CLINICAL STUDY

Association of Sunlight Exposure and Photoprotection Measures with Clinical Outcome in Systemic Lupus Erythematosus.

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ABSTRACT. This study was designed to explore the relationship of sunlight exposure and ultraviolet (UV) light protection measures with clinical outcome in systemic lupus erythematosus (SLE). A structured questionnaire was administered to sixty Puerto Rican SLE patients, to assess their attitudes and behavior regarding sunlight exposure and photoprotection measures. Medical records were reviewed to evaluate the clinical outcome measures that included: clinical manifestations, number of SLE-related hospitalizations, number of exacerbations and pharmacologic treatment. Almost all (98.3%) patients were well acquainted of sunlight effects on disease activity. Two thirds were exposed to direct sunlight for an average of less than one hour per day and 33.3% for one hour or more. Thirty patients (50%) reported use of sunscreen, with sun protective factor of 15 or greater, when exposed to sunlight. Less than 40% of patients regularly wore hat or long-sleeves clothes to protect from sunlight. Although there were some clinical differences between the groups with different sunlight exposure times, none reached statistical significance. Also, no significant differences were found between the groups in regards to sunlight protective clothes. However, patients that regularly used sunscreen had significantly lower renal involvement (13.3 vs. 43.3%), thrombocytopenia (13.3 vs. 40%), hospitalizations (26.7 vs. 76.7%), and requirement of cyclophosphamide treatment (6.7 vs. 30%) than patients that did not used it ($P < 0.05$). We conclude that use of sunscreen photoprotection was associated with a better clinical outcome in our SLE patients. These findings further support the importance and benefits of photoprotective measures in patients with SLE. *Key words: Systemic lupus erythematosus, Ultraviolet light, Photoprotection, Photosensitivity, Clinical outcome*

Prolonged sunlight exposure can be detrimental to patients with systemic lupus erythematosus (SLE) (1-3). One of the most common clinical manifestations in SLE is photosensitivity, manifested by the appearance of a skin rash as a result of a brief exposure to sunlight (1). Other skin lesions such as malar rash, discoid lupus and subacute cutaneous lupus can also be aggravated by sunlight exposure (2). Likewise, systemic manifestations such as arthralgia, arthritis, headaches and constitutional symptoms can also appear in patients with SLE after a brief or prolonged sunlight exposure (3).

The effect of sunlight in such patients appears to be mediated by ultraviolet (UV) light. Experimental data implicate UV-A (wavelengths of 320-400 nm) and UV-B (wavelengths of 290-320 nm) for this phenomenon (4-7). In murine lupus, exposure to UV-B light results in increased morbidity and mortality (8). In patients with SLE, irradiation of skin with UV-A and UV-B can induce lesions that are clinically and histopathologically consistent with SLE (4). This effect is seen even in patients with no previous history of photosensitivity. In addition to experimental UV light irradiation, some investigators found a high percent of SLE patients, specifically those with history of photosensitivity, who experimented flares of their symptoms when exposed to uncovered fluorescent lamps (3).

UV light induces and modulates the immune system in several ways. It has been shown that UV-B induces the

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release of tumor necrosis factor-alpha (TNF-α) from human keratinocytes (9). UV-A and UV-B increase the binding of antibodies to SSA and SSB antigens (10). UV radiation enhances the expression of interleukin-1 (IL-1) in the epidermis and augments circulating level of interleukin-6 (IL-6) (11,12). In addition, UV-B irradiated fibroblasts from lupus patients have increased cytotoxicity (13). These cytokines and immunologic functions altered by UV light have been also implicated in the immunopathogenesis of SLE (14). Therefore, UV light exposure might play an important role in disease expression and clinical course of lupus patients.

Study design and population. To our knowledge, there no clinical studies that explore the impact of UV light exposure and photoprotection measures on the disease manifestations and clinical outcome of SLE patients. The purpose of this study was to determine the clinical outcome of SLE patients based on the time of exposure to direct sunlight and the extent of the photoprotection measures.

Methodology

Study design and population. The study was performed in sixty Puerto Rican patients with SLE followed at the Rheumatology Clinic of the Ramón Ruiz Arnau University Hospital in Bayamón, Puerto Rico and the private practice of Drs. Vilá. All patients fulfilled the 1982 American College of Rheumatology (ACR) criteria for the diagnosis of SLE. Patients with drug-induced SLE were not included in this study. At the study visit, the patients were interviewed by the investigators using a structured questionnaire to identify factors related to the awareness of sunlight effects, symptoms upon sunlight exposure, time of sunlight exposure and photoprotection measures. Medical records were reviewed to obtain information of demographic factors, clinical manifestations, pharmacological treatment and the clinical course of disease. The period of data collection was from June 1995 to January 1996.

Study questionnaire.

Sunlight awareness and exposure-induced manifestations. SLE patients were asked if they were instructed about the potential deleterious effect of sunlight exposure and if they believed that sunlight can induce or exacerbate their condition. Also, they were inquired about the development of each of the following symptoms after a brief exposure (five minutes or less) to direct sunlight: skin redness on exposed areas, tiredness, fever, chills, anorexia, arthralgia and arthritis.

Sunlight time exposure. We asked the average daily exposure time to direct sunlight during the six months prior to the study visit. Exposure at work and outside activities were included. Patients were asked if sunlight exposure during there six months was the same prior to the study period and since diagnosis of SLE.

Sunlight protection. The questionnaire included information regarding the use of the following sunlight protection measures: sunscreen and protecting clothing such as hat, shirt with long-sleeves and long pants or skirts. It also explored the frequency of their use during direct sunlight exposure. The sunscreen evaluation included the sun protective factor (SPF) most commonly used.

Clinical manifestations and outcome. The presence or absence of the following clinical manifestations was determined for each patient: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, pericarditis, pleuritis, renal or neurologic involvement, anemia of chronic illness, hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia. The definition of these clinical features are described in the 1982 ACR criteria for the diagnosis of SLE (15).

Clinical outcome was evaluated by determining the following: 1) general clinical manifestations, 2) presence of major organ disease such as renal or central nervous system (CNS) involvement, 3) number of disease exacerbations, defined as the onset of new organ/system involvement or worsening of a previous coexisting condition that required modification of therapy, 4) number of hospitalizations due to disease exacerbation or complication related to SLE, and 5) treatment with immunosuppressive agents. The use and length of treatment was determined for the following drugs: high-dose corticosteroid (prednisone 60 or more mg daily or drug equivalent), medium-dose of corticosteroid (prednisone 11-59 mg daily or drug equivalent), low-dose corticosteroid (prednisone 1-10 mg daily or drug equivalent), hydroxychloroquine, azathioprine, methotrexate, oral cyclophosphamide therapy. The number of intravenous methylprednisolone and cyclophosphamide treatments were also determined.

Statistical analysis. Conventional Chi-Square test was used for analyzing quality differences between the study groups. When the expected value in one or more cells of the cross tables was less than 5, we used the Fisher Exact test. Mann-Whitney test was used to evaluate differences in continuous data. Logistic regression analysis was conducted to evaluate the association between sunscreen use and clinical outcome, controlled for length of sunlight exposure and presence of photosensitivity. A "P value" of less than 0.05 was taken to indicate statistical significance. The odds ratio (OR) was calculated to explore the risk of the study groups for each variable. An OR confidence intervals (CI) of 95% that did not include the "1" was taken to indicate statistical significance. The statistical

analysis was performed with the help of the Statistical Package for Social Sciences (SPSS) program (16, 17).

Results

General characteristics and clinical features. From the total of the 60 SLE patients, 56 (93.3%) were females. The mean age at onset of disease, diagnosis of SLE, and study visit were 33.4 ± 11.3, 34.7 ± 11.5, and 39.5 ± 11.5 years respectively. The mean duration of disease was 74 ± 52 months and the mean follow-up was 50 ± 42 months.

The most common clinical manifestations were arthralgia (96.7%), malar rash (73.3%) photosensitivity (71.2%), arthritis (66.7.%) and anemia (65.0%). Twenty (33.3%) patients had hair loss or alopecia. Oral ulcers occurred in one-third of patients. Major organ disease was less common. Renal involvement occurred in 28.3% and CNS disease in 15.0% of patients. Pleuritis occurred in 35.0% and pericarditis in 10.0%. Thrombocytopenia was detected in 26.7% of patients and leukopenia in 25.0%. Discoid rash was uncommon, only 13.3% had this condition. Forty-six (76.7%) patients had at least one episode of SLE exacerbation and 31 (51.7%) had to be hospitalized in at least one occasion due to lupus condition or associated complications.

Sunlight awareness and exposure-induced symptoms. All patients but one, received guidance at the time of diagnosis regarding the potential deleterious effect of sunlight to their disease. Forty-nine (81.7%) patients believed that sunlight might aggravate their disease. After brief exposure to direct sunlight the patients reported photosensitivity in 71.2%, arthralgia in 51.7%, joint swelling in 40.0%, anorexia in 76.7%, fever in 71.2%, tiredness in 66.7% and chills in 66.7%. In general, 80% of patients had at least one symptom associated with sunlight exposure.

Sunlight exposure and clinical outcome. The average daily exposure to direct sunlight in the study group was 1.1 hour. Forty (66.7%) of the sixty patients reported an average sunlight exposure of less than one hour per day. The other twenty (33.3%) patients reported an hour or more of daily exposure. The disease duration and follow-up in both groups was similar. Table 1 shows the presence of clinical manifestations, disease exacerbations and hospitalizations in the study groups. A higher percentage of photosensitivity (80.0% vs. 55.0%) and a lower percentage of renal involvement (22.5% vs. 40.0%) were observed in the group with lower sunlight exposure. However, the differences were not statistically significant. CNS involvement, exacerbations and hospitalizations were similar in both groups. Other studied clinical features were also similar (data not shown).

Table 1. Clinical outcome of SLE by daily time exposure to direct sunlight.

Complications	< 1 hr n=40 (%)	≥ 1 hr n=20 (%)	P-value
Photosentsitivity	32 (80.0)	11 (55.0)	0.47
Renal involvement	9 (22.5)	8 (40.0)	0.16
CNS involvement	6 (15.0)	3 (15.0)	1.00
Anemia	24 (60.0)	15 (75.0)	0.25
Leukopenia	10 (25.0)	5 (25.0)	0.91
Thrombocytopenia	10 (25.0)	6 (30.0)	0.68
Exacerbations	29 (72.5)	17 (85.0)	0.35
Hospitalizations	20 (50.0)	11 (55.0)	0.72

*Statistical significance (P<0.05)

Table 2 shows the percentage of patients treated with different immunosuppressive agents according to time exposure to direct sunlight. There were no differences between these groups. In addition, we found no statistically significant differences in the length of treatment for each of these pharmacologic agents between the exposure groups (data not shown).

Of the sixty patients, fifty-one (85.0 %) reported no sunlight exposure variation since the diagnosis of SLE. Thirty-five (68.6%) of these 51 cases had a sunlight exposure of less than one hour per day and sixteen (31.4%) had one or more hours per day of exposure. When the SLE clinical manifestations, complications and treatments in this exposure group of 51 patients were analyzed we observed a similar percent distribution as that obtained in the entire group. The only variation between the exposure groups was the frequency of photosensitivity. The group with less exposure time had higher photosensitivity (80.0%

Table 2. Pharmacological treatments of SLE patients by daily time exposure to direct sunlight.

Pharmacological treatments	< 1 hr n=40 (%)	≥ 1 hr n=20 (%)	P-value
Corticosteroid high-dose	20 (50.0)	11 (55.0)	0.72
Corticosteroid medium-dose	31 (77.5)	15 (75.0)	0.83
Corticosteroid low-dose	34 (85.0)	15 (75.0)	0.48
Hydroxychloroquine	23 (57.5)	11 (55.0)	0.54
Azathioprine	5 (12.5)	5 (25.0)	0.22
Cyclophosphamide IV	8 (20.0)	3 (15.0)	0.74
Methotrexate	1 (2.5)	2 (10.0)	0.26
Methylprednisolone pulse	9 (22.5)	8 (40.0)	0.16

*Statistical significance (P<0.05)

vs.50.0%) than the group with a longer exposure time (OR= 4, 95% CI:1.20-14.4).

Sunlight protection measures and clinical outcome. Thirty patients (50.0%) reported use of sunscreen during their exposure to direct sunlight. These patients used sunscreen with SPF of 15 or greater. Twenty-three (38.3%) patients of the sample used hat, seventeen (28.3%) wore clothing with long sleeves and fifty-two (86.7%) wore long pants or long skirts to protect themselves from the sunlight. Table 3 shows the clinical features and outcome of patients according to use of sunscreen. The group that did not use sunscreen had statistically significant higher frequency of renal involvement, thrombocytopenia, and hospitalizations when compared with the group which used this protection measure. Leukopenia, anemia and other clinical manifestations were similar in both groups. The disease duration between the groups was similar and not statistically different.

Table 3. Clinical manifestations of SLE patients by use of sunscreen.

Complications	Sunscreen		Odds Ratio
	Use (%)	No use (%)	(95% C.I.)
	n=30	n=30	n=60
Malar rash	26 (86.7)	18 (60.0)	2.65 (0.62-11.3)
Renal involvement	4 (13.3)	13 (43.3)	0.22 (0.06-0.86)*
CNS involvement	3 (10.0)	6 (20.0)	0.69 (0.13-3.60)
Anemia	16 (53.3)	23 (76.7)	0.39 (0.12-1.26)
Leukopenia	7 (23.3)	8 (28.6)	0.90 (0.26-3.10)
Thrombocytopenia	4 (13.3)	12 (40.0)	0.22 (0.06-0.85)*
Exacerbations	25 (83.3)	21 (70.0)	1.58 (0.42-5.98)
Hospitalizations	8 (26.7)	23 (76.7)	0.10 (0.03-0.35)*

The odds ration was derived from logistic regression models, controlled by length of direct sunlight exposure and the presence of photosensitivity.
C.I. denotes the confidence interval.
* Statistical significance (P<0.05 and C.I. ≠ 1)

Table 4 shows that patients who did not use sunscreen required intravenous cyclophosphamide treatment to control their disease more frequently than patients that used sunscreen. On the other hand, patients that used sunscreen were treated with hydroxychloroquine more frequently than patients that did not use sunscreen. The length of treatment with immunosuppressive drugs was similar in both groups.

There were no significant differences in clinical manifestations, clinical outcome or pharmacologic treatments between patients regarding their use of protective clothes (data not shown).

Table 4. Pharmacological treatments in SLE patients by use of sunscreen.

Pharmacological treatments	Sunscreen		Odds Ratio
	Use (%)	No use (%)	(95 % C.I.)
	n=30	n=30	n=60
Corticosteroid high-dose	11 (36.7)	20 (66.7)	1.18 (0.35-3.92)
Corticosteroid medium-dose	21 (70.0)	25 (83.3)	0.50 (0.14-1.81)
Corticosteroid low-dose	24 (80.0)	25 (83.3)	0.88 (0.22-3.59)
Hydroxychloroquine	22 (73.3)	12 (40.0)	3.68 (1.20-11.3)*
Azathioprine	6 (20.0)	4 (13.3)	1.61 (0.38-6.88)
Cyclophosphamide IV	2 (6.7)	9 (30.0)	0.18 (0.03-0.99)*
Methotrexate	2 (6.7)	1 (3.3)	1.58 (0.12-20.0)
Methylprednisolone pulse	6 (20.0)	11 (36.7)	0.39 (0.11-1.38)

The odds ratio was derived from logistic regression models, controlled by length of direct sunlight exposure and the presence of photosensitivity.
C.I. denotes the confidence interval
*Statistical significance (P<0.05 and C.I. ≠ 1)

Discussion

This study confirms that sunlight protective measures are important in the management of SLE. Patients that used sunscreen had lower renal involvement, thrombocytopenia and hospitalization rate than patients who did not use it. Eighty-three percent of SLE patients were aware of the potential damage of sunlight exposure to their condition, but only 50.0% of them used sunscreen protection. This low percent is not due to lack of medical attention or guidance, since 98.0% of patients acknowledged that they received instructions regarding photoprotection measures at the time of SLE diagnosis. As expected, the patients with cutaneous manifestations or malar rash used sunscreen more frequently than patients without these symptoms. This observation suggests that SLE patients with photosensitivity or cutaneous manifestations are more conscious of the sunlight damage and use sunlight protection measures more frequently. However, the differences in clinical outcome and treatment observed between the groups in regards to use of sunscreen were not related to photosensitivity and sunlight exposure since we controlled for these variables.

The better prognosis observed in patients that used sunscreen may be associated to other related factors. SLE patients that are aware of using sun protective measures might also have better socioeconomic status and personal health behavior such as nutritional habits, coping skills,

and problem solving skills. All these factors may influence the outcome of SLE. Further studies would be necessary to explore these possibilities. Previously, we have shown that low formal education, low annual family income, and lack of private health insurance in Puerto Rican patients with SLE are associated with a poor clinical outcome (18).

Sunlight protective clothing was not associated with a better prognosis in our patients. No clinical differences in manifestations, outcome or pharmacologic treatments were observed. This observation could be secondary to a lower SPF provided by their clothing. This study was performed in a tropical island where people wear clothes with light fabrics which have an estimated SPF in the range of 5 to 10 (19). None of our patients used special clothing for photosensitive patients which can provide an SPF up to 60-70 (19). It would be important, however, to conduct studies addressing the effect of high-SPF clothing on SLE activity and outcome.

Another important finding in this study is the high percentage of clinical manifestations, besides photosensitivity, that occur after a brief period of sunlight exposure. More than 65% reported constitutional symptoms and over 40% described joint pain or swelling. Only few other studies have examined this phenomenon. Similar to our study, Rhiner found that following exposure to sunlight a significant number of SLE patients develop tiredness, arthralgia and headache (3). UV light has several immunoregulatory effects. The release of cytokines such as IL-1 and TNF-α from UV radiated keratinocytes can induce the release of other regulatory cytokines, stimulate the production of chemokines involved in leukocyte migration and enhance the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) (20,21). Thus, sunlight exposure can potentiate the autoimmune reaction in SLE resulting in worsening of disease.

We found no significant differences in SLE clinical manifestations, complications or mode of treatment between the two groups with different sunlight time exposure. These findings should not be interpreted, however, that time exposure to direct sunlight is not important in SLE. The high variation of sunlight exposure throughout the day and year and the possibility of memory bias in the patients can affect the measure of the real time exposure. Furthermore, other sources of UV light were not examined. We did not determine the approximate exposure to indirect sunlight, for example, through room windows or automobile windows or UV light reflection by the ground. Exposure to fluorescent lamps light which emits UV-B was not measured either.

This study was performed in the Puerto Rican population which we believe is ideal to evaluate the role of sunlight exposure in SLE. Puerto Rico, a tropical island localized 18.5° North and 66.5° West in the Caribbean Sea, receives a significant and almost constant level of UV light all year round. The factors that affect sunlight radiation are quite constant throughout the year in this population. The radiation effect depends on several factors such as the angle of the sun exposure (latitude), daytime variation, season of the year and altitude. The atmosphere protection to the sunlight is inverse to the altitude of the persons living place. At high altitude, the atmosphere protection is less than at low levels. None of these variables were of concern in our study. Also, there are no significant differences in altitude in the studied region.

The study revealed that sunscreen use in SLE patients was associated with a lower severity of the disease and a better clinical outcome. On the other hand, we did not find any association between the time exposure to direct sunlight with the clinical manifestations, prognosis or treatments modality of these patients These findings suggest that lupus patients might be exposed to direct sunlight without suffering significant worsening of their disease, but only if they have taken adequate photoprotection measures. Nonetheless, we recommend SLE patients to reduce or maintain their sunlight exposure in the lowest possible level and to optimize the sunlight protective measures when exposed directly or indirectly to sunlight. These precautionary measures must be extended to artificial light exposure, where the UV light radiation is high, such as uncovered fluorescent lamps. We conclude that use of sunscreen appears to be very important in the management of SLE and its use should be greatly encouraged whenever a patient is exposed to any source of UV light.

Resumen

Este estudio fue diseñado para evaluar la relación entre la exposición a luz solar y las medidas de protección a luz ultravioleta con la evolución clínica del lupus eritematoso sistémico (LES). Se administró un cuestionario estructurado a sesenta pacientes puertorriqueños con LES, con el fin de explorar sus actitudes y conductas relacionadas a la exposición de luz solar y las medidas protectoras utilizadas contra ésta. Los expedientes clínicos se revisaron para evaluar la evolución de los pacientes incluyendo manifestaciones clínicas, número de hospitalizaciones relacionadas con LES, número de exacerbaciones y tratamiento farmacológico. Casi todos los pacientes (98.3%) estaban conscientes de los efectos de la luz solar sobre su enfermedad. Dos terceras partes se expusieron directamente a la luz solar por un promedio de menos de una hora diaria y el resto por una hora o

más. Treinta pacientes (50.0%) reportaron el uso de bloqueador solar, con un filtro de 15 o más, al momento de la exposición solar. Menos del 40% de los pacientes usaban regularmente sombrero o ropa protectora para exposición solar. A pesar de que hubo diferencias clínicas entre los grupos con diferentes tiempos de exposición, ninguna fue estadísticamente significativa. Tampoco hubo diferencias significativas entre los grupos que usaron ropa protectora y los que no la usaron. Sin embargo, los pacientes que usaron regularmente bloqueador solar tuvieron significativamente menos compromiso renal (13.3% vs. 43.3%), menos trombocito-penia (13.3% vs. 40.0%), menos hospitalizaciones (26.7% vs. 76.7%) y requirieron menos tratamiento con ciclofosfamida (6.7 vs. 30.0%) que aquellos que no lo usaron regularmente ($P<0.05$). Concluimos que el uso de bloqueador solar se asocia a un mejor pronóstico en nuestros pacientes con LES. Estos hallazgos sustentan la importancia de la protección solar en pacientes con LES.

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