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Rebecca Cleeton Date

Smoking Status and Cutaneous Manifestations Among Patients with Systemic Lupus Erythematosus (SLE)

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B.A., Kenyon College, 2005

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Abstract

Smoking Status and Cutaneous Manifestations Among Patients with Systemic Lupus Erythematosus (SLE)

By Rebecca Cleeton

Active smoking is a known risk factor for SLE development and has also been shown to cause significant cutaneous damage. In this pilot study we sought to evaluate the association between smoking behaviors and the severity of cutaneous manifestations among SLE patients. Our cross-sectional study was performed among lupus clinic patients, all of whom had a physician's diagnosis of SLE. Patients were assessed using a smoking questionnaire along with the Cutaneous Lupus Erythematosus disease Area and Severity Index (CLASI). Logistic and ordinal logistic regression models were used to estimate potential associations between smoking status and CLASI scores adjusting for race, sun exposure, and secondhand smoke. Current smoking status did not significantly increase the odds of more severe overall cutaneous manifestations (OR = 1.421, 95% CI = 0.408, 4.945), but when the CLASI was stratified into activity and damage sections, current smoking status was found to significantly increase the odds of having active skin manifestations among patients with SLE (OR = 4.522, 95% CI = 1.066, 19.187).

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I. Introduction

Lupus

Systemic lupus erythematosus (SLE) is an inflammatory, autoimmune disease that is characterized by flares and remissions. The disease acts by producing antibodies that can cause tissue damage and inflammation to almost every organ in the body. Lupus is difficult to diagnose because of its wide array of symptoms, which may include low blood count, hair loss, fever, fatigue, weight loss, skin rashes, arthritis-like symptoms, seizures, strokes, and oral lesions among others (Ginzler and Tayar 2008). Even though SLE is a very disabling and damaging disease, its etiology remains largely unknown. While genetic factors and hormones play a large role in disease development, certain environmental exposures may act as triggers (CDC 2010). Today, no cure exists for SLE, but there is the hope that in the search for finding a cause of disease scientists will find a cure as well.

It is estimated that SLE affects over 5 million people worldwide and premature death attributed to SLE complications will occur in 10-15% of all cases (LFA 2011). SLE is known to disproportionately affect particular demographics of the population. In particular, 80-90% of patients with SLE are women and the peak onset of SLE is among those that are ages 15-40 (Costenbader and Karlson 2005). It is also important to note that SLE rates are three times higher among black women than white women and that the disease is also more prevalent among women of American Indian, Hispanic, and Asian descent. Lastly, minority women are more likely to develop symptoms of SLE at earlier ages and encounter more severe organ complications (CDC 2008).

While genetic susceptibility is the main contributing factor in the etiology of SLE, new evidence points to the potential contribution of environmental factors in the risk for disease. Based on a compilation of case reports, it was estimated in 1975 that the concordance rate for SLE among monozygotic twins was around 60% (Block, Winfield et al. 1975). Two later studies, however, have shown the concordance rate to be approximately 25-35% among identical twins (Deapen, Escalante et al. 1992; Jarvinen, Kaprio et al. 1992). These more recent studies utilized national twin-study registries and are therefore more likely to better reflect true population rates. Such lower concordance estimates support the idea that there may be other influences involved in the etiology of SLE besides a genetic component (Cooper and Parks 2004).

Environmental factors that contribute to the development of SLE may include a range of compounds or infectious agents that induce some type of an immune reaction. Environmental pollutants, occupational exposures, as well as behavioral factors such as diet and smoking may all act as triggers for SLE development. Previous research has shown that a variety of factors ranging from ultraviolet radiation, to certain types of drugs, to smoking are all likely to contribute to disease onset (LFA 2011). This paper seeks to investigate the link between smoking behaviors and specific disease outcomes among SLE patients. In particular, we aim to gain a better understanding of smoking patterns as well as the direct and indirect roles that cigarette smoke plays in cutaneous manifestations of SLE.

Smoking

In developed countries cigarette smoking is the single largest preventable cause of death and disability. Although smoking rates have recently declined, cigarette smoking is still common worldwide and is on the rise in some groups, especially adolescents. It has been shown that smoking is strongly linked to a variety of pulmonary and cardiovascular diseases as well as cancers (Freiman, Bird et al. 2004).

Of particular interest to SLE, it has been shown that cigarette smoke plays a role in the development of certain autoimmune diseases including Grave's disease, primary binary cirrhosis, and rheumatoid arthritis (RA) (Costenbader and Karlson 2005). Other studies have observed a link between smoking and skin lesions in diabetes, AIDS, and lupus. Even more, although little evidence currently exists that links smoking and melanoma, acne, and eczema, research has demonstrated a strong association between smoking and a number of dermatologic conditions such as wrinkling, psoriasis, poor wound healing, hair loss, oral cancers, and squamous cell carcinomas (Freiman, Bird et al. 2004).

Studying cigarette smoke as an exposure variable is extremely difficult. Cigarette smoke is an impure mixture that is made up of a number of highly toxic components, such as nicotine, carbon monoxide, certain tars, and polycyclic aromatic hydrocarbons. How these chemicals act in the body is difficult to understand mechanistically, as they have to be considered together as well as independently of one another. Even more, both phases of cigarette smoke must be taken into consideration: the gaseous phase as well as the particulate phase. While both phases of these substances contain high amounts of free radicals, the cigarette smoke itself activates naturally-occurring sources of free radicals in

the body as well. These free radicals and toxins found in cigarette smoke are free to interact with DNA in the body and may cause certain gene activations or genetic mutations that spark the onset of autoimmune disease (Costenbader and Karlson 2005).

Cutaneous Manifestations of SLE

Approximately 72-85% of SLE patients have some form of skin involvement during some state of the disease (Dubois and Tuffanelli 1964). A wide range of these skin manifestations exist. The most common cutaneous manifestations include skin lesions, Raynaud's phenomenon, photosensitivity, mucous membrane lesions, butterfly rashes, urticaria, alopecia, discoid lesions, chilblains, oral ulcers, and dermal vasculitis (Yell, Mbuagbaw et al. 1996). Each of these manifestations can take on its own degree of severity and persistence. There is a great concern of morbidity among patients with painful skin lesions or disfiguring scars (Kole and Ghosh 2009).

II. Literature Review

Proposed mechanism

It is widely accepted that cigarette smoke contributes to the development of a number of autoimmune diseases. Research over the years has shown the pro-inflammatory effects of cigarette smoke mostly in the context of emphysema and cardiovascular disease (Ambrose and Barua 2004). It has been demonstrated that cigarette smoke both increases total peripheral blood leukocyte counts (Smith and Fischer 2001) as well as increases their export of tissue-damaging matrix metalloproteinases (Cooper, Dooley et al. 2001). Cigarette smoking has also been observed to be associated

with significant increases in IL-6 and C-reactive protein, which both serve as markers of inflammation (Tracy, Psaty et al. 1997). It has also been observed that there exists a long-lasting immunosuppressive effect from cigarette smoke on T-cell-dependent autoimmune responses. After the suppressive effect has stopped, however, autoantibodies return to surpra-elevated levels (Rubin, Hermanson et al. 2005).

A 2004 paper by Glinda Cooper suggests a potential mechanism for the role that cigarette smoke plays in disease activity, specifically for SLE patients. She suggests that tobacco smoke activates macrophages in the alveoli, which thereby increases free radical production as well as myeloperoxidase activity. Cooper goes on to propose that long-term exposure to cigarette smoke may decrease the general activity of natural killer cells as well as disrupt the secretion of proinflammatory cytokines. Such mechanisms may add to an overall immunosuppressive effect of smoking and therefore may result in a greater vulnerability to infections. Although little information currently exists regarding the effects of tobacco smoke on the development of autoimmune diseases in general, recent research suggests that a history of smoking is associated with the prevalence of antinuclear antibodies and rheumatoid factors (Cooper and Parks 2004).

In addition, other research has shown support that cigarette smoke may lead to the up-regulation of genes coding for Fas (CD5), (binding receptors that induce apoptosis) on lymphocyte cell surfaces. This increase in sensitivity of white blood cells to apoptotic signals could add to the amount of apoptotic material that is needed to be cleared. Patients at risk for SLE, who already have an inefficient clearance mechanism, could therefore be more at risk for autoimmunity (Costenbader and Karlson 2005).

Cigarette smoking and SLE meta-analysis

While evidence currently exists that supports the idea that cigarette smoking increases the risk of developing SLE, this association remains controversial. To date, a handful of case-control studies have found significantly increased odds ratios for the development of SLE in smokers, while a number of other studies have not reported a clear association.

A meta-analysis conducted by Costenbader *et al.* statistically combined the effect estimates of 7 case-control and 2 cohort studies in the United States and Europe (Figure 1). The results showed an overall weak, yet significant, association between current smoking and SLE development, with an odds ratio of 1.5 (95% CI = 1.1, 2.1) (Costenbader, Kim et al. 2004). No association with former smoking was seen in any of the studies that were taken into consideration in the meta-analysis (OR = 0.98, 95% CI = 0.75, 1.3). In addition, just one of these studies demonstrated evidence of a dose-response relationship between the risk of SLE and the number of pack years smoking. The remainder of the studies either did not investigate a dose effect or did not find any evidence of one (Costenbader and Karlson 2005).

It must be noted, however, that there existed a great deal of variation across the studies that were analyzed in the Costenbader meta-analysis. Differences in questionnaire response rates, the decision to include or remove certain confounders in the analysis, the timing of study questionnaires in relation to the onset of SLE, and even specific definitions of smoking status all varied widely across the studies (Costenbader and Karlson 2005). It is also possible that the variation found here may suggest that unknown factors (along with as differences in study designs and patient populations) might

profoundly affect the relationship between smoking and SLE (Rubin, Hermanson et al. 2005).

The meta-analysis went on to point out a number of potential sources of recall bias as well as a general lack of power exhibited across the studies. In addition to the methodological challenges associated with the present literature base, issues of heterogeneity further complicate the studies. Costenbader highlighted that the effects of low-tar filtered cigarettes on the quantities of inhaled toxins remain unknown, and even more, that we need to take into consideration the fact that the composition of cigarettes has changed a great deal over the years, which makes it difficult to compare studies. The authors also recommend that the types and severity of SLE among study participants be better documented when conducting these types of analyses. It is important to take into consideration the idea that genetic and racial compositions of examined populations may contribute to differing susceptibility to SLE. This fundamental meta-analysis leaves us with a limited body of knowledge in the field. The authors called for large-scale prospective cohort studies as well as animal models to gain a better understanding of the relationship between SLE and smoking (Costenbader and Karlson 2005).

Association between smoking and SLE disease activity

One of the most striking studies discussed in the Costenbader meta-analysis was one conducted by Ghaussy *et al*. (2003), which used medical outpatients as controls and found a remarkably higher effect estimate of cigarette smoking than the remainder of the studies (Costenbader and Karlson 2005). Similar to the present study, Ghaussy *et al.* used a questionnaire to estimate smoking status and then used the SLE Disease Activity Index (SLEDAI) to quantify disease activity and severity. The study found that current smokers

demonstrated significantly higher SLEDAI scores than former smokers and never smokers, even when adjusting for covariates such as alcohol use, current age, mean duration of SLE, income level, marital status, ethnicity, age of onset of SLE, education level, and therapy (OR = 6.69, 95% CI = 2.59, 17.30). Even more, it was found that former smokers were at higher risk for SLE development (OR = 3.62, 95% CI = 1.22, 10.70). The authors concluded that smoking is indeed associated with increased overall disease activity and severity in SLE patients (Ghaussy, Sibbitt et al. 2003).

Animal models

Animal models are useful in demonstrating the biological plausibility of certain hypotheses, especially when ethical limitations and potential psychological complications exist. A study by Rubin *et al*., which was first of its kind, examined the implications of cigarette smoke on the immune status of auto-immune-prone mice. The authors hypothesized that disease outcomes would be accelerated or exacerbated among animals that were predisposed to SLE if smoking did indeed have a fundamental causative relationship with the disease. Female MRL/Mp-lpr/lpr mice were assigned to groups that were exposed to different levels of cigarette smoke (0, 100 mg or 200 mg TPM/m^3) over the course of 4 weeks. Biological samples, which contained protein, IgG, and IgM were collected were collected every 2-4 weeks for 4 months (Rubin, Hermanson et al. 2005).

The authors went on to complement their animal models with human data. Newly diagnosed SLE patients that had not begun treatment with immunosuppressive medications were used in the study sample (n=119). This study group consisted of 88 non-smokers and 31 current smokers. It was important to capture the SLE patients pre-treatment in order to rule out confounding by therapeutic interventions. SLE disease

activity and severity were measured by the SLEDAI and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACRDI) respectively. Questionnaires were used to determine smoking statuses (current, former, and never), and autoantibody determinations were performed (Rubin, Hermanson et al. 2005).

The results of the Rubin *et al*. study were surprising. Unlike the meta-analysis performed by Costenbader *et al*., this study demonstrated that exposure to cigarette smoke actually suppressed IgG autoantibody development, and that autoantibody expression was augmented only after smoking stopped. Generally speaking, the results from this study showed that lupus-prone mice that were exposed to cigarette smoke in their early lives suppressed IgG autoantibody development, but not necessarily total immunoglobulin levels. Another interesting finding from this study was that the SLE patients who were currently smoking at the time of diagnosis were more likely to have neuropsychiatric problems and polyserositis than the other recently-diagnosed SLE participants, which is consistent with the findings of Ghaussy *et al*. (Ghaussy, Sibbitt et al. 2003; Rubin, Hermanson et al. 2005). From their findings, the authors suggested that SLE patients that currently smoke may intrinsically have a more severe disease than nonsmokers, and that any immunosuppressive effect of smoking is insufficient to affect the course of already-established SLE (Rubin, Hermanson et al. 2005).

Association between smoking and cutaneous manifestations of SLE

Perhaps most relevant to the proposed study is the 2009 study Turchin *et al*. conducted in which a prospective cohort of SLE patients was followed with annual assessments that included disease activity and damage scores (SLEDAI and

SLICC/ACRDI) along with patient demographic information and smoking histories. The authors concluded that current smoking was associated with total cutaneous damage (OR = 2.73, 95% CI = 1.10, 6.81) as well as with scarring (OR = 4.70, 95% CI = 1.04, 21.2). Even more, the authors found that current smoking was also associated with an active lupus rash (OR = 6.18, 95% CI = 1.63, 23.3) (Turchin, Bernatsky et al. 2009). While this study most closely resembles the proposed study, it uses a different disease outcome measure and it does not take secondhand smoke exposures into consideration.

Secondhand smoke

Lastly, it is important to consider the effects of secondhand smoke. Although passive exposure to cigarette smoke has been shown to be associated with certain chronic diseases, cancers, asthma, and coronary heart disease, it has rarely been studied in the context of SLE (Costenbader, Kim et al. 2004). Recent work has shown than there may be associations between early life smoke exposure and rheumatic conditions among female children. Even more, a recent study by Simard *et al*. showed that maternal smoking (relative risk (RR) = 0.9, 95% CI = 0.6, 1.4) and paternal smoking (RR = 1.0, 95% CI = 0.8, 1.3) did not increase the risk of SLE occurrence. Little other research has been conducted regarding secondhand smoke and SLE disease activity (Simard 2009).

The same molecular mechanisms likely play a role; although at a lower dose level and at less frequent exposure intervals. Perhaps little research has been conducted in this particular area because secondhand smoke is so difficult to define and quantify, and it also varies considerably by geographic location. Questions still remain about the mechanisms of cigarette smoke and its impact on immune function; investigating the effects of secondhand smoke is the next step, and a critical one in the world of SLE.

Specific Aims & Importance

Previous research indicates that smoking is a risk factor for development of SLE (Costenbader et al. 2004; Hardy et al. 1998; Simard et al. 2007). Even more, a number of recent studies have shown current smoking status to have an effect on the skin lesions in SLE patients (Frieman et al 2003; Turchin et al 2009). There is limited information, however, on past smoking or secondhand smoke and SLE disease activity. It is important to understand the risks of disease activity among SLE patients, especially when those risks are easily preventable. This pilot study will be another step in understanding the role that cigarette smoke plays in disease activity among SLE patients. Findings from this study may provide additional rationale for clinicians to emphasize smoking cessation among patients with SLE. In addition, the results of this pilot study can help determine if there is provocative evidence of an association between certain smoking behaviors and cutaneous manifestations of SLE disease activity, which may lead to larger studies that further investigate such relationships.

Hypothesis

The aim of this pilot study is to investigate the association between smoking status and disease severity and damage, specifically cutaneous manifestations, among patients with SLE. Based on previous studies it is hypothesized that a history of smoking or exposure to secondhand smoke might increase the risk or severity for skin lesions, rashes, and general cutaneous damage among SLE patients. In this study we look at measures of smoking status and exposure to secondhand smoke through patient questionnaires. We collected additional information regarding active lesions and previous

SLE-related skin damage through clinical diagnoses by physicians at Emory University Midtown and Grady Lupus Clinics.

III. Methods

Study Design

a. Sample

The study sample consisted of adults that were regularly in attendance at weekly Lupus Clinics at Emory University's Grady and Midtown Hospitals in Atlanta, Georgia. These clinics serve patients from all around Atlanta's greater metropolitan area. In order to be included in the study participants had to have had a current diagnosis of SLE by a physician. Subjects under the age of 18 were excluded from the study.

All patients that attended their scheduled clinic appointments between August 2010 and December 2010 and completed both the patient questionnaire and physician's assessment, the Cutaneous Lupus Erythematosus disease Area and Severity Index, or CLASI, were included in the study. If a patient only had one completed form, attempts were made to contact the patient outside of clinic hours or retrospectively collect data in order to obtain any missing information. It was not always possible to capture complete information for every patient seen at the clinics between the dates of the study, but attempts were made to gather as much information as possible on every patient that was seen. Over the course of the study, 72 patients completed both forms at the time of the visit. In order to gather a more complete data set some data was collected retrospectively. 34 patients completed a smoking questionnaire but were missing a CLASI. The attending

physician completed a CLASI form using his recollection with the assistance of medical notes and past medical records for each of these patients on their respective dates.

b. Recruitment

Consecutive patients were recruited in this study and data were abstracted from medical records. Chart reviews were conducted for all patients that were seen at the Lupus Clinics at Emory University's Midtown and Grady Hospitals between August 2010 and December 2010.

c. Procedures and Measures

Upon arrival at one of the Lupus Clinics, patients received a two-page questionnaire to fill out while they waited for their appointment. These questions were part of the standard of care collection of medical history for these patients and were added as part of their medical record.

It was estimated that it would take a patient between 2 and 10 minutes to complete the survey thoroughly. The questionnaire was based upon previously validated questions regarding smoking history, current smoking status, exposure to secondhand smoke, and sun exposure (Appendix 1). A majority of the questions regarding smoking behaviors were derived from the California Health Interview Survey, an annual survey that questions tens of thousands of Californians of different age groups about their overall health and health behaviors, such as smoking (Dubois and Tuffanelli 1964).

Targeted for an audience at a 7^{th} grade reading level, the questionnaire used simple vocabulary and made definitions of smoking behaviors very clear. "Smoking regularly" was defined in the questionnaire as having smoked 1 cigarette per day for at

least three months. The last two questions on the questionnaire pertained to sun exposure and were derived from a previously validated survey (Glanz, Yaroch et al. 2008).

During the patients' scheduled appointments at the clinic, trained physicians filled out the CLASI in person. This well-accepted and previously validated scale measures the current activity as well as the damage caused by the disease on the skin (Appendix 2) (Albrecht, Taylor et al. 2005).

The CLASI is laid out in the form of a table in which the columns denote varying scoring systems for particular clinical symptoms and the rows indicate anatomical regions. Activity and damage are scored separately, which is common for evaluations of SLE and other diseases that can cause severe persistent organ damage. Activity is scored in terms of mucous membrane involvement, acute hair loss, erythema, hypertrophy, and non-scarring alopecia, and damage is scored in terms of whether or not any dyspigmentation has occurred in skin lesions and whether or not they have remained visible for over 12 months. Dyspigmentation scores are doubled if these lesions are permanent. The scores are summed for total activity and damages scores (Albrecht and Werth 2007). In the current study, activity and damage scores were totaled for an overall CLASI score.

The CLASI is commonly used by rheumatologists today because the scores are easily quantifiable and it does not take too much time for a physician to complete. Even more, the CLASI is a good tool for rheumatologists to use because it is successful in evaluating relative improvement among patients (Albrecht and Werth 2007).

Albrecht and Werth, supporters of the CLASI, strongly urge that the CLASI only be used by dermatologists, rheumatologists, and nurses who have had training in the

cutaneous manifestations of SLE. The multifaceted presentations of the disease are sometimes difficult to evaluate so it is crucial that only trained professionals perform the evaluation (Albrecht and Werth 2007). In the present study, only rheumatologists filled out the CLASI.

The CLASI was also complemented with a physician's Global Assessment as assessed by a Visual Analog Scale. The scale was scored from 0 through 4 (0 meaning no activity and 4 meaning very severe activity), indicating the physician's overall impression of disease activity.

Information regarding patient demographics and other relevant information was collected through chart abstraction. Patient date of birth, age, date of SLE diagnosis, race/ethnicity, insurance, and gender were all collected and de-identified in the database. The information was abstracted in clinical report forms by the co-investigator of the study as far back as 6 months.

d. Confidentiality

De-identified data were abstracted on clinical report forms and later transferred to an excel database. An internal identifier was created to protect the identity of the participants and the data were transferred to an excel database. Only investigators knew how to decode the internal identifier and had access to the excel database, which was encrypted. Any written documentation regarding how to decode the internal identifiers will be destroyed at the end of the study.

e. *Informed Consent*

Informed consent and HIPAA were both waived for this study. As previously discussed, the study does not involve any risk to subjects nor does it have any negative

effects on the welfare or rights of the subjects. It is likely that the research would not be practicably carried out without the waivers and would take a great deal more time to carry out if waivers were required. Lastly, if new knowledge is gained from this study it is to be communicated to patient communities.

Data Analysis

A total of 109 patients completed both the CLASI and the smoking questionnaires at the two Lupus clinics between August 2010 and December 2010. All patients with two complete forms were included in the analysis of the study. The most recent evaluation was used in the analysis for any patient that had more than one appointment at the clinic. SAS 9.0 was used to perform appropriate analyses of variance as well as ordinal logistic and logistic regressions in order to assess the associations between smoking behaviors and disease outcome in the SLE patients.

Patients were defined as current smokers if they answered “yes” or “yes, occasionally” to question 5 on the survey “Do you currently smoke tobacco?”. Former smokers were defined as those who answered “no” to question 5 and “yes” to either question 1 “Have you smoked at least 100 cigarettes in your lifetime (100 cigarettes = 5 packs)?” or “have you ever smoked regularly (regularly = 1 cigarette, cigarillo or cigar per day for at least three months)?”. The last group, never smokers, was defined as answering no to questions 1, 2, and 5 described above.

Secondhand smoke exposure was defined as answering yes to any of questions 7 through 9, regarding exposure to secondhand smoke at home, in the workplace, and in the home as a child respectively or answering “some – 1 to 5 hours” or “a lot – more than 5

hours per day" to question 10 "on average, how often are you exposed to secondhand smoke per day?". Patients were considered to have encountered sun exposure if they described being in the sun for over 1 hour each day or having experienced a sunburn in the last year. Patients that answered "N/A" to question 12 "How many times in the last year have you had a sunburn?" were recorded as having no sunburns in the last year.

A series of ANOVAs were conducted to investigate the differences between mean total CLASI scores, mean CLASI Activity scores, mean CLASI Damage scores, and mean global physician's assessments. These analyses were performed for two different groupings: smoking status without secondhand smoke consideration (current smoker, former smoker, never smoker), as well as with secondhand smoke consideration (current smoker, former smoker with secondhand smoke exposure, former smoker without secondhand smoke exposure, never smoker with secondhand exposure, and never smoker without secondhand smoke exposure).

Chi-square analyses were conducted in order to see if the frequency of individual items on the CLASI differed significantly between current smokers vs. former and never smokers, as was done with SLEDAI scores in a previous study (Ghaussy, Sibbitt et al. 2003). Rows specifying anatomical locations on the CLASI (Appendix 2) were collapsed in order to perform appropriate tests because of the small sample size.

In order to perform an ordinal logistic regression for overall CLASI scores, CLASI scores were divided up into five score intervals (0 through 4, 5 through 9, 10 through 14, 15 through 19, and greater than 19) as previous authors did this their analyses using the CLASI (Klein, Moghadam-Kia et al. 2011).

An additional logistic regression was conducted for total CLASI Activity scores. In this case, scores were dichotomized by scores of 0 and scores of greater than 0 because of the right-skewed distribution of CLASI Activity scores. Race, sun exposure, and secondhand smoke exposure were all adjusted for in both logistic models. Insurance and disease duration were not included in the models as there were too many missing data for these variables (n missing = 54 and 17 respectively).

IV. Results

The demographics of the patients involved in the pilot study can be seen in Table 1. The mean age ± standard deviation across all patients was 40.9 (±12.85) and the mean duration of SLE was 8.19 (± 8.03) years. 95.24% of the participants were female and 88.35% were African American. Table 2 details study participant characteristics by smoking status.

The ranges and means of all outcome measures across all patients are detailed in Table 3. A wide range of scores existed for all differentiations of CLASI assessments. It can also be seen that the scores were skewed to the right.

Mean CLASI scores across different smoking groups are seen in Table 4. Mean total CLASI scores, mean CLASI Damage scores, and mean global assessment scores did not differ significantly among the three smoking groups. The mean CLASI Activity score, however, did differ across smoking groups (ANOVA, F = 6.58, p = 0.002). More specifically, current smokers ($\bar{x}$ = 6.455) had significantly higher CLASI activity scores than former or never smokers ($\bar{x}$ = 1.318 and 0.720 respectively).

When smoking status was further divided into 5 groups to include secondhand smoke exposures a similar outcome was observed (Table 5). While mean total CLASI scores, mean CLASI Damage scores, and mean global assessment scores did not differ significantly across the groups, mean CLASI activity scores did (ANOVA, $F = 3.22$, $p = 0.0156$).

Frequencies of individual CLASI items for respective smoking groups are shown in Table 6. Activity and damage manifestations were collapsed across all anatomical locations due to the small sample size. Current smokers exhibited significantly higher proportions of mucous membrane lesions and ulcers, active scale/hypertrophy, and dyspigmentation damage than former and never smokers (Chi-square, Fisher's $p= 0.0278$, 0.0072, and 0.0453 respectively).

Table 7 shows the odds ratios for the ordinal logistic regression (5 different outcome levels for the total CLASI score). Odds ratios compare the odds of being in the higher CLASI levels (a total CLASI score of 0-4) vs. being in the lower CLASI score levels detailed above. Because the assumption of the ordinal logistic model is that the odds ratios are the same no matter where the dichotomization of intervals occurs, the odds ratio also represents the odds of being in the highest three CLASI score levels compared to the lowest two CLASI levels, and the odds ratio comparing the highest two CLASI score levels to the lowest 3 CLASI score levels, etc. Variables of interest were assessed for confounding and the final model included variables that improved the precision of the effect estimates of interest (current smoking status and former smoking status).

The ordinal logistic regression analysis suggests that there is an increased odds of having a higher total CLASI score among current smokers and former smokers compared to never smokers when adjusting for secondhand smoke exposure, sun exposure, and race. Although not statistically significant, these data are suggestive that, given a diagnosis of SLE, the odds of having a higher total CLASI score are 1.421 (95% CI: 0.408, 4.945) times higher among current smokers compared to former and never smokers.

Odds ratios for smoking status and CLASI Activity scores are displayed in Table 8. The results from this logistic regression model indicate that there is an increased odds of having a CLASI Activity score greater than 0 among former smokers and current smokers compared to never smokers when adjusting for secondhand smoke exposure, sun exposure, and race. More specifically, these results suggest that given a diagnosis of SLE the odds of having a higher CLASI Activity score are 4.522 (95% CI: 1.066, 19.187) times higher among current smokers compared to former and never smokers.

V. Discussion

Response

The actual response rate of participants is unknown, as records that capture the total number of patients seen for SLE during Lupus Clinic hours at both hospitals between the start and stop dates of the study were not attainable. An attempt was made, however, to capture every patient that had an appointment during the time period of the study. It was not always possible to obtain both forms for the patient as the forms

circulated between the physicians, nursing staff, and researchers at two different clinics. 16 patients only had the CLASI form filled out and 34 patients only had a completed smoking questionnaire. All patients that were missing CLASI scores, however, were evaluated retrospectively by the attending physician and 3 of the 16 patients missing the smoking questionnaire were contacted via telephone to obtain missing information. Questionnaires were dictated over the phone and responses were recorded within a month of the patients' visit. IRB approval granted the pilot study the freedom to waive informed consent, so the issue of individuals refusing to participate is not applicable in this case.

Interpretation of Results

Average CLASI scores for this study were within a reasonable range. A study by Krathen *et al*. in 2008 that utilized the CLASI had similar ranges, except that there were more instances of "0" as a total CLASI score in the current pilot study. As in the Krathen study, mean damage scores were higher than mean activity scores. It is interesting to note, however, that the mean activity and damage scores in the Krathen study were much higher than those found in the current study. Sample size must be considered in this matter, however. Whereas the current study had a sample size of 109 the Krathen study only had a sample size of 17 (Krathen, Dunham et al. 2008).

In the current study group of SLE patients who visited the Lupus Clinics at Grady or Midtown Emory University Hospital, current smoking was shown to be associated with significantly increased cutaneous disease activity as measured by the CLASI compared to former and never smoking. This result is not surprising as a large base of literature suggests that tobacco use has a variety of effects on the skin and that smoking is

a risk factor for the development of SLE (Ghaussy, Sibbitt et al. 2003; Freiman, Bird et al. 2004; Turchin, Bernatsky et al. 2009). Recent studies have also demonstrated that being a current smoker is associated with cutaneous damage as well as with active skin manifestations (Turchin, Bernatsky et al. 2009).

Although there were significant differences across groups in regards to mean activity score, no differences existed between groups in regards to the mean global physician's assessments, mean damage scores, and mean total CLASI scores. This finding suggests that current smokers with SLE may have a higher occurrence of or more severe or prolonged instances of erythema and hypertrophy, mucous membrane lesions, or alopecia. Significant differences between smoking groups for other outcomes might be seen with a larger sample size.

Including secondhand smoke exposures in the smoking status categorizations appeared to have had little change on the differences in means across all outcome measures. Throughout the analyses exposure to secondhand smoke appears to have little effect on the outcome measures in the CLASI. One possible explanation for this finding may be that secondhand smoke is so difficult to measure and quantify.

Current smokers had a higher proportion of almost all individual manifestations on the CLASI when compared to former and never smokers. Scalp scarring was the only manifestation in which former and never smokers had a higher proportion of occurrences than current smokers, although this finding was not significant. The finding that current smokers had a significantly higher occurrence of activity (scale/hypertrophy), damage (dyspigmentation), and mucous membrane (lesions/ulcers) supports previous research

that current smoking impacts active skin lesions and general cutaneous damage (Turchin, Bernatsky et al. 2009).

As expected, in this study the odds of having a higher total CLASI score were higher, although not statistically significant, among current smokers when compared to never smokers. Even more, the odds of having any sign of an active manifestation was significantly higher among current smokers than never smokers. We can interpret this to mean that individuals with a diagnosis of SLE that smoke regularly are more likely to have more severe cutaneous manifestations than those who do not smoke, especially in regards to active manifestations when secondhand smoke exposure, race, and sun exposure are all taken into account.

Potential Bias

There are a few potential sources of bias embedded in this study. First of all, we cannot be certain of the causal relationship between smoking status and increased severity of cutaneous manifestations because of the cross-sectional study design. In order be sure of this association cigarette smoking would have had to have been introduced prospectively and in a randomized way, which would be unethical.

One particular source of potential bias in this pilot study has to do with the way in which the patients were evaluated. Physicians were not necessarily blinded to smoking status. It is possible that a number of physicians saw the completed smoking questionnaire, as they were the individuals who collected the form after the patient completed it in the waiting room, in most cases. It is also possible that physicians were aware of the patient's smoking status if it was indicated on the patients' chart or previous

medical records. If knowledge of the patient's smoking status influenced the physician's CLASI scoring, this could lead to bias.

Self-reported smoking information could potentially be associated with recall and social expectation bias. If the surveys had been anonymous perhaps patients would have been more inclined to answer the questions regarding smoking behaviors truthfully. Still, patients filled out the questionnaire in the privacy of the waiting room or their appointment room. There were two instances, however, of a patient indicating that they had never smoked on the smoking questionnaire, but in the chart review it was later found that the patient had been a regular smoker in previous years. Although there is the possibility of complications associated with recall and social expectation most investigators have concluded that self-reports of smoking status are adequate for use in epidemiological studies (Petitti, Friedman et al. 1981).

Lastly, it is important to note that sources of bias associated with selection of subjects were minimized by collecting the data prospectively as opposed to retrospectively, in most cases. Additionally, the study was able to capture almost all patients that visited the lupus clinics throughout the duration of the study and confirmation of SLE diagnoses and CLASI evaluations by a physician ruled out potential self-report bias of the outcome.

Limitations & Uncertainty

One of the limitations of this pilot study was that multiple physicians were responsible for completing the CLASI forms. Even more, rheumatology residents

changed every month and had to be trained on how to properly fill out CLASI forms. This may have led to inconsistency in how patients were scored.

Another limitation of the study was the retrospective chart review that a handful of patients underwent. There was a desire for more power in the study because of the small sample size so in order to remedy this, the attending physician went back and retrospectively assessed the skin manifestations of 34 patients that had completed a smoking questionnaire.

A handful of potential confounders were not analyzed in this pilot study. Although disease duration and insurance were both measured, there were a number of missing values for both variables (n missing = 17 and 53 respectively). A handful of disease duration values were missing because the original SLE diagnosis date was not found in the patient's medical records. Insurance information was missing mainly because the Grady electronic medical chart system did not grant researcher access to insurance information for all patients. Other potential confounders that would have ideally been considered in this study include cumulative organ damage, other skin conditions, alcohol use, therapeutic interventions, education level, and hydroxychloroquine (antimalarial) use (Ghaussy, Sibbitt et al. 2003; Turchin, Bernatsky et al. 2009).

Although the study population was limited, it is likely that the results can be applied to a wider range of individuals. Although the pilot study was considerably made up of African American females, this demographic is prominent among SLE patients. 80-90% of SLE patients are women (Costenbader and Karlson 2005), and African American females are three times more likely to develop SLE than white females (CDC 2008). The

population demographics in this study are also reflective of Atlanta's population demographics; 61.4% African American (Bureau of the Census 2000) as compared to the national average of 12.3% African American (Bureau of the Census 2000).

VI. Conclusions

Summary

Taken together, these data are suggestive of an association between smoking tobacco products and cutaneous manifestations among SLE patients. Despite the small sample size, the study had enough power to find statistically significant results that suggest a strong association between current smoking status and more severe active skin manifestations among individuals with SLE. The findings from this study support recommendations by physicians to urge patients with SLE to quit smoking in order to possibly avoid greater cutaneous activity.

Recommendations

Additional studies are needed to further investigate the role that tobacco smoke plays in regards to cutaneous manifestations of SLE, especially when considering secondhand smoke exposures. Larger studies that include confounders that were not addressed in the current pilot study should focus on the long-term effects of smoking on cutaneous outcomes among SLE patients.

VII. References

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VIII. Tables and Figures:

Figure 1. Costenbader et al. 2004. Odds ratios from meta-analysis.

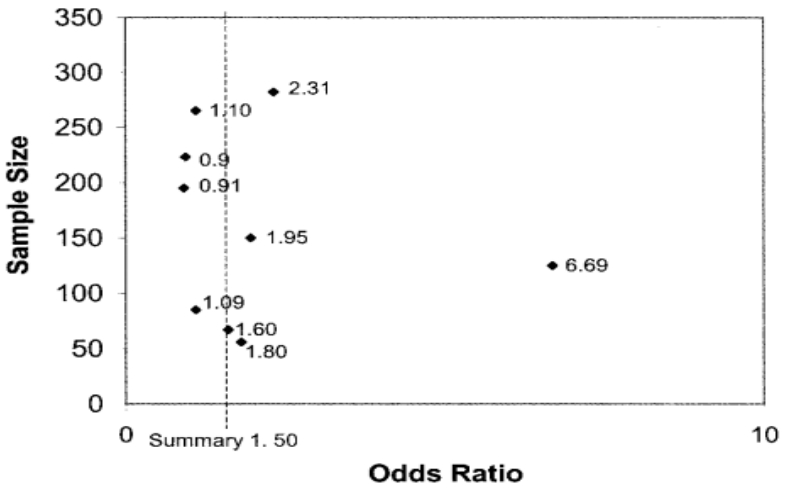


Figure 1. Funnel plot of the odds ratio of systemic lupus erythematosus (SLE) developing in current smokers compared with never smokers, in the 7 case–cohort studies and 2 cohort studies. The absence of studies in the lower left section of an inverted funnel, where small studies with negative results would lie, implies the presence of potential publication bias. Sample size refers to the number of SLE cases in each study. The summary estimate of the odds ratio of SLE in smokers versus nonsmokers is represented by the broken vertical line.

Figure 2. Krathen et al. 2008. Distribution of CLASI scores.

Table 3. Summary of Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores

	Low score (subject no.)	High score (subject no.)	Mean ± SD
Activity			
Dermatology	3.4 (7)	32.8 (1)	15.6 ± 10.6
Rheumatology	4.6 (4)	31.4 (1)	14.1 ± 9.1
Damage			
Dermatology	0.2 (8)	38.8 (14)	20.2 ± 13.1
Rheumatology	2.2 (3)	36.0 (11)	22.0 ± 13.1

Table 1. Demographics (n=109)

Characteristic	Number (%)
Sex (n missing = 3)	
Female	100 (95.24)
Male	5 (4.76)
Race (n missing = 4)	
African American	91 (88.35)
White	8 (7.77)
Hispanic	3 (2.91)
Other	1 (0.97)
Insurance (n missing =54)	
Not Insured (self pay)	4 (7.41)
Managed Care	24 (44)
Medicaid	15 (27.78)
Medicare	11(20.37)
Age (mean) (n missing = 3)	40.9
Disease duration (mean years) (n missing = 17)	8.19

Table 2. Demographics by smoking status (n=109)

	Smoking Status			
	Current	**Former**	**Never**	**All**
Total Subjects				
Women	10	21	69	100
Men	1	1	3	5
Mean current age	38.27	50.27	38.44	40.9
Mean disease duration (years)	4.89	7.47	8.89	8.19
Ethnic Group				
African American	10	19	62	91
White	1	2	5	8
Hispanic	0	0	3	3
Other	0	1	0	1

Table 3. Distribution of CLASI scores

	Percentile							
Outcome Measure	**0**	**10**	**25**	**50**	**75**	**90**	**100**	**Mean (± SD)**
Total CLASI	0	0	0	5	10	15	59	6.52 (8.21)
Activity Score	0	0	0	0	1	4	50	1.43 (5.15)
Damage Score	0	0	0	4	8	12	36	5.09 (6.06)
Physician's Global Assessment	0	0	0	0.25	0.50	1	2.50	0.36 (0.55)

Table 4. Mean CLASI scores by smoking status

Smoking Status	Mean CLASI Score	n	p value
Current	11.91	11	0.0697
Former	6.14	22	
Never	5.84	75	

Smoking Status	Mean Activity Score	n	p value
Current	6.45	11	0.0020*
Former	1.32	22	
Never	0.72	75	

Smoking Status	Mean Damage Score	n	p value
Current	5.45	11	0.9588
Former	4.82	22	
Never	5.12	75	

Smoking Status	Mean Physician Global Assessment Score	n	p value
Current	0.66	11	0.1628
Former	0.36	22	
Never	0.32	75	

*Denotes significant result ($\alpha = 0.05$)

Table 5. Mean CLASI scores by smoking status, including secondhand smoke exposure

Smoking Status	Mean CLASI Score	n	p value
Current	11.91	11	0.1431
Former + SHS	7.28	18	
Former no SHS	6.42	3	
Never + SHS	5.14	45	
Never no SHS	1.33	29	

Smoking Status	Mean Activity Score	n	p value
Current	6.45	11	0.0156*
Former + SHS	1.61	18	
Former no SHS	0	3	
Never + SHS	0.73	45	
Never no SHS	0.72	29	

Smoking Status	Mean Damage Score	n	p value
Current	5.45	11	0.7221
Former + SHS	5.67	18	
Former no SHS	1.33	3	
Never + SHS	5.69	45	
Never no SHS	4.41	29	

Smoking Status	Mean Physician Global Assessment Score	n	p value
Current	0.66	11	0.3122
Former + SHS	0.32	18	
Former no SHS	0.70	3	
Never + SHS	0.34	45	
Never no SHS	0.30	29	

*Denotes significant result ($\alpha = 0.05$)

Table 6. Frequency of individual CLASI items

Manifestation	Current Smokers %	Former and Never Smokers %	Fishers p	Significant
Alopecia	25	13	0.2444	
Recent Hair Loss	38	18	0.1473	
Scalp Scarring	25	48	0.1495	
Mucous Membrane (lesion or ulcer)	25	2	0.0278	*
Dyspigmentation of active lesions	38	37	0.2979	
Activity - Erythmea	63	46	0.2042	
Activity - Scale/Hypertrophy	38	3	0.0072	*
Damage - Dyspigmentation	88	51	0.0453	*
Damage – Scarring/Panniculitis	25	7	0.1362	

Table 7. Odds ratios and 95% confidence intervals from ordinal logistic regression analysis for smoking status and overall CLASI scores

		95% Confidence Limit	
Effect	Odds Ratio	Lower Limit	Upper Limit
Current smoker	1.421	0.408	4.945
Former smoker	1.189	0.463	3.054
SHS exposure	0.548	0.237	1.270
Sun exposure	1.025	0.470	2.236
Race	2.108	0.547	8.119

SHS exposure = secondhand smoke exposure. N missing = 10. Reported odds ratios are relative to never smokers and control for current smoking status, former smoking status, race (African American vs non African American), sun exposure (yes, no), and exposure to secondhand smoke (yes, no).

Table 8. Odds ratios and 95% confidence intervals from logistic regression analysis for smoking status and CLASI Activity scores

Effect	Odds Ratio	95% Confidence Limit Lower Limit	95% Confidence Limit Upper Limit
Current smoker	4.522*	1.066	19.187
Former smoker	1.236	0.401	3.808
SHS exposure	0.461	0.156	1.365
Sun exposure	0.627	0.232	1.696
Race	0.315	0.080	1.238

SHS exposure = secondhand smoke exposure. N missing = 10. Reported odds ratios are relative to never smokers and control for current smoking status, former smoking status, race (African American vs non African American), sun exposure (yes, no), and exposure to secondhand smoke (yes, no).

VIII. Appendix

1. SLE Smoking Questionnaire.

LUPUS CLINIC: Smoking history information update

Dear Patient: we would greatly appreciate you taking a few minutes to complete the following questions. This information has been incorporsted as part of our follow up standard assessment. This information will be kept confidential in your medical record.

Date:_____

Patient Name:_____

Please circle only one answer:

1) Have you smoked at least 100 cigarettes in your lifetime (**100 cigarettes = 5 packs**)?

   Yes No I don't know

2) Have you ever smoked regularly (**regularly = 1 cigarette, cigarillo or cigar per day for at least three months**)?

   Yes No I don't know

   If NO please skip to Question 5

3) At what age did you start smoking tobacco regularly? _____

4) When did you stop smoking tobacco regularly?
   I have not quit smoking
   I quit within the last week
   I quit within the last month
   I quit within the last 6 months
   I quit within the last year
   I quit within the past five years
   I quit over 5 years ago

5) Do you currently smoke tobacco?

   Yes, regularly Yes, occasionally No

   If NO please skip to Question 7

CONTINUED ON BACK

6) On average, how many times do you smoke per day?
   Number of packs? _____
   Number of cigarettes? _____

7) Are you currently exposed to secondhand smoke at home (**secondhand smoke = smoke exhaled by another smoker**)?

   Yes No I don't know

8) Have you ever been exposed to secondhand smoke at your workplace?

   Yes No I don't know

9) Were you exposed to secondhand smoke in the home as a child (**child = under 18 years of age**)?

   Yes No I don't know

10) On average, how often are you exposed to secondhand smoke per day?
   Never – 0 hours
   Rarely – 0 to 1 hour
   Some – 1 to 5 hours
   A lot – more than 5 hours per day

11) On average, how many hours are you in the sun each day?
   0 – 1 hour
   1 – 2 hours
   2 – 3 hours
   4 – 6 hours
   More than 6 hours

12) How many times in the last year have you had a sunburn?_____

2. CLASI Scoring System

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Extent

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

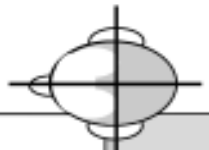
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	