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Review Article

Organ damage in systemic lupus erythematosus

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ABSTRACT

Damage reflects the irreversible changes that occur in systemic lupus erythematosus (SLE) patients as a consequence of the disease, its treatment or comorbidities. The pattern of damage increases in a steady linear fashion over time. At least half of all patients with SLE will have some form of organ damage 10 years after their diagnosis. Factors associated with the occurrence of damage include older age, disease duration, male gender, non-Caucasian ethnicity, disease activity, corticosteroid use, poverty, hypertension and abnormal illness behaviors. In contrast, antimalarials are protective against damage. Since damage predicts further damage and mortality, prevention of damage accrual should be a major therapeutic goal in SLE. Novel therapies for SLE that achieve better control of the disease and with corticosteroid-sparing properties, may lead to improved outcomes in patients as they will reduce damage accrual and improve survival.

Daño orgánico en lupus eritematoso sistémico

Palabras clave:
Lupus eritematoso sistémico
Daño
Actividad de la enfermedad
Corticoesteroides
Mortalidad

RESUMEN

El daño refleja los cambios irreversibles que se producen en los pacientes con lupus eritematoso sistémico (LES) como consecuencia de la enfermedad, de su tratamiento o por causa de comorbilidades. El patrón de daño aumenta de forma lineal, constante a lo largo del tiempo. Al menos la mitad de todos los pacientes con LES presentará alguna forma de daño orgánico 10 años después de haber sido diagnosticados. Entre los factores asociados con el desarrollo de daño encontramos la edad avanzada, la duración de la enfermedad, el sexo masculino, la etnia no caucásica, la actividad de la enfermedad, el uso de corticoesteroides, la pobreza, la hipertensión y comportamientos anormales de la enfermedad; por otra parte, los antimaláricos protegen contra el daño de la enfermedad. Puesto que la presencia de

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daño es un predictor de daño adicional y de mortalidad, la prevención de acumulación de daño deberá ser un objetivo terapéutico fundamental en LES. Los tratamientos novedosos para el LES que logren un mejor control de la enfermedad y que tengan propiedades ahorradoras de corticoesteroides, podrían lograr mejores desenlaces en los pacientes, pues reducirían el daño acumulado y mejorarían la sobrevida.

SLE is a chronic inflammatory and debilitating disease characterized by flares, progressive organ damage and increased mortality.[1,2] Survival in SLE patients has gradually increased from the 1950s to the mid-1990s, and then has plateaued.[2] Therefore, as survival in SLE patients has improved, organ damage tends to accrue over time as a consequence of disease activity and/or the therapies used to abate it.[3] We will examine the factors associated with the development of organ damage, the distribution of organ damage, the pattern of damage accrual over time, the impact of damage on health-related quality of life (HRQoL) and mortality, and the measures used to prevent damage in SLE patients.

Concept of damage in SLE

Damage is a concept that reflects irreversible changes that occur in SLE patients as a result of the disease itself, its treatment, and SLE-associated comorbidities, such as cardiovascular (CV) disease or malignancies.[4] It is assessed with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI), a validated instrument that documents an irreversible change in an organ or system that has been present for at least six months since the onset of SLE, except for some manifestations such as myocardial infarction or stroke which are recorded as they occur.[5] Damage, as measured by the SDI, is a cumulative construct; therefore, the longer the disease duration, the more the damage accrual.

The SDI consists of 41 items covering 12 organ systems. The SDI records damage occurring in SLE patients, regardless of its cause (Table 1). Most of these items are not weighted, and each item scores 1 regardless of the impact on the patient function with the exception of end-stage kidney disease, which scores 3. Some items can score 2 for recurrent events (e.g., repeated strokes or avascular necrosis at two sites) if they occur at least 6-months apart.[4,5] The maximum score is 47, although patients rarely score greater than 12.[4] The SDI has the ability to identify damage accrued in both active and inactive disease. It is widely used to measure cumulative damage in SLE both in longitudinal studies and in drug trials.[6]

In addition to the SDI, the Lupus Damage Index Questionnaire (LDIQ) and the Brief Index of Lupus Damage (BILD) were developed to assess damage in SLE. Both are based on the SDI.[7,8] The LDIQ, is a patient self-administered organ damage instrument that includes 56 questions to assess each SDI domain and was designed to be administered as a written survey. The LDIQ has a moderately high correlation with the SDI ($r_s = 0.50$).[7] BILD is another patient reported damage index, has only 26 items and was designed to be administered by an interviewer in person or over the telephone. BILD had a moderate-to-high correlation with the SDI ($r_s = 0.64$).[8]

Pattern of organ damage accrual over time

Most longitudinal studies have reported a progressive linear increase in the SDI scores over time, even after several years (Figure 1).[9–19] For example, in the Hopkins Lupus Cohort, the mean rate of increase in the SDI score was 0.13 per year after diagnosis.[20] Gladman, et al. found that the mean SDI score increased over time in a linear pattern in an inception cohort followed for at least 15 years.[10] They observed three patterns of organ damage accrual over time: a first pattern characterized by a progressive increase in the prevalence of an specific organ system damage, as in musculoskeletal (MSK) and ocular systems; a second pattern with peaks at 5 and 15 years, as in CV and neuropsychiatric (NP) systems; and a third pattern characterized by a minimal increase in the occurrence of an specific organ system damage over 15 years, as in skin and renal systems.[10] Similarly, the SLICC international inception cohort by Urowitz et al., showed that disease activity in newly diagnosed SLE patients decreased and remained low over the first 5 years, while damage progressively increased over this time, especially corticosteroid-related damage (cataracts, osteonecrosis, and osteoporosis). In contrast, non-corticosteroid dependent damage (renal, pulmonary, gastrointestinal, gonadal failure and malignancy) remained constant throughout the observation time.[17] Likewise, in the LUMINA (*Lupus in Minority populations, Nature versus nurture*) cohort disease activity tended to decrease while damage tended to increase over time.[11] Taraborelli et al. in an Italian cohort, also found a linear increase of organ damage accrual after a mean follow-up of 13 years.[18] In contrast, Becker-Merok and Nossent found in a Norwegian study that damage increased in a linear pattern over the first 10 years, with subsequent flattening.[13]

Studies in juvenile-onset SLE also showed a progressive linear increase in damage which was associated with a decrease in disease activity.[14,19] These studies also indicated that in pediatric patients, damage accrued more rapidly than in adults with SLE.[14,19]

Frequency of damage in longitudinal studies

The frequency of damage reported in longitudinal studies progressively increases over time ranging between 3% and 40% at

Table 1 – The Systemic Lupus International Collaborating Clinics / American College of Rheumatology (SLICC/ACR) Damage Index (SDI).*[5].

Organ (system)	Item	Score	Maximum score
Ocular (Either eye, by clinical assessment)	Any cataract, ever	1	
	Retinal changes OR optic atrophy	1	2
Neuropsychiatric	Cognitive impairment (e.g. memory deficits, difficulty with calculation, poor concentration, difficulty with spoken or written language, impaired performance level) OR Major psychosis	1	
	Seizures requiring therapy for at least six months	1	
	Stroke, ever (score 2 if more than 1) OR resection not for malignancy	1 (2)	
	Cranial OR peripheral neuropathy (excluding optic neuropathy)	1	
	Transverse myelitis	1	6
Renal†	Estimated or measured glomerular filtration rate < 50%	1	
	Proteinuria 24h, ≥ 3.5 g	1	
	OR End-stage renal disease (regardless of dialysis or transplantation)	3	3
Pulmonary	Pulmonary hypertension (right ventricular prominence, or loud P2)	1	
	Pulmonary fibrosis (physical and chest radiograph)‡	1	
	Shrinking lung (chest radiograph)	1	
	Pleural fibrosis (chest radiograph)	1	
	Pulmonary infarction (chest radiograph) OR resection not for malignancy	1	5
Cardiovascular	Angina OR coronary artery bypass	1	
	Myocardial infarction, ever (score 2 if more than 1)	1 (2)	
	Cardiomyopathy (ventricular dysfunction)	1	
	Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	1	
	Pericarditis for six months, OR Pericardiectomy	1	6
Peripheral vascular	Claudication for six months	1	
	Minor tissue loss (pulp space)	1	
	Significant tissue loss, ever (e.g. loss of digit or limb) (score 2 if more than 1 site)	1 (2)	
	Venous thrombosis with residual swelling, ulceration, OR venous stasis	1	5
Gastrointestinal	Infarction OR resection of bowel (below duodenum), spleen, liver, or gallbladder, ever, (score 2 if more than 1 site)	1 (2)	
	Mesenteric insufficiency	1	
	Chronic peritonitis	1	
	Stricture OR upper gastrointestinal tract surgery, ever	1	
	Pancreatic insufficiency requiring enzyme replacement or with pseudocyst	1	6
Musculoskeletal	Muscle atrophy or weakness	1	
	Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1	
	Osteoporosis with fracture OR vertebral collapse (excluding avascular necrosis)	1	
	Avascular necrosis, ever (score 2 if more than one)	1 (2)	
	Osteomyelitis	1	
	Ruptured tendons	1	7
Skin	Scarring chronic alopecia	1	
	Extensive scarring of the skin or panniculus other than scalp and pulp space	1	
	Skin ulcers (excluding thrombosis) for more than 6 months	1	3
Gonadal	Premature gonadal failure (secondary amenorrhea, prior to age 40)	1	1
Endocrine	Diabetes (regardless of treatment)	1	1
Malignancy	Malignancy (exclude dysplasia) (score 2 if more than 1 site)	1(2)	2

* Damage (non-reversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at-least 6-months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

† Total number of cumulative points is 3.

‡ If available. Chest radiograph, only if clinically indicated.

one year, between 33% and 64% at five years, between 51% and 81% at 10 years, and between 55% and 79% at 15 years of follow-up.[9–19] Variations in the prevalence reported in these studies at different times during the follow-up may be due to: (1) differences in the ethnic groups included in the different cohorts; (2) the age of the cohort or the calendar year in which patient recruitment began; for example, patients from the cohorts recruited in the 1970s were often treated with higher corticosteroid doses for longer periods than they are nowadays; this may explain the higher progressive increase in corticosteroid-related damage in these patients; (3) differences in the definition of disease duration at baseline among

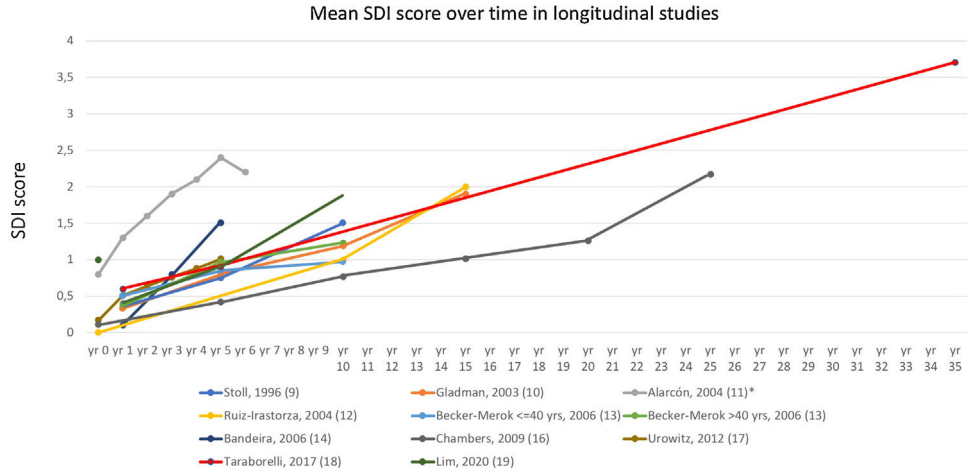

Figure 1 – Pattern of organ damage accrual in systemic lupus erythematosus over time in various longitudinal studies.[9–19]*The lower score at a later time in the LUMINA cohort (11) is due to the reduction in the number of patients followed.

the different studies; and (4) in pediatric studies, the SDI was modified adding the item "growth failure", a frequent cause of damage specific to the pediatric SLE population.[14,19] Table 2 summarizes the data from these longitudinal studies.

The findings from these studies suggest that faster rates of damage accrual are observed during the first years of the disease.[9–19] However, the occurrence of new damage continues year after year, so that most patients will have at least one damage item during their long-term follow-up.[3,16,18]

Figure 2 depicts the accrual of damage over time; it shows that damage develops in a steady linear fashion over the first 10 years of follow-up with apparent subsequent flattening.[9–19] This apparent stabilization may be related to a higher mortality in those patients with higher damage, which may attenuate the mean total damage scores in the population over time.[3]

Organ damage distribution in the different systems

Damage in early stage of the disease

The most common early damage reported in different cohorts occurs in the NP[9,10,15,16,18,21–23] and in the MSK systems.[9,16,22] The occurrence of damage in the NP system is probably corticosteroid-related while the occurrence of MSK damage has been definitely related to corticosteroids; this is the case for osteonecrosis, osteoporosis with fractures or vertebral collapse, while the presence of deforming arthritis is mostly due to the disease itself.[10,22] These findings may reflect a deleterious impact of high-dose corticosteroids used to abate the high lupus activity even in early stages of the disease.

Stoll, et al in a British cohort observed that one year after the SLE diagnosis the most common early organ damage occurred in the MSK system (11.3%) and in the NP system (7.5%).[9] Similarly, in another British study, Chambers et al. found that one year after the SLE diagnosis the most common early damage occurred in the NP (2.6%) and in the MSK systems (2.2%) with stroke and deforming/erosive arthritis as the main contributors of these types of damage, respectively.[16]

In the LUMINA cohort, the most frequent types of organ damage in patients with disease duration of ≤5 years at enrollment were NP (14%) and skin damage (9%).[21] Cognitive impairment was the most common item among those patients with NP damage whereas alopecia and skin scarring were the most frequent items among those with skin damage. Hispanics were more likely than African Americans and Caucasians to present cognitive impairment whereas African Americans exhibited alopecia and skin scarring more frequently than either Hispanics or Caucasians at both enrollment and last visits.[21]

In the Toronto Lupus cohort, where the majority of the patients were Caucasians, the most common early organ damage (disease duration <1 year) occurred in the CV system (9.5%) and it was mostly due to angina, myocardial infarction and valvular heart disease. The second most common early damage occurred in the NP system (6.9%) and it was mostly due to seizures that required prolonged anticonvulsant treatment.[10]

On the other hand, in an Argentine population of lupus patients, the most frequent types of early organ damage were renal (35.9%) and NP (22.4%). Renal damage was mainly attributed to proteinuria and decreased creatinine clearance while stroke and cognitive impairment were responsible for the earliest NP damage.[15]

In the Hopkins Lupus Cohort, when evaluating the first organ damage events by organ system, MSK (20.3%) and ocular damage (15.8%), were the most frequent types of organ damage and they were mostly due to osteoporotic fractures and cataracts, respectively. These results suggest that corticosteroid-related damage may be present prior to any other type of organ damage in SLE patients over time.[22]

In an Italian study with a predominantly Caucasian population, the most damaged systems one year after diagnosis were

Table 2 – Data from longitudinal studies on damage: The Systemic Lupus International Collaborating Clinics / American College of Rheumatology (SLICC/ACR) Damage Index (SDI)*

Author; year (Ref)	Country	Ethnicity (%)	Disease duration at baseline	Follow-up duration	Baseline SDI (SD)	Last SDI (SDI)	Damage prevalence (year of follow-up: %)
Stoll et al., 1996 (9)	United Kingdom	Caucasian (66.3%) Afro-Caribbean (18.8%) Asian (11.3%) Mixed ethnic origin (3.8%)	Not reported Inception cohort	1 year 5 years 10 years	0.4 (0-3) at 1 year	1.5 (0.5) at 10 years	1 year: 32.5% 5 years: 51.3% 10 years: 67.6%
Gladman et al., 2003 (10)	Canada Toronto Lupus Cohort	Caucasian (87.7%) Black (6.9%)	Inception cohort	< 1 year 5 years 10 years 15 years	0.33 (0.89)	1.9 (1.99) at 15 years	Not reported
Alarcón et al., 2004 (11)	United States (LUMINA)	Hispanic (23.3%) African-American (43.5%) Caucasian (32.2%)	Inception cohort ≤ 5 years	1 year 2 years 3 years 4 years 5 years 6 years	0.8 (0.1)	2.2 (0.4) at 6 years	Not reported
Ruiz-Irastorza et al., 2004 (12)	Spain	White (100%)	Inception cohort	1 year 10 years 15 years	0 (0-5)	2 (0-6) at 15 years	1 year: 36% 5 years: 55% 10 years: 66% 15 years: 79%
Becker-Merok et al., 2006 (13)	Norway	Caucasian (97%)	27.3 months (0-283)	1 year 5 years 10 years	Patients ≤ 40 years old at diagnosis 0.5 (0.0) Patients > 40 years old at diagnosis 0.38 (0.0)	1 year: 3% 5 years: 42% 10 years: 62% 0.97 (1.0) 1.23 (1.0) at 10 years	
Bandeira et al., 2006 (14)	Italy and Brazil	Caucasian (81%) Brazilian (19%)	Juvenile SLE patients enrolled within 12 months of SLE diagnosis	1 year 3 years 5 years	0.1 (0.5)	1.5 (1.9) at 5 years	1 year: 8.8% 3 years: 50.9% 5 years: 56.4%
Cassano et al., 2007 (15)	Argentina	Not reported	7.6 ± 5.7 years	1 year 2 years 5 years 10 years	0.52 (0.9)	2.46 (2.1) at 10 years	1 year: 36% 2 years: 46% 5 years: 64% 10 years: 81%
Chambers et al., 2009 (16)	United Kingdom	White (72%) Black (14%) Indo Asians (10%) Others (4%)	Follow-up from diagnosis	1 year 5 years 10 years 15 years 20 years 25 years	0.11	1.26 at 20 years 2.17 at 25 years†	1 year: 10% 5 years: 33% 10 years: 51% 15 years: 55% 20 years: 65% 25 years: 100%†
Urowitz et al., 2012 (17)	SLICC inception cohort; International registry from 27 centers in North America, Europe and Asia	White (55%) African American (12%) Asian (14%) Hispanic (16%) Others (2%)	Inception cohort, mean disease duration: 5.5 ± 4.1 months	0 year 1 year 2 years 3 years 4 years 5 years	0.17 (0.57)	1.01 (1.34) at 5 years	0 year: 11.1% 1 year: 32.2% 2 years: 36.9% 3 years: 41.3% 4 years: 45.0% 5 years: 49.7%

Table 2 (*Continued*)

Author; year (Ref)	Country	Ethnicity (%)	Disease duration at baseline	Follow-up duration	Baseline SDI (SD)	Last SDI (SDI)	Damage prevalence (year of follow-up: %)
Taraborelli et al., 2017 (18)	Italy	Caucasian (95%)	Follow-up from diagnosis	1 year 5 years 10 years 35 years	0.6 (0.89)	0.9 (1.19) at 5 years 3.7 (1.5) at 35 years ‡	1 year: 40% 5 years: 56% 10 years: 70% 35% years: 94%‡
Lim et al., 2020 (19)	Malaysia	Malay (61.7%) Chinese (28.4%) Indian (6.4%) Others (3.5%)	Pediatric SLE cohort Onset of symptoms to diagnosis: 2 months (1-4) Diagnosis to data collection: 6.3 years (3.6-9.0)	1 year 5 years 10 years	0.4	1.9 at 10 years	1 year: 31.9% 5 years: 50.0% 10 years: 60.0%

* Median (SD) SDI reported
† Only 5 patients with 25 years of follow-up
‡ Only 10 patients with 35 years of follow-up

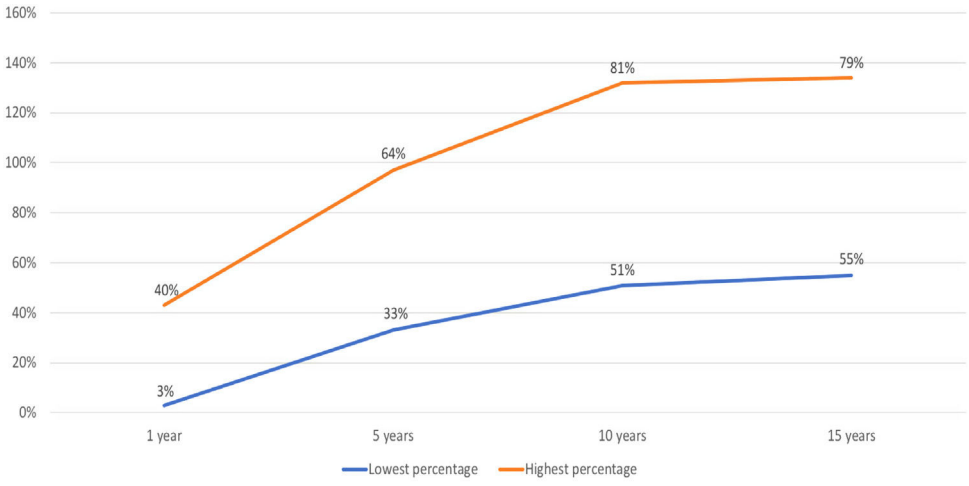

Figure 2 – Frequency of damage accrual over time in longitudinal studies.[9–19].

ocular (13%) and NP (12%).[18] Ocular damage was attributed to the occurrence of cataracts that were explained by the use of fluocortolone, a steroid that was frequently used in Italy until the early 2000s. In this study, antiphospholipid syndrome (APS) and anticardiolipin (aCL) antibodies played a role in the development of NP damage.[18]

In Colombian SLE patients followed during 31.5 months, NP (13%) and renal (6.8%) were the most frequent types of organ damage. Antiphospholipid (APL) antibodies, the number of flares, and a daily prednisone dose >7.5 mg had a significant impact on damage occurrence.[23]

Damage in the late stages of the disease

After 10 years or more of follow-up of two British cohorts, and one Argentine study, organ damage was more frequently found in the kidneys, the MSK and the NP systems.[9,15,16] Stoll, et al. and Chambers, et al., after 10 and 15 years of follow-up, respectively, found that renal damage (32.4% and 14%, respectively) and MSK damage (22.1% and 21.7%, respectively) were the most frequent types of organ damage in the British SLE population.[9,16] Chambers, et al. observed that half of the patients who developed renal damage had a glomerular filtration rate <50%, while 30% of these patients went on to develop end-stage renal disease. They also found that 50% of MSK damage was attributed to deforming/erosive arthritis, whereas 32% was due to muscle atrophy or weakness and the remainder was attributed to osteoporosis with fracture and avascular necrosis.[16] The findings in this study reflect that in late stages of the disease, both, the disease itself (renal damage, and deforming/erosive arthritis) and corticosteroid therapy (muscle atrophy, osteoporosis with fracture and avascular necrosis) contribute to damage accrual in a similar proportion.

Cassano, et al. found that over a ten-year follow-up, the renal system was the most frequent type of damage (23.4%)

mainly due to proteinuria.[15] CV (14.8%), NP (14.3%) and MSK (14.0%) were the most frequently affected systems in this study with a 10-year follow-up. CV damage was mostly due to pericarditis and valvular heart disease; NP damage was attributed to cognitive impairment, psychosis, and stroke, and MSK damage was mostly due to avascular necrosis. After 10 years of follow-up, the impact of the disease on damage accrual was mostly reflected in the renal system, but also in the CV and NP systems; whereas corticosteroid-associated damage mainly affected the MSK system.[15]

In a cross-sectional study of Colombian SLE patients with a mean disease duration of 10.5 ± 8.8 years, NP (20.2%), renal (11%), and peripheral vascular (11%) were the most frequent types of organ damage.[24] In another cross-sectional study of Brazilian SLE patients with a median disease duration of 10.6 (1.5-28.8) years, the pattern of damage distribution included the skin (50.5%) and MSK (35.2%) as the most commonly affected domains. Excessive sunlight exposure may explain the high frequency of skin damage in this population.[25] Similarly, in Cuban SLE patients with a mean disease duration of 8.2 ± 5.3 years, MSK (18.8%) and skin (16.3%) were the most frequent types of organ damage. Skin damage was also attributed to too much sunlight exposure in the Caribbean region.[26]

In the LUMINA cohort, NP (20%), renal (16%) and ocular (15%) were the most common organ systems damaged at last visit. Cognitive impairment, proteinuria, and cataracts, respectively, were the main damage contributors in these organ systems, which confirms the multifactorial nature of damage, in which both corticosteroids and disease activity play a role.[21] On the other hand, in the Hopkins Lupus Cohort the most common types of organ damage occurring over time were MSK (20.3%) and ocular damage (15.8%), with osteoporotic fractures and cataracts representing 12.4% and 13.4% of the total number of organ damage events, respectively. These results suggest the risk of developing corticosteroid-associated damage, particularly affecting the MSK and ocular systems.[22]

In the Toronto Lupus Cohort, 15 years after diagnosis, more than half of the patients had already developed MSK damage (54.7%). This was mostly due to a progressive increase in number of patients with avascular necrosis, deforming arthritis and muscle atrophy. Ocular damage (31.5%) was the second most common type of organ damage and it was attributed to an increase in the occurrence of cataracts after 5 years.[10]

Taraborelli et al, observed that the CV system was relevant after five years of follow-up, reaching 20% of affected patients at 35 years. However, ocular, MSK and NP systems (40% each) were the most frequent types of organ damage at 35 years of follow-up.[18] The occurrence of damage in these systems was attributed to the higher prevalence of cataracts, osteoporotic fractures, and stroke as part of APS, respectively.[18] The cumulative occurrence of the most common organ systems damaged over time in different cohorts is summarized in Table 3.

Risk factors for developing organ damage

Age at diagnosis. The association between older age at SLE diagnosis and the occurrence of damage has been reported.[27–32]

Karlson et al. in a US cohort of SLE patients balanced in terms of ethnicity and socioeconomic status to minimize confounding, found an association between older age at SLE diagnosis and cumulative organ damage.[27] Similarly, in the Toronto Lupus Cohort, age at SLE diagnosis was a strong predictor of damage occurrence after adjusting for potential confounders.[28]

Maddison et al.[29] compared SLE patients diagnosed after 54 years of age (late-onset SLE) versus patients diagnosed before age 40 (younger-onset SLE). SDI scores were higher in the late-onset group, both one and five years after diagnosis. However, the rate of damage accumulation over five years, was not significantly different between the two groups.[29] In contrast, Becker-Merok and Nossent found no difference in SDI scores, between patients aged ≤ 40 at diagnosis and those diagnosed after 40, after one, five, and 10 years of follow-up.[13]

Appenzeller et al., compared SLE patients who developed SLE at age 49 or older (late-onset SLE) with patients younger than 49 years at SLE diagnosis and found that late-onset SLE patients had significantly higher SDI scores. They also observed a correlation between SDI scores and age of disease onset in the late-onset group.[30] Similarly, in a nested case–control study within the LUMINA cohort, late-onset lupus (age at diagnosis ≥50 years) was independently associated with both damage accrual and any damage at last visit.[31] Pinto-Peñaranda et al., also found that patients ≥50 years old at diagnosis accrued damage three times faster than those diagnosed between the ages of 16 and 25.[23]

Older age and disease duration. Age and disease duration are closely correlated as one may be a confounder or a proxy for the other.[3] It is logical that the longer someone has lupus the higher the likelihood of developing damage, due to both the disease itself and the effects of treatment. Thus, it is expected that disease duration would be associated with the occurrence of damage.[27,28,33–35]

The association between older age and SDI scores, has also been identified in different lupus cohorts[11,20,21] In the Hopkins Lupus Cohort, older age along with hypertension and current corticosteroid dosage emerged as the strongest predictors of damage in the multivariable analysis.[20]

In the LUMINA cohort, using a Poisson regression analysis adjusted for disease duration, older age was found to be an independent predictor of SDI at the last visit.[21] In another study from the LUMINA cohort, data from a longitudinal analysis also found that older age was a significant predictor of damage accrual along with previous damage, disease activity, and corticosteroid use.[11]

In the SLICC Inception Cohort, older age was associated with both the development of damage in patients without damage at baseline, as well as the progression of damage in

Table 3 – Cumulative occurrence of the most frequent types of organ damage over time in different longitudinal cohort studies.

Author (Ref); year, country					Follow-up time			
Stoll, et al (9); 1996, United Kingdom					n = 80 patients			
	1 year	%	5 years	%	10 years	%		
	Musculoskeletal	11.3	Renal	17.1	Renal	32.4		
	Neuropsychiatric	7.5	Neuropsychiatric	13.2	Neuropsychiatric	22.1		
	Renal	5	Musculoskeletal	13.2	Musculoskeletal	22.1		
	Pulmonary	5	Peripheral vascular	6.6	Peripheral vascular	10.3		
	Skin	3.8	Skin	6.6	Cardiovascular	8.8		
Alarcón, et al (21); 2001, United States (The LUMINA cohort)					n = 258 patients			
	At baseline	Mean disease duration: 20.1 ± 16.9 months		%	At last visit	Mean disease duration: 61.3 ± 27.7 months		%
	Neuropsychiatric			14	Neuropsychiatric			20
	Skin			9	Renal			16
	Renal			7	Ocular			15
	Ocular			6	Skin			13
	Pulmonary			5	Musculoskeletal			12
Gladman, et al (10); 2003, Canada (The Toronto Lupus Cohort)					n = 73 patients			
	< 1 year	%	5 years	%	10 years	%	15 years	%
	Cardiovascular	9.5	Musculoskeletal	21.8	Musculoskeletal	31.5	Musculoskeletal	54.7
	Neuropsychiatric	6.9	Cardiovascular	13.7	Cardiovascular	16.4	Ocular	31.5
	Gastrointestinal	5.5	Neuropsychiatric	12.3	Ocular	15.1	Cardiovascular	28.7
	Skin	4.1	Skin	8.2	Neuropsychiatric	12.3	Neuropsychiatric	20.5
	Musculoskeletal	2.8	Ocular	8.2	Skin	11	Skin	13.7

Table 3 (*Continued*)

Cassano, et al (15); 2007, Argentina					n = 197 patients			
	1 year	%	5 years*		%	10 years†		%
	Renal	35.9		Renal	23.2	Renal		23.4
	Neuropsychiatric	22.4	Musculoskeletal		17.5	Cardiovascular		14.8
	Cardiovascular	14.6	Cardiovascular		12.5	Neuropsychiatric		14.3
	Skin	9.7	Neuropsychiatric		12.4	Musculoskeletal		14.0
	Peripheral vascular	7.8	Ocular		8.6	Skin		8.6
Chambers, et al (16); 2009, United Kingdom					n = 232 patients			
	1 year		5 years		10 years		15 years‡	
	Neuropsychiatric	2.6	Neuropsychiatric	11.2	Neuropsychiatric	14.7	Musculoskeletal	21.7
	Musculoskeletal	2.2	Renal	6.9	Renal	12.9	Renal	14.0
	Skin	2.2	Musculoskeletal	5.6	Musculoskeletal	12.1	Neuropsychiatric	12.5
	Gastrointestinal	1.7	Skin	3.9	Skin	5.2	Peripheral vascular	8.4
	Peripheral vascular	0.9	Peripheral vascular	3.4	Peripheral vascular	4.7	Cardiovascular	7.7
Al Sawah, et al (22); 2015, United States (The Hopkins Lupus Cohort)				n = 2265 patients followed between 1987 and 2012				
	First organ damage (n = 826)			%§	Any organ damage (n = 1428)			%a
	Musculoskeletal			20.3	Musculoskeletal			20.3
	Ocular			16.3	Ocular			15.8
	Neuropsychiatric			15.5	Neuropsychiatric			13.4
	Pulmonary			11.4	Pulmonary			11.6
	Cardiovascular			6.6	Cardiovascular			9.0
Taraborelli, et al (18); 2017, Italy					n = 511 patients			
	1 year			%	35 years			%
	Ocular			13	Ocular			40
	Neuropsychiatric			12	Neuropsychiatric			40
	Skin			8	Musculoskeletal			40

* At five years there were 123 patients on follow-up
† at 10 years there were 52 patients on follow-up
‡ at 15 years there were 143 patients on follow-up
§ % from the total of patients who developed first organ damage
a % from the total of patients who developed any organ damage; LUMINA (Lupus in Minority populations, Nature versus nurture)

patients with damage at baseline. The investigators from the SLICC cohort found a non-linear effect of age, with the effect of aging being most pronounced in older patients. For example, some damage items such as cataracts, osteoporosis, coronary artery disease, and stroke are more frequent as the general population ages. Thus, older SLE patients may be more sensitive to the additional effects of SLE and treatment adverse effects due to reduced organ reserve.[36]

The effect of age on damage seems to be independent of disease duration. In fact, when both disease duration and age are examined together, these variables independently influence damage. For example, in a multiethnic Canadian cohort, older age and longer disease duration were included in the final regression model ($R^2 = 0.27$) for higher damage score which also included higher disease activity, current prednisone treatment, cyclophosphamide treatment, and low income.[34] Karlson et al, found that older age at diagnosis and longer disease duration independently predicted the occurrence of damage in a multivariate model that also included lower caloric intake, higher disease activity at diagnosis, and lower occupational prestige at diagnosis as predictors of organ damage.[27] Similarly, data from the Peruvian Almenara Lupus Cohort showed that age at diagnosis and disease duration were independently associated with new damage occurrence.[32]

Gender. Male gender is also a predictor of damage. Using data from the LUMINA cohort, Andrade et al. assessed the impact of patient's gender on SLE outcome. They found that male gender is a strong predictor of baseline damage and is a predictive factor of further damage over the course of the disease, but particularly, early on. The accelerated accrual of damage in male SLE patients may partly be explained by the shorter time to diagnosis observed among these patients and also by the higher frequency of abnormal health behaviors.[37] Moreover, Bruce et al, also found higher rates of no damage-to-damage changes among males, but not in the progression from baseline damage to increased damage.[36]

Ethnicity. Different studies have shown that damage accrual is higher among non-Caucasian populations. For example, in a British lupus cohort, significantly higher SDI scores at five and 10 years, and higher renal damage score at 10 years, were observed in Afro-Caribbean and Asian populations as compared to Caucasians.[9] Maddison et al, also found higher SDI scores in non-white patients compared to white patients at one and five years after SLE diagnosis.[29]

In the LUMINA cohort, the baseline SDI scores were significantly higher in African Americans compared with Hispanics (from Texas and Puerto Rico), and Caucasians; likewise, the proportion of patients with some baseline damage was significantly higher in African Americans (49%) than in Texan Hispanics (37%), Puerto Rican Hispanics (23%), and Caucasians (40%). At last visit, about 10 years after enrollment, Texan Hispanics and African Americans had accumulated more damage than Caucasians and Puerto Rican Hispanics and the proportion of patients with SDI >0 was higher in African Americans (74%) and Texan Hispanics (70%) than in Caucasians (58%) and Puerto Rican Hispanics (37%).[38] When examining only patients who had yet to accrue any damage, the rate of damage accrual among Texan Hispanics was faster than in patients from the other ethnic groups.[39]

Bruce et al., reported that compared to Caucasians from Europe or Canada, USA patients of African ancestry had a higher risk of progressing from no damage to damage, while Asians had a lower risk of developing damage. USA patients of African ancestry, also had a higher risk of progressing from baseline damage to higher damage when compared with Caucasians in Europe or Canada.[36]

Disease activity. Longitudinal studies have shown the contribution of disease activity to organ damage accrual.[11,21,22,36,39–44] Disease activity *per se* can lead to organ damage if not properly treated. However, there may be some confounding factors such as drug therapy, which may lead to organ damage.[40] In this context, Bruce found a significant interaction between the SLEDAI-2K and corticosteroid use for transition from no damage to new damage, suggesting that the association between disease activity and evolution to damage is stronger in patients taking corticosteroids. SLEDAI-2K score was also significantly associated with both, the development of damage in patients without damage at baseline as well as the progression from baseline damage to greater damage.[36]

In the LUMINA cohort, disease activity [measured with the Systemic Lupus Activity Measure (SLAM)] was shown to independently contribute to damage accrual.[21] Higher disease activity was also a predictor for shorter time to the occurrence of initial damage along with Texan Hispanic ethnicity, thrombotic events, and prednisone dose of < 10 mg/d.[39] Similarly, Stoll et al. found that over 5 years, high disease activity [measured with the British Isles Lupus Assessment Group (BILAG) index] over the entire period of study or the average number of A-flares, were both predictors of an "adverse outcome" defined as mortality or increase in damage scores. Thus, patients with increased damage had higher total BILAG scores and a higher number of A-flares.[41] Becker Merok and Nossent found that over 11.9 years of follow-up, patients who accrued damage had significantly higher baseline SLEDAI scores and higher weighted average SLEDAI scores.[13] Lopez et al., also showed that disease activity as measured by global BILAG score during a 12-month observation period predicted the risk of subsequent organ damage after adjustment for other potential predictive factors such as age, gender, disease duration, pre-existing damage and drug therapy.[42]

Data from Latin American Group for the Study of Lupus (GLADEL, *Grupo Latino Americano de Estudio del Lupus*) revealed that the number of flares, regardless of severity, increases the risk of damage accrual independently of other known risk factors, while remission and low disease activity decreased the risk of new and severe new damage.[43,44]

Corticosteroids. Corticosteroid treatment is an important contributor to damage accrual in SLE patients.[10,11,20–23,28,34,36] Some complications associated with corticosteroid therapy are reversible (e.g., diabetes, hypertension, obesity) while others (e.g., avascular necrosis, osteoporotic fractures, and cataracts) constitute irreversible damage.[10] In an inception lupus cohort, Gladman et al. categorized the SDI items according whether they were definitively (ocular, MSK), possibly (CV, peripheral vascular disease, NP, diabetes) or independently (renal, pulmonary, gastrointestinal, skin, premature gonadal failure, malignancy) associated with corticosteroid use. Overall, a significant proportion of damage was possibly

or definitely attributed to corticosteroid therapy over the first year of SLE (58%) and after 15 years (80%).[10]

The contribution of corticosteroid therapy to the risk of organ damage in lupus was assessed in the Hopkins Lupus Cohort.[22,45,46] The research team found that organ damage was associated with cumulative prednisone dose (osteoporotic fractures, coronary artery disease, cataracts), high-dose prednisone (avascular necrosis, stroke), and pulse methylprednisolone (cognitive dysfunction). The cumulative corticosteroid dose was most strongly associated with osteoporotic fractures with a 2.5 increased risk per each decade of prednisone at 10 mg/day. The association between cumulative prednisone dose and an increased risk of coronary artery disease is probably due to increased corticosteroid-associated atherosclerotic risk factors (hypertension, hypercholesterolemia, diabetes mellitus and obesity).[45] Another study from the Hopkins Lupus Cohort showed that the risk of developing damage increases about 50% with an average cumulative prednisone dose of ≥6-12 mg/day, compared with little risk with the average cumulative doses of prednisone <6 mg/day.[46] The risk of corticosteroid use on overall damage was also quantified by dose cut-off points. Patients exposed to higher prednisone doses (≥7.5 mg/day) during follow-up were significantly more likely to develop any new organ damage over time than those who received <7.5 mg/day. Prednisone doses ≥7.5 mg/day also increased the risk of developing cataracts, osteoporotic fractures and CV damage. Furthermore, patients exposed to a mean prior prednisone dose ≥20 mg/day were twice more likely to develop damage than those treated with <7.5 mg/day, whereas a reduction of 1 mg/day in mean prednisone dose reduces the risk of future damage by 3%.[22]

In the LUMINA cohort, the influence of corticosteroids on damage accrual was also demonstrated.[21,38,39] Early analysis of the cohort showed that the maximum corticosteroid dose along with Texan Hispanic ethnicity, older age, number of ACR criteria met, disease activity, abnormal illness-related behaviors, poverty, and acute-onset lupus were independent predictors of damage accrual.[21] When assessing predisposing factors to initial damage, prednisone dose <10 mg/day was significantly associated with a shorter time-to-initial damage, while a prednisone dose of 10-30 mg/day was associated with a longer time-to-initial damage. This finding suggests a protective effect of moderate prednisone doses; however, as treatment duration was not ascertained, it is possible that this result applies only to patients who received this range of prednisone dose for a relative short, rather than a long, period of time.[39]

In the SLICC cohort, corticosteroid treatment was also significantly associated with the development of damage in patients free of damage at baseline and with the progression of damage in patients with baseline damage.[36]

Immunosuppressants. Among the immunosuppressants, cyclophosphamide has been associated with higher SDI scores. Cyclophosphamide may contribute to damage through its specific side effects such as malignancies and premature gonadal failure; however these manifestations are not common among the types of organ damage.[22,35] Thus, such association may reflect the fact that cyclophosphamide is often administered to patients with severe, life-threatening disease and a high percentage of them develop organ damage.[35]

Peschken et al. found that the most important variables for a damage prediction model were older age, longer disease duration, low income, prednisone treatment, higher disease activity, and cyclophosphamide use. However, the authors indicated that cyclophosphamide in this model may reflect disease severity rather than a causal association between treatment and damage, since the analyses were performed in a prevalent cohort where past treatment patterns and the timing of damage accrual were unknown.[34] Ravelli et al. reported that an increasing number of cyclophosphamide pulses was strongly associated with the presence of damage in juvenile-onset SLE. Again, the authors considered that this association may reflect a higher frequency of damage in more severely affected patients rather than specific side effects of the medication.[33]

Previous damage. Damage has been found to be a predictor of further damage by several investigators.[11,22,47] Once damage occurs in SLE, further damage ensues, specially if disease activity persists.[11] Moreover, the rate of damage accrual is higher in patients with existing damage.[3]

Metabolic syndrome. In SLE patients, the metabolic syndrome has been associated with CV events, and with organ damage at baseline and damage accrual subsequentently.[48–52] In addition to CV complications, baseline metabolic syndrome has been strongly associated with renal and endocrine (diabetes mellitus) damage.[51] Moreover, the presence of diabetes mellitus in SLE patients has been associated with a shorter time to the development of NP damage.[53]

Other risk factors. Ruiz-Irastorza et al. reported that the presence of APL antibodies was an independent predictor of damage (SDI ≥1) and was independently associated with severe damage (SDI >2) at five years.[54] Similarly, Pinto-Peñaranda et al. found that APL antibodies were also predictors of damage occurrence in Colombian SLE patients. This finding probably explains why NP damage was the most frequent type of organ damage and stroke was its main contributor in this population.[23] In fact, APL antibodies have been found to be independent predictors of NP damage.[55] The presence of anti-dsDNA, anti-Smith, and anti-Ro was also associated with higher SDI scores in Puerto Rican SLE patients.[56] Other factors associated with damage included hypertension,[20,23,35,36] number of ACR criteria met,[21,38] abnormal illness-related behaviors,[21] poverty,[38] and higher serum uric acid levels.[32]

The SLICC frailty index (FI)

Recently, using data from the SLICC inception cohort a frailty index (SLICC-FI) as a measure of vulnerability to adverse outcomes among SLE patients has been developed.[57] In this inception cohort, higher baseline SLICC-FI values predicted damage accrual in incident SLE, supporting the fact that this instrument is a valid health measure for identifying SLE patients who are at increased risk of developing significant organ damage.[58]

Protective effect of antimalarials on the risk of damage accrual

Antimalarials protect SLE patients from damage accrual.[36,59,60] In a nested case-control study, in an inception cohort from the University of Toronto Lupus Clinic, hydroxychloroquine (HCQ) use was associated with less damage at 3 years after SLE diagnosis, after adjusting for disease duration, disease activity, steroid dose, and calendar year of diagnosis.[59] In the LUMINA cohort, Fessler et al. after a propensity score (PS) adjustment for differences between HCQ users and non-users, found that HCQ usage may prevent the occurrence of damage, particularly in patients who had not yet accrued any damage.[60] Furthermore, in the SLICC inception cohort, antimalarial use was associated with reduced damage progression, particularly in patients with baseline damage.[36] This protective effect of antimalarials against damage development is probably due to their role in preventing disease flares, their corticosteroid-sparing properties, and their favorable effects on different metabolic risk factors.

Effects of belimumab on damage development. Belimumab has beneficial effects on long-term damage development.[61,62] The results of two ongoing continuation studies that enrolled SLE patients who completed the Belimumab trials BLISS-52 or BLISS-76 showed low rates of organ damage accrual.[61] These rates were lower than those reported in other cohorts.[11,36] The mean change from baseline in SDI score was 0.2 at years 5-6, and 85.1% of patients had no changes in their SDI score.[61] The lower rate of damage accrual in this population may be due to the exclusion of patients expected to have higher rates of damage accrual such as those with lupus nephritis and CNS disease.[61] Urowitz et al., compared organ damage progression in SLE patients treated with belimumab in the BLISS long-term extension trial with PS-matched patients treated with standard SLE therapy from the Toronto Lupus Cohort. They found that PS-matched patients receiving belimumab had significantly less organ damage progression compared to patients receiving standard SLE therapy.[62] These effects of belimumab on damage accrual may be partly due to its role in reducing flares and its glucocorticoid-sparing effects.

Organ damage and health-related quality of life (HRQoL) in SLE

Although impaired HRQoL is consistently demonstrated in SLE patients, there is some debate about whether it is associated with organ damage, in light of the conflicting results reported in different cross-sectional studies.[63] For example, in studies from China,[64] USA,[65] Perú,[66] and Mexico,[67] higher damage was found to be associated with lower HRQoL, but in Canadian studies such association was not found.[68,69] The poor correlation between HRQoL and damage accrual suggests that variables other than those directly attributable to damage have a significant impact on patients perceived QoL; for example, SLE patients with fibromyalgia may not have any accrued damage, but, they may have poorer HRQoL than SLE patients without fibromyalgia.[63,68] Recently, a meta-analysis that explored the relationship between organ damage and HRQoL in SLE patients, found negative correlations between damage and the domains of the short 36 Health Survey (SF-36) and the Lupus Patient-Reported Outcome (LupusPRO). Organ damage was more negatively correlated with the physical component summary, compared to the mental component summary of the SF-36.[70]

Organ damage and mortality in SLE

A systematic review with a meta-analysis of high-quality studies from around the world showed a consistent association between organ damage in SLE and increased mortality. Twenty-one longitudinal cohort studies evaluating the association between organ damage and mortality in SLE patients were selected. The meta-analysis of 10 studies that evaluated SDI as a continuous variable found that each 1-unit increase in SDI was associated with a 34% increased risk of death. The 11 remaining studies, excluded from the meta-analysis because of their varying populations and analyses, consistently identified an association between increasing organ damage and higher mortality.[71]

In the Toronto Lupus Cohort, early damage was associated with a lower 10-year survival. Twenty-five percent of lupus patients who exhibited early damage died within 10 years of the disease, versus only 7.3% with no early damage.[72] Data from LUMINA showed that poverty, disease activity, and organ damage are strong predictors of mortality in lupus patients.[73] In addition, renal damage was the strongest damage domain predictive of poor survival in SLE.[74]

Prevention of damage

Since damage is a predictor of subsequent damage and death, the Treat-to-Target-in-SLE working group highlighted that prevention of damage accrual should be a major therapeutic goal in SLE.[75] Damage development is determined by different factors that can be divided into the potentially modifiable (corticosteroids, disease activity, and hypertension) and the non-modifiable (age at disease onset, gender, disease duration, and ethnicity).[3] Therefore, if a patient is at risk of damage, early measures must be taken to prevent the development of damage in those free of damage at baseline, as well as the progression of damage in patients with baseline damage.

Thus, a multidimensional approach to damage prevention has been suggested based on a better control of disease activity, the prevention of flares, minimizing or if possible withdrawal of corticosteroid doses, and the use of antimalarials from disease onset, and close hypertension control.[36,75]

Since a significant interaction between disease activity and corticosteroid treatment in the development of new damage has been shown, novel SLE therapies for improved control of the disease in addition to their corticosteroid-sparing properties would be clinically important for reducing organ damage in lupus patients.

Conclusions

SLE damage accumulates over time and predicts further damage and mortality. Thus, patients at risk of damage must be identified early on. Modifying the course of the disease with effective and corticosteroid-sparing therapies will reduce damage accrual and lower the mortality in SLE patients. Additionally, due to the beneficial effects of antimalarials, these should be considered in all SLE patients unless contraindicated. Finally, since comorbidities also contribute to the development of damage, adjunctive therapies (antihypertensives, lipid-lowering agents, bone-protecting agents and antiplatelet/anticoagulants) should also be considered in SLE patients.

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Appendix A. Supplementary material

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