

Cigarette Smoking and Cutaneous Damage in Systemic Lupus Erythematosus

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ABSTRACT. Objective. To evaluate the association between cigarette smoking and cutaneous damage in systemic lupus erythematosus (SLE).

Methods. Our study was performed in SLE clinic registry cohort patients, all of whom fulfilled revised American College of Rheumatology criteria for SLE; patients are followed prospectively with annual assessments that include collection of demographic variables, smoking history, disease activity (SLE Disease Activity Index version 2000, SLEDAI-2K), medications, and damage scores (Systemic Lupus International Collaborating Clinics/ACR Damage Index). Cumulative cutaneous damage scores were used for the primary analyses. Logistic and logit regression models were performed to examine potential associations between current smoking and cutaneous damage, controlling for age, sex, race, lupus disease duration, antimalarial or immunosuppressant use, and anti-DNA and anti-SSA antibody status.

Results. Of our sample (N = 276), 92% were women and 73.7% were Caucasian; the mean age was 45.1 years, mean disease duration 13.5 years, and 17.5% were current smokers. In the regression analyses, current cigarette smoking was associated with total cutaneous damage (OR 2.73, 95% CI 1.10, 6.81) and with scarring (OR 4.70, 95% CI 1.04, 21.2). In additional analyses, current smoking was also associated with active lupus rash (OR 6.18, 95% CI 1.63, 23.3).

Conclusions. Current cigarette smoking may be associated with cutaneous damage and active lupus rash in SLE, suggesting another reason to emphasize smoking cessation in patients with SLE. (First Release Nov 1 2009; J Rheumatol 2009;36:2691-3; doi:10.3899/jrheum.090403)

Key Indexing Terms:

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Up to 85% of patients with systemic lupus erythematosus (SLE) develop skin involvement over their disease course¹, frequently leading to skin damage and/or irreversible alope-

cia. Tobacco-induced premature skin aging and alopecia in the general population have been under study for several years². Moreover, smoking may decrease the effectiveness of antimalarial agents^{3,4}, often used to control cutaneous manifestations of SLE. We conducted an observational study evaluating the possible association between smoking status and cutaneous damage in SLE.

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MATERIALS AND METHODS

Our study population was the McGill University Health Centre (MUHC) lupus clinic registry cohort. The study was approved by the MUHC ethics review board, with written patient consent. All patients in this cohort fulfill revised American College of Rheumatology (ACR) criteria for SLE and are followed prospectively with annual assessments. Cumulative damage is assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (DI). Evaluation of SLE disease activity includes the SLE Disease Activity Index (year 2000 version, SLEDAI-2K). We included data up to the last clinic assessment for each subject, as of May 2006.

Our primary outcome was cutaneous damage recorded in the SLICC/ACR DI (alopecia; extensive scarring; and skin ulceration). Cutaneous damage scores vary from 0 to 3, items must be present > 6 months and are considered irreversible. We assessed the effects of current smoking (i.e., whether or not the subject smoked at the time of the last clinic assessment) on cutaneous damage, using multivariate ordered logit regression, which allows the outcome to be categorical (range 0–3). The ordered logit regression model (“ordered logistic” or “proportional odds”

regression) produces an odds ratio (OR), which assumes the same relative effect for a given level of the outcome compared to lower levels. In secondary analyses, we also assessed the effects of current smoking on cutaneous disease activity, by performing ordered logit regressions, with the outcome categorized as to whether the subject had 0, 1, 2, or 3 of the cutaneous features of active lupus (rash, oral ulcers, alopecia) that appear on the SLEDAI-2K.

We performed additional secondary analyses assessing the effects of smoking on separate cutaneous damage items scores (e.g., scarring, alopecia), with logistic regressions, dichotomizing the outcome as whether or not a subject scored positive on the item of interest.

All multivariate regression models examined the effect of current smoking status for each outcome of interest, controlling for demographics and clinical factors. These included continuous variables for age and time since SLE diagnosis, as well as dichotomous variables for sex, Caucasian ethnicity, antimalarial and immunosuppressant use, and anti-DNA and anti-SSA (anti-Ro) antibody positivity. Variables related to drugs and antibody positivity reflected the patient's current status at the last study visit.

RESULTS

The sample comprised 276 subjects: 92% were women and 73.7% were Caucasian. The mean age was 45.1 years (SD 15.0) and the mean time since SLE diagnosis was 13.5 years (SD 10.7). Of these 276 patients, 137 (49.6%) reported ever smoking, 48 of whom (17.5% of the entire cohort) were current smokers. Thirty-eight percent of patients were positive for anti-SSA antibody. The majority of patients (77.8%) were currently treated with antimalarials, while nearly one-third (31.1%) were taking immunosuppressant drugs. In total, 22.2% had some cutaneous damage recorded on the DI; 16.4% had alopecia only, 4.0% had only scarring, and 1.8% had both (no patient had skin ulceration).

In the multivariate logistic regression analysis (Table 1), being a current smoker was significantly associated with cutaneous damage overall. In the multivariate logistic regression analyses, where the outcome was alternatively limited to single DI items, the OR for scarring confirmed a significant association with smoking, and the OR for alopecia suggested a strong trend for an association. Current smokers also had trends towards higher lupus cutaneous

activity, as measured by the SLEDAI-2K, but this appeared to be largely driven by the specific item of rash (OR 6.18, 95% CI 1.63, 23.40), with imprecise estimates otherwise. A robust association between total SLEDAI-2K scores was not seen in exploratory multivariate linear regressions. We also did not see a strong association between current smoking and total DI scores in exploratory multivariate analyses, using either ordered logit or linear regressions.

DISCUSSION

In the general population, tobacco use is linked to premature skin aging and alopecia. The mechanisms by which smoking may exert these effects are many. Cigarette smoke has both acute and chronic deleterious effects on the dermal and hair papilla microvasculature⁵ and on hair follicle DNA. Tobacco exposure causes imbalances in the protease/anti-protease systems that control the hair growth cycle, and promotes excess proinflammatory cytokines, which can cause follicular inflammation and fibrosis. Specifically, smoking disrupts the homeostasis of elastic tissue^{6,7} and collagen⁸, with altered matrix metalloproteinase-1 (collagenase) expression, possibly leading to collagen degradation⁹. All these are possible mechanisms that may also accelerate cutaneous damage and alopecia in SLE.

Being a current smoker was significantly associated with both cutaneous damage and active dermatological manifestations in our sample. Recent work has suggested that cigarette smoking is a risk factor for the development of SLE^{10,11} and may mediate the risk of autoimmune disease conferred by certain susceptibility genes, perhaps through immune reactions to autoantigens^{12,13}. Tobacco may also promote lupus activity in established disease, and has been associated with dsDNA autoantibody production^{14,15}. Moreover, smoking may interfere with the effect of antimalarial therapy, used to treat cutaneous lupus^{3,4} and other SLE manifestations.

Table 1. Odds ratios (95% confidence intervals) from multivariate logistic and ordered logit analyses*.

	SLEDAI-2K			SLICC/ACR DI		
	Alopecia	Rash	Total Cutaneous	Alopecia	Scarring	Total Cutaneous
Current smoking	1.08 (0.27, 4.38)	6.18 (1.63, 23.40)	1.83 (0.69, 4.89)	1.95 (0.75, 5.06)	4.70 (1.04, 21.18)	2.73 (1.10, 6.81)
Age (yrs)	0.10 (0.95, 1.05)	1.01 (0.95, 1.07)	0.99 (0.95, 1.03)	1.00 (0.97, 1.04)	1.01 (0.95, 1.07)	1.00 (0.97, 1.04)
Female	**	0.90 (0.07, 11.69)	1.09 (0.20, 5.77)	2.78 (0.32, 24.24)	**	3.51 (0.41, 9.88)
Caucasian	0.94 (0.23, 3.87)	4.20 (0.39, 45.58)	1.43 (0.44, 4.66)	1.12 (0.38, 3.27)	0.31 (0.05, 1.87)	0.83 (0.30, 2.28)
Disease duration	1.02 (0.96, 1.09)	0.97 (0.90, 1.04)	0.99 (0.95, 1.04)	1.05 (1.00, 1.09)	1.02 (0.95, 1.11)	1.05 (1.00, 1.09)
Antimalarial use [†]	1.29 (0.32, 5.09)	2.86 (0.47, 17.46)	1.74 (0.58, 5.21)	2.28 (0.79, 6.62)	0.32 (0.07, 1.41)	1.63 (0.63, 4.23)
ANA positivity [†]	1.53 (0.28, 8.23)	0.49 (0.10, 2.34)	0.79 (0.27, 2.27)	0.79 (0.29, 2.16)	0.61 (0.12, 3.13)	0.74 (0.29, 1.92)
Anti-dsDNA positivity [†]	1.23 (0.35, 4.28)	3.93 (0.89, 17.36)	1.66 (0.63, 4.42)	0.65 (0.23, 1.83)	**	0.54 (0.20, 1.48)
Anti-SSA antibody [†]	1.76 (0.51, 6.15)	1.09 (0.26, 4.64)	1.22 (0.46, 3.20)	1.74 (0.70, 4.34)	0.47 (0.09, 2.41)	1.36 (0.57, 3.22)

* Logistic analyses when the outcome was a single item, and ordered logit analyses when the outcome was the total cutaneous score (or overall total score).

[†] All clinical variables reflect current status at time of study visit. ** Sex was perfectly correlated with alopecia on the SLEDAI-2K, and with SLICC/ACR-DI scarring; thus this variable had to be removed from the given model for proper estimation. Similarly, anti-dsDNA positivity was perfectly correlated with SLICC/ACR-DI scarring, and had to be removed from the model when examining this outcome. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index, version 2000. SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

We acknowledge that although we used validated measures of SLE activity and damage, these tools have limitations as their definitions of alopecia differ (one, a measure of activity; the other, a measure of chronicity). Another limitation is that we did not measure whether smoking is simply a marker for inadherence and poor lifestyle practices (such as sun exposure), which could confound relationships with activity and damage. Finally, we did not attempt to correlate previous smoking and amount of tobacco with cutaneous damage or activity. This might have caused nondifferential misclassification of exposure; hence, we may have underestimated true effects.

We demonstrated that current cigarette smoking is associated with the presence of cutaneous damage (and active lupus rash) in SLE. Further study of the pathogenesis is warranted. Meanwhile, we have yet another reason to counsel lupus patients to quit smoking.

REFERENCES

1. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. *Br J Dermatol* 1996;135:355-62.
2. Ernster VL, Grady D, Miike R, Black D, Selby J, Kerlikowske K. Facial wrinkling in men and women, by smoking status. *Am J Public Health* 1995;85:78-82.
3. Moghadam-Kia S, Chilek K, Gaines E, Costner M, Rose ME, Okawa J, et al. Cross-sectional analysis of a collaborative Web-based database for lupus erythematosus-associated skin lesions: prospective enrollment of 114 patients. *Arch Dermatol* 2009;145:255-60.
4. Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment. *J Am Acad Dermatol* 2000;42:983-7.
5. Tur E, Yosipovitch G, Oren-Vulfs S. Chronic and acute effects of cigarette smoking on skin blood flow. *Angiology* 1992;43:328-35.
6. Laurent P, Janoff A, Kagan HM. Cigarette smoke blocks cross-linking of elastin in vitro. *Am Rev Respir Dis* 1983;127:189-92.
7. Weitz JI, Crowley KA, Landman SL, Lipman BI, Yu J. Increased neutrophil elastase activity in cigarette smokers. *Ann Intern Med* 1987;107:680-2.
8. Knuutinen A, Kokkonen N, Risteli J, Vahakangas K, Kallioinen M, Salo T, et al. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. *Br J Dermatol* 2002;146:588-94.
9. Lahmann C, Bergemann J, Harrison G, Young AR. Matrix metalloproteinase-1 and skin ageing in smokers. *Lancet* 2001;357:935-6.
10. Costenbader KH, Kim DJ, Peerzada J, Lockman S, Nobles-Knight D, Petri M, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum* 2004;50:849-57.
11. Washio M, Horiuchi T, Kiyohara C, Kodama H, Tada Y, Asami T, et al. Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study. *Mod Rheumatol* 2006;16:143-50.
12. Pedersen M, Jacobsen S, Garred P, Madsen HO, Klarlund M, Svejgaard A, et al. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. *Arthritis Rheum* 2007;56:1446-53.
13. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;54:38-46.
14. Ghaussy NO, Sibbitt W Jr, Bankhurst AD, Qualls CR. Cigarette smoking and disease activity in systemic lupus erythematosus. *J Rheumatol* 2003;30:1215-21.
15. Freemer MM, King TE Jr, Criswell LA. Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. *Ann Rheum Dis* 2006;65:581-4.