

## Red cell distribution width correlates with fatigue levels in a diverse group of patients with systemic lupus erythematosus irrespective of anaemia status

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### ABSTRACT

**Objective.** *Fatigue remains a debilitating feature of systemic lupus erythematosus (SLE). Although in some cases this may be the result of intercurrent fibromyalgia, mood disorder or untreated metabolic syndrome, in many cases the cause is unclear. The aim of this study was to investigate the relationship between fatigue and red cell distribution width (RDW), a measure of variability in erythrocyte size and volume.*

**Methods.** *A total of 225 patients were recruited from three clinics in England and Australia. Patients completed the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Score or 12-item Short Form survey (SF-12) to measure fatigue, which was compared with RDW and haemoglobin. In a subgroup of 72 patients, markers of disease activity were also assessed for correlation with fatigue using univariate and multivariate analysis with fatigue as the dependent variable.*

**Results.** *In all three groups, significant correlations between fatigue and RDW were observed ( $p < 0.001$ ;  $p = 0.02$ ;  $p < 0.001$  respectively) and this was preserved in multivariate analysis. There was no correlation between fatigue and haemoglobin in two groups (with the correlation between RDW and fatigue remaining significant in non-anaemic patients in the third group). In subgroup analysis, fatigue was not associated with any measures of disease activity.*

**Conclusion.** *We report a reproducible, statistically significant association between RDW and fatigue levels in a diverse population of patients with SLE. The findings of this study raise the possibility of a potential novel biological basis for fatigue in those in whom there is a lack of an alternate explanation.*

### Introduction

The majority of patients with systemic lupus erythematosus (SLE) report fatigue with 80–90% describing this as the single most debilitating symptom (1, 2). Previous studies have found no apparent correlation between fatigue and disease activity (3). The cause of fatigue in SLE is poorly understood and poses significant challenges for both patient and clinician. Fibromyalgia (4), depres-

sion (5) and metabolic disorders (such as hypothyroidism) (6) can all lead to fatigue and are commonly seen in SLE. However, in a large number of cases the cause is unexplained, thus representing a significant area of unmet need.

Red cell distribution width (RDW), a measure of variation in erythrocyte size and volume, has been found to be higher in patients with SLE than healthy controls (7) and shown to correlate with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and SLE Disease Activity Index 2000 (SLEDAI-2K) (8). Furthermore, elevated RDW at diagnosis of SLE has been reported to predict poorer clinical outcomes (9). In this study, we aimed to investigate whether there is an association between RDW and fatigue in patients with SLE for the first time.

### Methods

#### Patient recruitment

Three groups of patients were recruited from specialist Lupus Clinics in London (United Kingdom) and Sydney (Australia). All eligible participants fulfilled American College of Rheumatology (ACR) criteria and provided informed consent.

#### Ethics approval

Fatigue data and samples from all patients were obtained with informed consent and after approval from local ethics committees in the UK (ref. 11/LO/0330 and ref. 11/WM/0033) and from the Research and Ethics Office, South Western Sydney Local Health District (Ethics number SWSLHD HREC 10/23 Inflammatory Targets of SLE) in Australia. This study complies with the declaration of Helsinki.

#### Group 1 (test group)

Patients with juvenile-onset lupus (diagnosed before the age of 16) were recruited from the Young Adult Lupus Clinic at University College London Hospital (UCLH), UK. Fatigue was measured using the validated Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score v. 4. This 13-domain questionnaire generates a numerical score (0–52), where a lower score represents more fatigue.

Haemoglobin (Hb), RDW and markers of disease activity including ESR, Complement C3 (C3), double-stranded DNA binding (dsDNA), CRP and SLE-DAI-2K were recorded at the same visit. Anaemia was defined as per World Health Organisation (WHO) guidance (Hb <120 g/L in women and <130 g/L in men).

#### Group 2 (validation group)

Patients with adult-onset SLE were recruited from the UCLH Adult Lupus Clinic and completed the 12-item Short Form survey v. 2 (SF-12). This validated quality of life questionnaire consists of 12 items across 8 domains including one specifically relating to vitality. Responses are transformed to a numerical scale (0–100) with a lower vitality score indicative of higher levels of fatigue. As with Group 1, Hb and RDW were collected.

#### Group 3 (second validation group)

Patients with adult-onset lupus were prospectively recruited from the Lupus Clinic at Liverpool Hospital, Sydney (Australia). Fatigue was measured using the FACIT Fatigue score (as in Group 1) and Hb and RDW were recorded.

#### Statistical analysis

Spearman's rank or Pearson's correlation were used to determine significance between independent variables. T-test or Mann Whitney test were used for comparisons between two groups. In Group 1, multivariate linear regression analysis was conducted with

**Table I.** Demographic and clinical characteristics of the three study groups (n=225).

Characteristic	Group 1	Group 2	Group 3	p-value
Number of patients	72	106	47	
Mean age [years] (SD)	21.3 (±4.4)	43.7 (±14.1)	46.4 (±15.9)	<0.001 <sup>a</sup>
Female (%)	65 (90%)	101 (95%)	44 (94%)	0.42
Ethnicity (%)				
Caucasian	23 (32%)	61 (58%)	17 (36%)	
Afro-Caribbean	18 (25%)	29 (27%)	0	
South Asian	22 (31%)	10 (9%)	5 (11%)	
East Asian	4 (6%)	0	19 (40%)	
Other	5 (6%)	6 (6%)	6 (13%)	
Mean Hb [g/L] (SD)				
Range	128.7 (±16.8) 76-171	123.9 (±16.5) 74-155	126.4 (±14.8) 96-156	0.28
Mean RDW [%] (SD)				
Range	14.2 (±1.9) 12.0-22.0	14.2 (±1.7) 11.9-21.1	13.3 (±1.7) 10.7-18.8	0.001 <sup>b</sup>
Fatigue Score				
Mean FACIT score (SD)	33.4 (±14.8)		29.9 (±12.7)	0.13
Mean Vitality score (SD)		45.5 (±10.3)		
Mean disease duration [years] (SD)	8.0 (±4.7)	15.5 (±9.7)	9.9 (±6.6)	<0.001 <sup>c</sup>

<sup>a</sup> Significant difference between Cohort 1 and Cohorts 2, 3.

<sup>b</sup> Significant difference between Cohort 3 and Cohorts 1, 2.

<sup>c</sup> Significant difference between Cohort 1 and Cohort 2; and between Cohort 2 and Cohort 3.

FACIT Fatigue score as the dependent variable. RDW and markers of disease activity (dsDNA, C3, ESR, CRP and SLEDAI-2K) were independent variables.

## Results

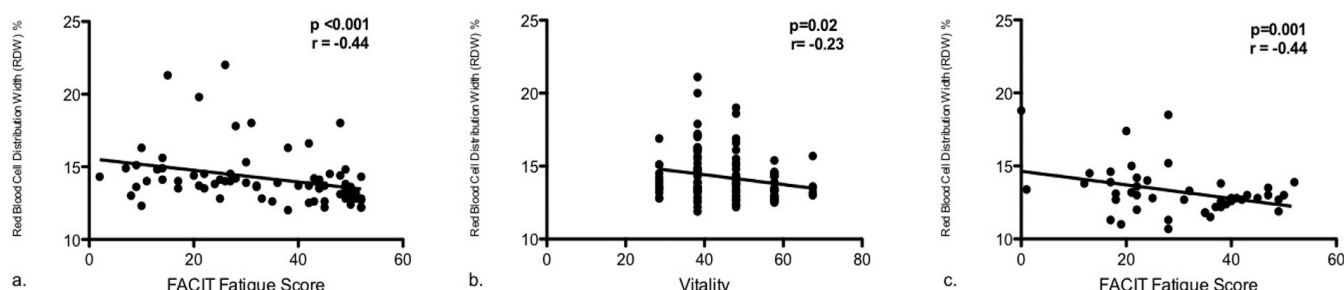
### Patient demographics

A total of 225 patients were recruited across the three groups. Demographic details are summarised in Table I. The defined upper limit of the normal range for RDW in the UK based groups was higher (11.5–14.5%) than those used in the Australian group (11.6–14.0%). A statistically significant difference was seen in RDW between the two UK

based groups and the Australian group, likely to be representative of this inter-laboratory variation.

### Variables associated with fatigue in Group 1

As shown in Figure 1a, FACIT Fatigue score correlated negatively with RDW ( $p < 0.001$ ;  $r = -0.44$ ). A correlation between FACIT and Hb was also noted, although to a lesser degree ( $p = 0.01$ ;  $r = -0.30$ ). Therefore, to assess if the correlation between RDW and FACIT remained independent of anaemia status, those who were anaemic were excluded ( $n = 21$ ). The correlation between FACIT and RDW remained significant in



**Fig. 1.** A statistically significant correlation was observed between RDW and levels of fatigue in all three groups of patients with SLE. For both FACIT and Vitality domain of SF-36 lower scores imply worse fatigue; thus negative correlation between RDW and FACIT or Vitality score means that high RDW is associated with more fatigue.

a) Group 1 – patients with juvenile-onset SLE from UCLH, London ( $n = 72$ ) showed a negative correlation between RDW and FACIT Fatigue score; b) Group 2 – patients with adult-onset SLE recruited from UCLH, London ( $n = 106$ ) showed a negative correlation between RDW and Vitality domain of SF-12; and c) Group 3 – patients with SLE adult-onset lupus from Liverpool Hospital, Sydney ( $n = 47$ ) showed a negative correlation between RDW and FACIT Fatigue score.

non-anaemic patients (n=51;  $p=0.001$ ;  $r=-0.44$ ).

FACIT Fatigue score did not correlate with C3 ( $p=0.17$ ), dsDNA binding ( $p=0.40$ ), CRP ( $p=0.10$ ) or SLEDAI-2K ( $p=0.60$ ) by univariate analysis. A borderline correlation was seen with ESR ( $p=0.05$ ;  $r=-0.23$ ). After adjusting for disease activity in multivariate analysis, only RDW ( $p=0.02$ ) and ESR ( $p=0.03$ ) were independently associated with FACIT Fatigue score.

#### Validation groups

Figure 1b shows that in Group 2 Vitality scores also correlated negatively with RDW ( $p=0.02$ ;  $r=-0.23$ ) although there was no statistically significant association with Hb ( $p=0.25$ ). In Group 3, FACIT Fatigue score again correlated with RDW ( $p=0.03$ ;  $r=-0.32$ ), as shown in Figure 1c. There was no correlation between FACIT Fatigue score and Hb ( $p=0.87$ ).

#### Discussion

In this study, we demonstrate for the first time, a significant correlation between fatigue and a biological marker in SLE. Our results demonstrate an association between elevated RDW and higher levels of fatigue in three groups of patients of varying age, ethnicity and disease duration in two countries. The results have been validated using two different fatigue scores. Our findings support previous evidence suggesting fatigue does not typically correlate with disease activity (3, 10).

An elevated RDW is commonly an early marker of iron deficiency (11), which is a well-described cause of fatigue, ultimately as a result of anaemia. However, our findings suggest that the correlation between fatigue and RDW is independ-

ent of Hb. Another possible explanation is Functional Iron Deficiency (FID), of which RDW has been suggested as a surrogate marker (12). Compared with absolute iron deficiency, FID occurs in the context of normal iron concentrations, although iron cannot be mobilised or released from stores at an adequate rate to meet physiological demands. There is a growing evidence to support the role of FID in the pathogenesis of fatigue in a number of chronic conditions including malignancy, Parkinson's disease and cardiac failure (13-15).

There are some limitations in this study. We appreciate fatigue is a heterogeneous symptom and contributory factors may include intercurrent mood disorders, fibromyalgia and sleep disturbance.

In conclusion, we report the novel findings of a large-scale study of a diverse group of patients with SLE that provides evidence supporting a possible biological basis for the pathogenesis of fatigue in a subgroup of patients.

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