



## Editorial comment

# Factors associated with development of target organ damage in patients with systemic lupus erythematosus<sup>☆</sup>



## Factores asociados al desarrollo de daño de órganos blanco en pacientes con Lupus Eritematoso Sistémico

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Systemic lupus erythematosus is the prototype of autoimmune disease, which is characterized by generating a commitment of multiple organs including the joints, skin, kidneys, and the nervous system, among others. Due to this multisystemic commitment, the presence of the disease is associated with greater mortality of the population that suffers from it. The prevalence of the disease is variable depending on the population in which the follow-up is carried out. Most of the information available regarding the epidemiological behavior of the disease comes from the follow-up of cohorts of patients in countries of Europe and North America. The information concerning the behavior of systemic lupus erythematosus in Latin American populations is very scarce, which increases the need to promote the development of more studies that allow to perform this profiling of patients.<sup>1</sup>

The pathophysiology of systemic lupus erythematosus covers multiple aspects including genetic, hormonal and environmental factors, which is the foundation of the great complexity of the study of this disease, and of the way in which its clinical presentation can vary in different populations.

More than 100 genetic loci have been associated with the development of lupus, each one with a different level of association. The majority of the genetic polymorphisms associated with the development of the disease are involved with mechanisms of regulation of the immune response, mainly in the presence of cellular particles containing nucleic acids. Other alterations at the genetic level are associated with the development of deficiencies in complement proteins and aberrant activation of immune cells.<sup>1</sup>

The mechanisms associated with the development of damage of target organs are responsible for the development of the clinical manifestations of the disease. One of the main mechanisms studied is the activation of the complement cascades secondary to the presence of deposits of immune complexes, as well as the recruitment of neutrophils that constantly release degrading enzymes and reactive oxygen species that lead to tissue damage. In addition, it has been identified the presence of aberrant functioning monocytes in areas with constant pro-inflammatory stimulus, where they develop uncontrolled tissue repair activity. It has been identified the presence

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of infiltrates of B and T lymphocytes in the interstitium that are associated with the development of kidney failure. This is the most common mechanism in glomerulonephritis.<sup>2</sup>

There are many cascades of release of multiple cytokines derived from cells of innate and adaptive immunity, which contribute to the maintenance of chronic pro-inflammatory environments that lead to the alteration of the endothelium. The structural and functional damage secondary to this pro-inflammatory environment leads to the development of dysfunction of arterial and venous vessels, development of thrombotic events and premature atherosclerosis in patients with lupus. These thrombotic and microangiopathic events are responsible for the compromise of the nervous system and for part of the renal involvement. In addition, when the keratinocytes of the skin are exposed to ultraviolet light, they induce apoptosis, release of antigenic material and development of an autoimmune response.<sup>1,2</sup>

Given the increase in morbidity and mortality of the patients with systemic lupus erythematosus secondary to the commitment of target organs, arose the need to develop a method that could objectively measure the presence of this involvement of target organs and its severity. As a result, the damage index for systemic lupus erythematosus of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SDI) was developed in 1996. This index consists of a list with 12 domains; each of them corresponds to a specific system and has subcategories of the pathologies that can occur in this system. A score of 1 is assigned to each component. A score of 2 will be assigned in case of repeated episodes of the same commitment in a period of less than 6 months. In order to avoid confusing the presence of organic damage and effects of active inflammation, it is set as a criterion that each element must be present for at least 6 months. This instrument provides the opportunity to evaluate the cumulative damage and has demonstrated to be valid and reliable in clinical practice.<sup>3</sup>

In order to be able to predict which patients with systemic lupus erythematosus have greater risk to present damage of target organs, the studies associated with this topic have focused on the identification of the risk factors that could be associated with the development of these complications. For example, in 2012 Petri et al. published a study in a cohort of patients with lupus in the United States, where they observed that the annual rate of increase of the SDI score was of approximately 0.13 each year. The factors that were associated with higher rates of damage included patients of advanced age, men, African-Americans, low-income population, low educational level, hypertension, and having positive lupus anticoagulant and proteinuria. After the analysis of the different variables using logistic regression, they concluded that the main detectors of organ damage in the patients are advanced age, presence of arterial hypertension and use of corticosteroids. The main protective factor identified was the use of hydroxychloroquine.<sup>4</sup>

In 2015, Young et al., published a study on the development of target organ damage in a cohort of Korean patients with lupus. They observed that the increase of the SDI was 0.4-1.1 in average, observing the main peaks of organ damage at 6 and 10 years of follow-up. The main target organs involved were musculoskeletal, followed by renal and neuropsychiatric

commitment. They concluded that Korean patients with lupus show lower disease activity and less target organ damage compared with other Asian populations.<sup>5</sup> Seong-Kyu et al., published in 2017 a study on organ damage in Korean population, where they evaluated the association between comorbidities and the development of organ damage. They observed that the presence of organ damage was associated with greater presence of comorbidities, higher disease activity and the use of higher average doses of corticosteroids.<sup>6</sup>

Taraborelli et al., in 2016, focused their studies on determining the contribution of the presence of antiphospholipid antibodies in the development of target organ damage in patients with lupus. As a result, it was observed that 33% of the patients in the Italian cohort had antiphospholipid antibodies, which were associated with an increased risk of target organ damage. Likewise, they identified that the older age and being a man are also associated with an increase in the SDI.<sup>7</sup> In 2017, the same group published a study in which they evaluated the prevalence, predictors and progression of the target organ damage in patients with lupus. They observed that 69% of the patients had some type of damage, 49% of them had mild/moderate damage and 19% had severe damage. The presence of a longer duration of the disease, greater activity, presence of Raynaud's phenomenon, chronic alopecia and cerebral ischemic events is more associated with involvement of target organs. In addition, they observed that the presence of antiphospholipid syndrome and anti-cardiolipin antibodies were predictive factors for the development of neuropsychiatric lupus.<sup>8</sup> Another study conducted in Italian population was the one of Conti et al., published in 2016, where the objective was to evaluate the target organ damage due to the SDI and the association between demographic and clinical characteristics. As a result, they observed that 35% of the patients presented some type of target organ damage, where the most involved system was the musculoskeletal. The main associated factors were advanced age, longer duration of the disease, relapses and the use of corticosteroids. Like in the previous studies in Italian patients, it was observed an association between the presence of antiphospholipid syndrome and the development of neuropsychiatric commitment.<sup>9</sup>

The foregoing were some examples of the studies that have been conducted with the purpose of identifying the risk factors associated with the development of organ damage in patients with lupus. However, studies of this type in populations of Latin American countries are scarce. In Colombia, the main study on the subject was published by Medina et al., in 2013, in which they determined the clinical characteristics, the development of organ damage and the quality of life in Colombian patients with lupus in Bogota. The study was conducted based on the follow-up of a cohort during 6 months. As a result, it was observed that 45% of patients with lupus had some type of target organ damage, being the most frequent the presence of neuropsychiatric compromise (20.2%), followed by renal (11%), peripheral vascular (11%), pulmonary (9.2%) and musculoskeletal (6%) involvement.<sup>10</sup>

The study "Organ damage in a cohort of Colombian patients with systemic lupus erythematosus: characterization and associated factors", developed by Luis Fernando Pinto et al., from the Pablo Tobón Uribe Hospital, consists in a retrospective cohort developed with the purpose of

identifying the factors and manifestations that characterize the development of target organ damage in Colombian patients from the city of Medellín. All patients meet at least 4 classification criteria for systemic lupus erythematosus established by the ACR, with *de novo* diagnosis, which allows identifying the development of target organ involvement during the follow-up. SELENA-SLEDAI was used to measure the disease activity, and SDI to determine the target organ involvement. The variables included were demographic (age at diagnosis, gender), clinical (time of follow-up, presence of lupus nephritis, presence of arterial hypertension, disease activity by SELENA-SLEDAI initial and during the follow-up, relapses), and laboratory (antiphospholipid antibodies, cardiolipins,  $\beta$ 2- glycoprotein-1, lupus anticoagulant, anti Rho, anti-DNA) and pharmacological (doses of prednisolone, use of pulses of methylprednisolone, cyclophosphamide, azathioprine and mycophenolate).

The results show that the majority of patients were diagnosed with the disease at an age between 16 and 50 years (85%), and 14% after 50 years of age. The target organ commitment was registered in 29.8% of the patients and it was severe in 14% of the cases. The proportion of patients with target organ damage was progressively increasing during the follow-up period. The main organ commitment was at the neuropsychiatric level (13%), followed by renal (6.8%), vascular (5.6%) and pulmonary (4.3%) involvement. The main determinants of the development of organ damage according to the study were the presence of 2 or more relapses (adjusted OR 2.72), average doses of prednisolone higher than 12.5 mg/day (adjusted OR: 5.15) and the presence of antiphospholipid antibodies (adjusted OR: 10.9).

This study has a great academic value, taking into account that it makes a good characterization of the population with lupus in Colombia (in this case Medellín). It makes an adequate selection of significant variables in the development and course of the disease. The results shown were consistent with the previous study that had been conducted by Medina et al., in 2013 in the city of Bogotá. An advantage of the present study with respect to the one of 2013 is that it included a greater number of patients, as well as the type of study, since being a cohort it allows a better determination of factors that predispose to the development of organ damage. Both studies demonstrated that, in Colombian population, the main target organ commitment is at the neuropsychiatric level, followed by the renal involvement. Comparing with the literature in other populations, changes in the behavior are observed, since for example in the Korean and Italian cohorts, the main target organ commitment was at the musculoskeletal level.

Other of the great values of the study is focused in the role of the presence of antiphospholipid antibodies in the patients with lupus. This is a strength when comparing it with the study of Medina, since the latter did not measure this variable. The contribution of the study regarding the antiphospholipid antibodies is that their presence was the one with the greatest association with the development of organ damage. Taking into account the results of the studies of Taraborelli that link the presence of antiphospholipids with the development of neuropsychiatric compromise, the results of Pinto et al. are consistent in the main association between the presence of antiphospholipids and the most common involvement, which

is the development of neuropsychiatric involvement in the Colombian population.

A possible disadvantage is that, preferably, a stratification on the presence or not of antiphospholipids in the patients who presented neuropsychiatric commitment should have been done in order to determine if the results are really consistent with the literature of studies in other populations.

Another great contribution of this study and that shows consistency of the behavior of the Colombian population with that of other countries is the relationship established between the presence of relapses and the use of corticosteroids, with a greater risk of target organ involvement. However, another contribution of this study is that it takes into account the dose used on average by each patient as a determinant of the organic commitment.

This study represents an advance in relation to the objective of characterizing the Colombian population with systemic lupus erythematosus and the identification of the factors that may predispose to the development of complications of the disease secondary to target organ damage. Although the study was only conducted in a single health center and there is not much information regarding studies in other populations, it is a first step in the determination of the behavior of the disease in the country. It is noteworthy that the authors themselves are aware of these limitations and of the requirement to replicate this type of studies in cohorts of other health centers of the country in order to have data with greater statistical significance and more representative, or that show variations between regions regarding this behavior.

## Conflict of interest

The authors declare that they do not have any conflict of interest.

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