



# Malar rash is a predictor of subclinical airway inflammation in patients with systemic lupus erythematosus: a pilot study

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## Abstract

**Background** Systemic lupus erythematosus (SLE) is a chronic, auto-immune, multi-organ disease that can affect both the skin and the lungs. Malar rash is a common skin manifestation of SLE and is linked to SLE disease activity, whereas lung involvement is a generally negative prognostic factor for these patients. However, a sensitive and non-invasive screening tool for potential lung involvement in SLE patients is still not available.

**Methods** This study aimed to investigate the relationship between malar rash and airway inflammation in adult SLE patients who were not known to have any lung involvement (clinical or radiologic). The study comprised of the measurement of the concentration of NO in exhaled breath or fraction of exhaled nitric oxide (FeNO) and levels were compared between those with and without malar rash. This tool is considered as a sensitive and non-invasive method that is routinely used in patients with asthma or other respiratory diseases to identify airway inflammation.

**Results** A total of 125 patients (100 females, 25 males) were enrolled during the study period from January 2011 to December 2014. Patients with malar rash ( $N = 35$ ) had a significant decrease in serum levels of C4 ( $p < 0.05$ ) compared to patients without malar rash ( $N = 90$ ). The mean levels of FeNO in overall patients were  $36.44 \pm 8.87$  ppb. A statistically significant difference in FeNO<sub>50</sub> values between patients with malar rash ( $43.46 \pm 6.72$  ppb) and without ( $29.43 \pm 3.64$  ppb) was found ( $p < 0.001$ ). FeNO<sub>50</sub> values were inversely correlated only with serum C4 ( $p < 0.01$ ). However, no correlation between FeNO<sub>50</sub> values and SLE clinical disease activity scores was found.

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**Conclusions** The presence of a malar rash may predict sub-clinical airway inflammation in SLE patients. Further prospective studies are needed to confirm the usefulness of FeNO measurements in monitoring SLE-associated airway inflammation.

**Keywords** Airway inflammation · FeNO · LFA-REAL · Malar rash · Systemic lupus erythematosus

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, auto-immune, multi-organ disease that is more prevalent in women, and a considerable social burden in terms of healthcare costs [1, 2]. These patients may present with a wide variety of clinical manifestations, and the course of the disease is characterised by remitting periods and relapses, the latter usually occurring in the form of flares. The main facial cutaneous manifestation is represented by malar rash, fixed erythema involving cheeks and the bridge of the nose, but sparing the nasolabial folds [3]. Its incidence is estimated to be 22.9% in SLE patients [4], and it is still not certain whether the presence of a malar rash is associated with more aggressive SLE [1, 3]. In fact, lung involvement is a severe complication of SLE and, although its prevalence is still uncertain, some authors have estimated that lung lesions become clinically evident in 3–17% of patients [4]. The localisation and intensity of respiratory system involvement may vary from pleural and parenchymal disease (pleural effusion and pleurisy, acute lupus pneumonitis, acute respiratory distress syndrome, diffuse alveolar haemorrhaging, chronic interstitial pneumonitis, shrinking lung syndrome), to vascular (pulmonary hypertension, thromboembolic disease, acute reversible hypoxemia) and airway disease (upper airway disease, chronic obstructive pulmonary disease). Respiratory system involvement can be the presenting symptoms of SLE or can appear several months after SLE diagnosis [5]. In any case, although the exact relationship between disease flares and pulmonary inflammation is still unclear, pulmonary involvement is an established prognostic factor in SLE disease [6]. Thus, Drucker et al. [4] suggested that patients with a malar rash have higher severity scores at the initial visit and exhibited Adjusted Mean Systemic Lupus Erythematosus Disease Activity Index 2000 (AMS) at 1 and 5 years higher than SLE controls.

Airway inflammation can be assessed using the non-invasive and sensitive fraction of exhaled nitric oxide (FeNO) test, which is routinely used to monitor asthma disease activity and predict attacks [7]. The FeNO test has experimentally been found to be effective in detecting the presence of sub-clinical airway inflammation in patients with systemic auto-immune/inflammatory diseases such as psoriasis [8–12]. Due to the large respiratory involvement in SLE patients, we explored if the skin manifestation, malar rash, has a potential link with an early, subclinical lung involvement assessed by FeNO test. The secondary aim was to determine whether the characteristics of airway inflammation are different in patients with and without malar rash.

## Materials and methods

### Study population

This multi-centre, cross-sectional study analysed FeNO levels in consecutively enrolled adult SLE outpatients aged 25–55 years between January 2011 and December 2014 and compared the observed levels to those reported in the healthy population [11].

The diagnosis of SLE was made according to the Systemic Lupus International Collaborating Clinics classification criteria [13]. The study inclusion criteria were as follows: no history of respiratory symptoms; a lack of current immunosuppressive therapies (4-week washout for systemic treatments or 2 weeks for topical therapy); a forced expiratory volume in the first second to forced vital capacity ratio (FEV1/FVC) of  $> 0.8$ ; a FEV1 of  $> 80\%$  of the predicted value; a forced expiratory flow (FEF) of 25–75%  $> 65\%$ ; normal diffusing capacity of the lung for carbon monoxide (DLCO) and no parenchymal, airway, pleural or vascular abnormalities revealed by high-resolution computed tomography (HRCT) and negative radioallergosorbent test (RAST). The exclusion criteria were as follows: an inability to perform the lung function and FeNO tests, a restrictive or mixed restrictive/obstructive ventilatory pattern or asthma, smoking or allergies.

Written informed consent was obtained from all the subjects, and the study was approved by the local Ethics Committee and conducted in accordance with the principles of the amended Declaration of Helsinki.

### Study design

The patients were preliminarily examined by two independent rheumatologists and two independent dermatologists, who evaluated disease activity using the Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL), the Systemic Lupus Activity Measure (SLAM) and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) [13]. Each score discordance was resolved by discussion; however, if the latter did not achieve the agreement, a third rheumatologist or dermatologist was consulted. System-related upper respiratory lymph node enlargement and inflamed oral mucosa were criteria for postponing the FeNO test. All patients underwent a chest computed tomography (CT), spirometry and diffusing capacity of the lung for carbon monoxide

(DLCO) test to rule out the presence of any other primary or secondary lung disease. All patients were tested to confirm the presence of anti-nuclear antibodies (ANAs), with the lower cutoff titre being raised from 1:40 to 1:160 in order to enhance the sensitivity of the analysis; anti-Smith, anti-ribonucleoprotein (RNP) and double-stranded DNA antibody (anti-ds-DNA) were also assessed.

### FeNO measurements

FeNO levels were measured using a high-resolution, chemoluminescence nitric oxide analyser with a sensitivity of 0.06 ppb and an upper measuring limit of 100 ppb (Ecomedics AG CLD 77AM, Ecomedics; Durnten, Switzerland) in patients who were receiving long-term therapy for SLE (for at least 6 months before being enrolled in the study). The analyser was calibrated at 0 ppb and 100 ppb in accordance with the manufacturer's recommendations using a certified nitric oxide mixture (96 ppb) in nitrogen (Messer S.p.A., Collegno, Turin, Italy). Environmental air was monitored, and the tests were not performed if there were > 11 ppb of FeNO at a constant flow rate of 50 mL/s. All measurements were made in accordance with the recommendations of the American Thoracic Society [14, 15]. FeNO was measured at a flow rate of 50 mL/s using the single-breath technique, and the mean of three reproducible measurements for each patient was used as the reference value. The patients underwent the tests in the morning before the lung function assessments in order to avoid exertion as a potential confounding factor.

### Statistical analysis

All variables were preliminarily assessed using the Kolmogorov-Smirnoff test in order to establish their parametric behaviour. The continuous data were expressed as mean values and also the standard deviation if normally distributed and compared using Student's *t* test (parametric data) or the Mann-Whitney test (non-parametric data). The influence of the categorical variables was estimated using the chi-squared test. Multivariate analysis was finally performed. A *p* value of < 0.05 was considered significant. The analysis was conducted using the R statistical software, version 3.2.4 (Free Software Foundation, Inc., Cambridge, MA, USA).

## Results

### Patient characteristics and FeNO levels

Table 1 shows the anthropometric and clinical characteristics of the 125 enrolled patients (100 females, 80%). Patients with malar rash had a significant decrease in serum levels of C4 compared with patients without malar rash (*p* < 0.05). The

mean FeNO level in all study groups was  $36.44 \pm 8.87$  ppb: mean levels of  $43.46 \pm 6.72$  ppb and  $29.43 \pm 3.64$  ppb were detected in patients with and without malar rash, respectively. The difference in FeNO<sub>50</sub> values between the two groups was statistically significant ( $W = 42$ , *p* < 0.001). FeNO<sub>50</sub> levels correlated inversely only with serum C4 levels (*p* < 0.01). There was no correlation between FeNO<sub>50</sub> values and SLE disease activity expressed by, LFA-REAL, SDI or SLAM scores in either group. Multivariate analysis confirmed that malar rash is linked to FeNO (*p* < 0.005) and but not to decreased C4 serum levels.

## Discussion

This is the first study to show that adult SLE patients with malar rash and no lung involvement (clinical or radiologic) have higher levels of FeNO than those without malar rash. However, levels of FeNO were not found to be correlated with SLE disease activity. This suggests that high FeNO levels in the presence of normal functional indexes may be an early marker of lung involvement in adult SLE patients. Furthermore, FeNO was correlated with serum C4 levels, a well-known biomarker of disease activity in SLE [13], although after adjusting for multivariate analysis, this significant association was not revealed. In general, all typical lung manifestations of SLE, including vasculitis, interstitial pneumonia and pulmonary hypertension, are known to increase FeNO [14–16].

Furthermore, lung involvement in SLE is still controversial, as in adults, it may appear in either the early or late stages of disease [17]. However, lung involvement tends to be more prevalent and late manifestation of SLE disease in children [18, 19], who were normally found to have high FeNO levels and a decreased Tiffeneau index, both of which correlate with disease activity [20].

Rolla et al [12] found that FeNO levels correlated with disease activity in a cohort study of 27 adult SLE patients; however, the study included patients with decreased small airway functional capacity, in contrast to our study, where the patients had no involvement of the lung.

Malar rash is an acute skin manifestation linked to SLE disease activity, and TNF polymorphisms [19], and widely considered as a pathognomonic feature for SLE. It affects 22.9% of SLE patients [4], but its frequency varies depending on patients' ethnicity, gender and age [19]. The exact pathogenic process behind this form of erythema is still unclear, although several factors may play a role in its development including genetics [20] and auto-antibody profiles, such as anti-ribosomal P [21], anti-Smith and anti-rRNP antibodies [22].

Although it has been described to be relevant in only 3% of SLE patients at the time of diagnosis, lung involvement may

**Table 1** Demographics and clinical characteristics

Demographic characteristics	Population (n = 125)		Univariate analysis (p value)	Multivariate analysis (p value)	
	Malar rash (n = 35)	No malar rash (n = 90)			
Age (mean ± SD, years)	43 ± 13.5	44 ± 12.90	0.8	> 0.05	
Gender (female:male)	25:10	72:18	1	> 0.05	
Body mass index (mean ± SD, kg/m <sup>2</sup> )	27.1 ± 3.01	26.4 ± 2.95	0.5	> 0.05	
Disease characteristics					
Disease duration (mean ± SD, years)	10.2 ± 9.87	9.4 ± 10.5	0.6	> 0.05	
LFA-REAL (mean ± SD, mm)	101.66 ± 26.02	118.34 ± 13.34	0.75	> 0.05	
SLAM total (mean ± SD)	7.5 ± 4.2	7.7 ± 3.9	0.8	> 0.05	
SDI total (mean ± SD)	1.5 ± 1.3	1.6 ± 1.3	0.8	> 0.05	
C3 (mean ± SD, range 90–180 mg/dL)	94 ± 8.5	96 ± 13.0	0.2	> 0.05	
C4 (mean ± SD, range 10–40 mg/dL)	27 ± 3.4	31 ± 2.2	0.001	0.08	
Immunological profile					
ANA	Titres (median)	1:640	1:640	0.9	> 0.05
	Pattern	Homogeneous	Homogeneous	0.8	> 0.05
Anti-ds-DNA (mean ± SD, IU/mL)*	16 ± 2.4	18 ± 0.3	0.4	> 0.05	
Anti-Smith (mean ± SD, IU/mL)	12/35	32/90	0.8	> 0.05	
Anti-RNP (mean ± SD, IU/mL)	4/35	11/90	0.8	> 0.05	
Airway assessment					
FEV1 (mean ± SD, L)	3.26 ± 0.31	3.35 ± 0.2	0.5	> 0.05	
FVC (mean ± SD, L)	4.2 ± 0.32	4.38 ± 0.17	0.3	> 0.05	
FEV1/FVC (mean ± SD, %)	84.7 ± 6.1	86 ± 3.4	0.5	> 0.05	
DLCO (mean ± SD, mL/min/mmHg)	23.05 ± 5.07	24.3 ± 4.7	0.4	> 0.05	
FeNO	43.46 ± 6.72	29.43 ± 3.64	< 0.0001	0.001	

*LFA-REAL*, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; *SLAM*, Systemic Lupus Activity Measure; *SDI*, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; *Anti-RNP*, Autoantibodies anti-ribonucleic proteins; *C3*, Complement fraction 3; *C4*, Complement fraction 4; *FEV1*, Forced expiratory volume in 1 s; *FVC*, Force of vital capacity; *DLCO*, Diffusion Lung of Carbon Oxide; *FeNO*, Fraction of Exhaled Nitric Oxide

\*Anti-dsDNA antibodies were measured by Farr method

be an important prognostic marker, and its incidence tends to increase to 17% during the course of the disease [23]. Lung inflammation via the NF-KB signalling pathway is responsible for the induction and transcription of inducible nitric oxide synthase (iNOS), the enzyme that leads to NO release in the airways, which can be detected by the FeNO test [24]. This makes FeNO<sub>50</sub> measurements a highly sensitive and non-invasive method of screening and assessing early lung conditions in SLE patients [25] as none of the clinical SLE severity scores (LFA-REAL, SLAM or SDI) were found to be correlated with FeNO levels.

Malar rash was chosen as a possible predictive marker of SLE-related airway inflammation because it is easy to detect and has been linked to a high SLE disease activity. Furthermore, a discrepancy between lung involvement (particularly sub-clinical damage) and findings reported by the different available tools for lung assessment has been reported. Indeed, DLCO only correlates with disease duration, HRCT with the Tiffeneau index (FEV1/FVC) [23], and magnetic resonance findings are rarely associated with SLE-related pleuritis.

Interestingly, it has been reported that all described pulmonary comorbidities in SLE increase FeNO levels [13]. Therefore, the malar rash can be a very useful tool for preliminary assessment of airway inflammation in patients with SLE. Nevertheless, it is not possible to rule out that malar rash may simply indicate a more aggressive disease course and higher disease activity.

Our study has several limitations that should be acknowledged. Firstly, FeNO values were also found to be elevated in other conditions such as eosinophilic esophagitis [26] and RA [27]. However, both diseases were linked with respiratory disease involvement [16, 28, 29]. Furthermore, patients were not followed to explore the possible development of clinical respiratory disorder.

In conclusion, the malar rash may be a valuable, indirect and qualitative marker of subclinical airway inflammation in SLE patients. Further prospective studies are needed to confirm the usefulness of FeNO measurements in monitoring the airway inflammation associated with SLE.

## Compliance with ethical standards

**Statement of human and animal rights** All the procedures used in this study involving human beings were carried out in accordance with the ethical standards of the institutional and national research committees and the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

Informed consent was obtained from all the patients who participated in the study.

**Disclosures** None.

## References

- Arkema EV, Simard JF (2015) Cohort profile: systemic lupus erythematosus in Sweden: the Swedish Lupus Linkage (SLINK) cohort. *BMJ Open* 14:e008259
- Bragazzi N-L, McGonagle D, Watad S, et al (2018) Immunogenicity, safety and tolerability of anti-pneumococcal vaccination in systemic lupus erythematosus patients: an evidence-informed and PRISMA compliant systematic review and meta-analysis. *Autoimmun Rev* 8:73–92
- Kuhn A, Bijl M (2008) Pathogenesis of cutaneous lupus erythematosus. *Lupus* 17:389–393
- Drucker AM, Su J, Mussani F (2016) Prognostic implications of active discoid lupus erythematosus and malar rash at the time of diagnosis of systemic lupus erythematosus: results from a prospective cohort study. *Lupus* 25:376–381
- Hamdani MA, Saud Al-Arfaj AR, Parvez K et al (2015) Pulmonary manifestations of systemic lupus erythematosus patients with and without antiphospholipid syndrome. *Pak J Med Sci* 31:70–75
- Mittoo S, Fell CD (2014) Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med* 35:249–254
- Kim MA, Shin YS, Phamle D et al (2014) Adult asthma biomarkers. *Curr Opin Allergy Clin Immunol* 14:49–54
- Malerba M, Radaeli A, Olivini A et al (2014) Exhaled nitric oxide as a biomarker in COPD and related comorbidities. *Biomed Res Int* 2014:271918
- Malerba M, Damiani G, Radaeli A, Ragnoli B, Olivini A, Calzavara-Pinton PG (2015) Narrow-band ultraviolet b phototherapy in psoriasis reduces pro-inflammatory cytokine levels and improves vitiligo and neutrophilic asthma. *Br J Dermatol* 173:1544–1545
- Damiani G, Radaeli A, Olivini A, Calzavara-Pinton P, Malerba M (2016) Increased airway inflammation in patients with psoriasis. *Br J Dermatol* 175:797–799
- Kharitonov SA, Barnes PJ (2006) Exhaled biomarkers. *Chest* 130:1541–1546
- Rolla G, Brussino L, Bertero MT, Colagrande P, Converso M, Bucca C, Polizzi S, Caligaris-Cappio F (1997) Increased nitric oxide in exhaled air of patients with systemic lupus erythematosus. *J Rheumatol* 24:1066–1071
- Petri M, Orbai A-M, Alarcón G-S, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sánchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG Jr, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G Jr, Magder LS (2012) Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 64(8):2677–2686
- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (Fe) for Clinical Applications (2011) An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 184:602–615
- Malerba M, Damiani G, Carpagnano G et al (2016) Values in Elderly People for Exhaled Nitric Oxide (VEPENO) study. *Rejuvenation Res* 19:233–238
- Santus P, Rizzi M, Radovanovic D, Airoidi A, Cristiano A, Conic R, Petrou S, Pigatto PDM, Bragazzi N, Colombo D, Goldust M, Damiani G (2018) Psoriasis and respiratory comorbidities: the added value of fraction of exhaled nitric oxide as a new method to detect, evaluate, and monitor psoriatic systemic involvement and therapeutic efficacy. *Biomed Res Int* 2018:3140682. <https://doi.org/10.1155/2018/3140682>
- Alamoudi OS, Attar SM (2015) Pulmonary manifestations in systemic lupus erythematosus: association with disease activity. *Respirology* 20:474–480
- Deerojanawong J, Learthichalak P, Chanakul A, Sritippayawan S, Samransamruajkit R (2017) Exhaled nitric oxide, pulmonary function, and disease activity in children with systemic lupus erythematosus. *Pediatr Pulmonol* 52:1335–1339. <https://doi.org/10.1002/ppul.23742>
- Brunner HI, Holland M, Beresford MW, Ardoin SP, Appenzeller S, Silva CA, Flores F, Goilav B, Wenderfer SE, Levy DM, Ravelli A, Khunchandani R, Avcin T, Klein-Gitelman MS, Feldman BM, Ruperto N, Ying J, the PRCSG and PRINTO Investigators (2018) American College of Rheumatology Provisional Criteria for Global Flares in Childhood-Onset Systemic Lupus Erythematosus. *Arthritis Care Res* 70:813–822. <https://doi.org/10.1002/acr.23557>
- Ahmed HH, Taha FM, Darweesh HS, Morsi HM (2014) Association between TNF promoter 2308 G>A and LTA 252 A>G polymorphisms and systemic lupus erythematosus. *Mol Biol Rep* 41:2029–2036
- Sanchez E, Nadig A, Richardson BC, Freedman BI, Kaufman KM, Kelly JA, Niewold TB, Kamen DL, Gilkeson GS, Ziegler JT, Langefeld CD, Alarcon GS, Edberg JC, Ramsey-Goldman R, Petri M, Brown EE, Kimberly RP, Reveille JD, Vila LM, Merrill JT, Anaya JM, James JA, Pons-Estel BA, Martin J, Park SY, Bang SY, Bae SC, Moser KL, Vyse TJ, Criswell LA, Gaffney PM, Tsao BP, Jacob CO, Harley JB, Alarcon-Riquelme ME, on behalf of BIOLUPUS and GENLES, Sawalha AH (2011) Phenotypic associations of genetic susceptibility loci in systemic lupus erythematosus. *Ann Rheum Dis* 70:1752–1757
- Shi ZR, Cao CX, Tan GZ, Wang L (2015) The association of serum anti-ribosomal P antibody with clinical and serological disorders in systemic lupus erythematosus: a systematic review and meta-analysis. *Lupus* 24:588–596
- Li J, Leng X, Li Z et al (2014) Chinese SLE treatment and research group registry: III. Association of autoantibodies with clinical manifestations in Chinese patients with systemic lupus erythematosus. *J Immunol Res* 2014:809389
- Cervera R, Khamashta MA, Font J et al (1993) Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* 72:113–124
- Roos AB, Mori M, Grönneberg R et al (2014) Elevated exhaled nitric oxide in allergen-provoked asthma is associated with airway epithelial iNOS. *PLoS One* 28:e9001

26. Stanga SD, Page SL, Dinakar C (2012) The role of exhaled nitric oxide (FENO) in eosinophilic esophagitis: a pilot study to evaluate the correlation of exhaled nitric oxide and esophageal eosinophils. *J All Clin Immunol* 129:AB97
27. Thornadtsson A, Lind A, Weitoft T, Högman M (2018) Altered levels of exhaled nitric oxide in rheumatoid arthritis. *Nitric Oxide* 76:1–5
28. Rubinstein E, Rosen RL (2018) Respiratory symptoms associated with eosinophilic esophagitis. *Pediatr Pulmonol* 53:1587–1591
29. Shaw M, Collins BF, Ho LA, Raghu G (2015) Rheumatoid arthritis-associated lung disease. *Eur Respir Rev* 24:1–16

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