present in 11 patients (9.1%) and ACPA was present in 6 patients (5.0%) out of 121 patients with IIM. This prevalence was lower than reported in previous studies. Hence, although RF and ACPA are prevalent in IIM, the presence of these antibodies does not seem to be clinically relevant and therefore should not guide therapeutic decisions. Glintborg et al (e000710) explored whether switching from originators to biosimilars for cost reasons (non-medical switching) in patients with **inflammatory arthritis** impacts on the use of healthcare resources. In an observational cohort study from the DANBIO register, 769 switchers, 1484 outpatient contacts, 6718 visits and 9243 days with services (693 on switch date) were identified. Mean visit rate was 3.89 before and 3.95 after switch (p=0.35). Total number of services was 19,752 (2019 on switch date). Mean service rates before/after switch and clinical visits per week per patient appeared similar before/after switch, with peaks every ≈8 weeks, parallel to infliximab infusion dosing. Hence, no evidence of increased use of outpatient health resources following switch from originator to biosimilar infliximab was found. Bischoff-Ferrari et al. (e000678) assessed the possible benefit of vitamin D in **osteoarthritis** (OA). Although observational studies suggest that increased vitamin D intake and higher 25-hydroxyvitamin D levels may prevent structural progression of knee OA, all four recent clinical trials testing vitamin D supplementation found no such benefit among patients with early to moderate OA not yet at the stage of surgery. In this trial, older adults aged 60 years and older undergoing unilateral total knee replacement due to severe knee OA were included. The primary endpoints were symptoms (Western Ontario and McMaster Universities Arthritis Index pain and function scores) assessed at baseline, 6, 12, 18 and 24 months in both knees, and the rate of falls over 24 months.The trial compared standard of care dose of vitamin D (800 IU per day) with a high dose (2000 IU per day) to explore if higher doses were more effective. The authors showed that a 24-month treatment with daily 2000 IU vitamin D were not significantly more beneficial or harmful than a daily standard dose of 800 IU among older adults undergoing unilateral total knee replacement.

MISCELLANEOUS

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Rheumatoid arthritis (RA) is characterized by progressive joint damage that may start early in the course of the disease. Van der Heijde et al (Clin Rheumatol 37:2381) reported on the evaluation of structural damage progression based on clinical response, in patients who received no treatment or limited treatment with conventional synthetic disesase-modyfing anti-rheumatic drugs (csDMARDs) and were biologic naïve. These patients were then randomized to either baricitinib, methotrexate or the combination of both. Authors found that independently of treatment, baseline factors significantly associated with an increased risk of structural damage progression included higher hsCRP, CDAI score, smoking, female sex and lower body mass index. Patients achieving sustained DAS28-hsCRP ≤ 3.2 or SDAI score ≤ 11 were less likely to have structural damage progression at week 52. Upadacitinib, a selective inhibitor of Janus kinase 1, was effictive in phase 2 studies in patients with moderate and severe RA. Burmester et al (Lancet 2018 391:2503-12) reported the safety and efficacy of upadacitinib in RA patients with inadequate response to csDMARDs in a randomized, double blind, placebo-controlled phase 3 trial. Upadacitinib showed significant improvements in clinical signs and symptoms of patients with RA with a good safety profile. Genovese et al (Lancet 2018 391:2513-24) reported that upadacitinib led to rapid and significant improvements compared with placebo over 12 weeks in RA patients refractory to biologic treatment of the same trial. In **systemic lupus erythematosus** (SLE), Wallace et al (Lancet 2018; 392:222-31) reported the results of a double-blind, multicentre, randomized, placebo-controlled, 24-week phase 2 trial with baricitinib. Authors found significant improvements in signs and symptoms of active SLE patients who were not adequately controlled despite standard of care therapy. Landewé et al (Lancet 2018; 392:134-44) reported that in patients with active non-radiographic axial **spondyloarthritis** who had achieved sustained remission with adalimumab, continued therapy was associated with significantly more patients maintaining remission when compared to treatment withdrawal. Rotondo et al (Scand J Rheumatol 47:311-18) found evidence for increase in finger blood flow, evaluated by laser Doppler flowmetry following iloprost infusion, in **systemic sclerosis** patients with Raynaud's phenomenon, despite a short time effect. Mesenchymal stromal cells (MSCs) have been proposed as a safe treatment option for knee **osteoarthritis** (OA). Lamo-Espinosa et al (J Transl Med 16:213) reported that a single intra-articular injection of autologous bone marrow MSCs is safe and provided greater functional improvement compared to hyaluronic acid in patients with knee OA.

• EDUCATIONAL EVENTS

• SEPTEMBER - OCTOBER 2018

SEPTEMBER 2018

8th EULAR Course on Capillaroscopy

- **When and Where: 13 – 15 Sep 2018, Genoa, Italy**
- **Website: https://esor.eular.org/theme/lc_eular/layout/enrol.php?id=14**

27th International Complement Workshop 2018

- **When and Where: 16 – 20 Sep 2018, Santa Fe, Mexico City, Mexico**
- **Website: https://www.complement.org/icw-2018/**

OCTOBER 2018

19th EULAR Postgraduate Course 2018

- **When and Where: 1 – 3 Oct 2018, Budapest, Hungary**
- **Website: https://esor.eular.org/theme/lc_eular/layout/home/course.php?id=23**

EULAR Brussels Conference 2018

- **When and Where: 8 – 9 Oct 2018, Brussels, Belgium**
- **Website: https://www.eular.org/public_affairs_brussels_conference.cfm**

British Society for Paediatric and Adolescent Rheumatology (BSPAR) Conference

- **When and Where: 17 – 19 Oct 2018, Southampton, UK**
- **Website: https://www.rheumatology.org.uk/Professional-Development/Education-Events/Conferences/Paediatric-annual-conference/Register/**

ACR/ARHP Annual Congress 2018

- **When and Where: 19 – 24 Oct 2018, Chicago, IL, USA**
- **Website: https://www.rheumatology.org/Annual-Meeting/**

Cytokines 2018: 6th Annual Meeting of the International Cytokine & Interferon Society

- **When and Where: 27 – 30 Oct 2018, Boston, MA, USA**
- **Website: https://boston.cytokinesociety.org/**

THE 3RD EULAR REGISTERS AND OBSERVATIONAL DRUGS MEETING

The EULAR RODS meetings have evolved into a course in which faculty and attendees are delivering and suggesting content. This course aims to provide insights into practical and methodological aspects of registers and drug observational studies, data handling and analysis, promoting and facilitating collaborative work through a series of interactive lectures, workshops and round table discussions.

The course structure and content builds on previous RODS meetings and direct feedback from participants and also brings attention to novel aspects around future applications of registers. It incorporates innovative and disruptive methodology.

In this unique 1,5 days meeting, attendees will have an opportunity to network and have a one-to-one interaction with experts in the field, as well as to present own ideas in the form of posters and oral presentations. Evaluation and feedback from participants and instructors will have many different formats (open text in the “Board of innovation” and interactive learning during lectures and workshops).

The next EULAR RODS Meeting

will take place on

30 November - 1 December 2018 in Amsterdam, The Netherlands

REGISTRATION OPEN

COURSE BURSARIES ALSO AVAILABLE

For information and to register visit:
https://esor.eular.org/theme/lc_eular/layout/enrol.php?id=12

THE EULAR ON-LINE COURSES

All EULAR courses, as electronic ways of continuous medical education in rheumatology, are managed by a scientific course committee responsible for the structure and content of the courses and for ensuring regular quality control and advancement. Teams of expert authors are regularly reviewing and updating the courses to keep up with the newest developments in the field.

REGISTRATION OPEN SINCE END OF JUNE 2018 – CLOSING ON 30 NOVEMBER 2018

Course	Duration	Registration and More Information
13th EULAR On-line Course on Rheumatic Diseases	2 years	https://www.eular.org/edu_online_course.cfm
10th EULAR On-line Course on Connective Tissue Diseases (CTD)	9 months	https://www.eular.org/edu_online_course_ctd.cfm
8th EULAR On-line Course on Systemic Sclerosis (SSc)	9 months	https://www.eular.org/edu_online_course_ssc.cfm
7th EULAR On-line Introductory Ultrasound Course	7 months	https://www.eular.org/edu_online_course_msus.cfm
5th EULAR / PReS On-line Course in Paediatric Rheumatology	9 months	https://www.eular.org/edu_online_course_paediatric.cfm
4th EULAR On-line Course for Health Professionals	9 months	https://www.eular.org/edu_online_course_hpr.cfm
NEW! EULAR On-line Course on Imaging in RMDs	1 year	https://esor.eular.org/theme/lc_eular/layout/enrol.php?id=5

The EULAR On-line Courses on Rheumatic Diseases, CTDs, SSc and US are also available as APP

THE OPINION OF TWO PARTICIPANTS:

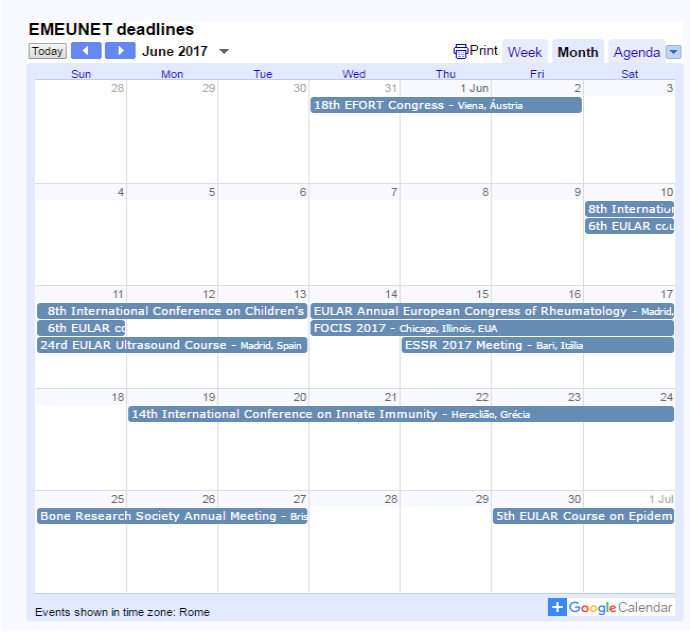
"Ultrasonography is essential for the training of Rheumatologists and represents a key aspect of patient's evaluation. The EULAR On-line Introductory Ultrasound Course offers theoretical basic skills on musculoskeletal ultrasound in rheumatic diseases as well as in healthy subjects. The high quality of contents as well as the experience of the Faculty are the two main reasons to join this course. Moreover, the website is straightforward and very easy to use. Upon passing the final examination, EULAR releases a certificate. This course is very useful for Rheumatologists who would like to acquire a basic theoretical knowledge on musculoskeletal ultrasound."

"I attended the EULAR On-line Introductory Ultrasound Course. It is a well structured basic course on ultrasonography that is divided in different modules according to the different anatomical sites. Each module includes specific exercises and the final test. I found this course very interesting and it provided me with a complete overview of ultrasonography in rheumatology. I would recommend this course as to me it was overall more useful and formative compared to some different on-site courses I previously attended."

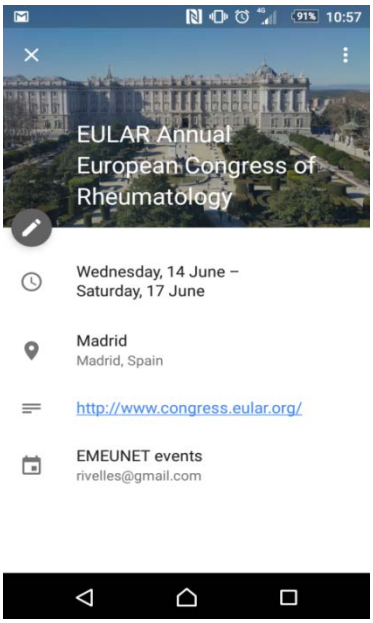
THE EMEUNET CALENDAR

The official EMEUNET calendar is now up and running on our website
http://emeunet.eular.org/calendar.cfm

In 2016, EMEUNET launched a new initiative to have a shared calendar of events and deadlines. We decided to use google, as it offers the advantage of allowing synchronization with computers and mobile devices.



The calendar is fully customizable and members can decide to get notifications by email or on the mobile



To follow this calendar and transfer it into your calendar manager in any device (laptop, tablet, phone), please see the instructions here.

If you are an apple user, we have been informed that in some cases, possibly after a system update), the synchronization is lost. If this happens, you will need to set again the synchronization at this address https://www.google.com/calendar/iphoneselect
Here you can find detailed instructions on how to synchronize apple devices with the google calendar.

The EMEUNET calendar has been up and running for two years, with the aim to ensure that our members would never loose a deadline or a conference! We hope you have found it useful. If you have any comment or suggestion please let us know by sending an email to emeunet@eular.ch

2000 AND COUNTING!!

EMEUNET CELEBRATES 2000 MEMBERS

EMEUNET recently reached the milestone of 2000 members. What started by a small group of visionaries, has now grown into a dynamic community throughout Europe and beyond.

We are grateful to each and every member personally, but we would particularly like to pay tribute to our **Country Liaisons** who have constantly promoted EMEUNET in their countries throughout the past ten years.

Keep up the good work!

Jakob Höppner, a medical student from Berlin, is the Nr. 2000 EMEUNET member and was interviewed by the Newsletter Subgroup Leader, Antonis Fanouriakis, on the occasion:

Q: Jakob, how did you first hear about EMEUNET?

I learnt about EMEUNET from my group leader, who is a member of the EUSTAR collaborators for systemic sclerosis. Then, I saw a Facebook post that said “become a EMEUNET member”. So, I checked the website and decided to sign up.

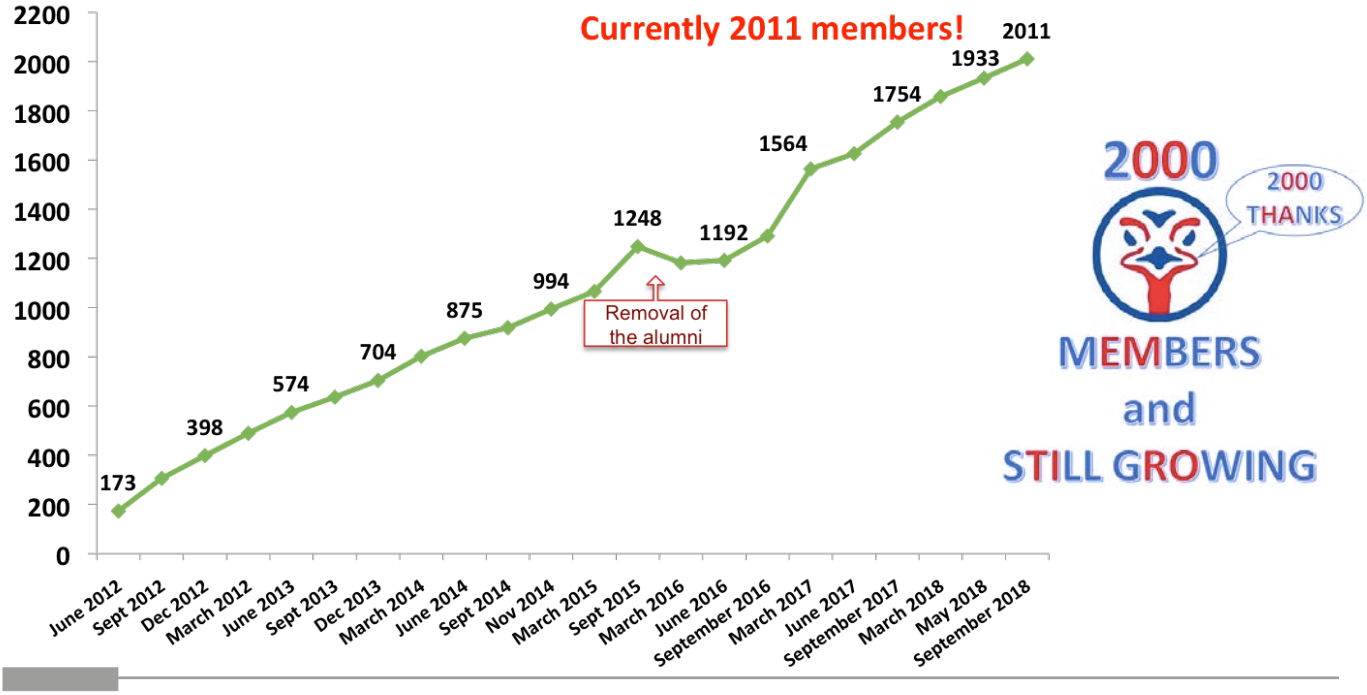
Q: Why did you decide to become an EMEUNET member?

Currently, I am a medical student working on my doctoral thesis on systemic sclerosis. After my studies, I would like to specialize in rheumatology. I thought EMEUNET was a good way to get regular updates on news in rheumatology. Moreover, I’m very interested in the education section and the online courses.

Jakob, with the EMEUNET Newsletter Subgroup leader, Antonis

Q: Which EMEUNET initiative do you think would be more useful for your professional work?

I think the educational offers are the most interesting for me at this point. However, I also find the mentoring program great and I would love to participate during my further education.



JOIN EULAR TASK FORCES AND COMMITTEES

Young investigators of EMEUNET are an integral part of all task forces and committees working on new EULAR recommendations. This is a wonderful chance for EMEUNET to increase its visibility and for you to accelerate your academic career.

The last call came in May from the EULAR Task Force on prevention and management of osteoporotic fractures

Take a look at emails from EMEUNET and find the opportunity most suitable for you!

SHARE YOUR IDEAS!

Over the years EMEUNET has developed several projects covering different topics and areas of interest. However, we appreciate any suggestions and welcome new ideas to expand on what we currently offer to EMEUNET members. Make your voice heard and share your ideas with us!

It is easy, just write down some lines to summarize your proposal and send it either via email at emeunet@eular.ch or through our website (http://emeunet.eular.org/contact_us.cfm). Don't forget to provide your contacts so we can come back to you for additional details!

More information about EMEUNET can be found at **http://emeunet.eular.org**

www.facebook.com/EMEUNET

www.twitter.com/EMEUNET

http://www.linkedin.com