The second hit: comorbidities in systemic lupus erythematosus

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Patients with systemic lupus erythematosus (SLE) now benefit from an improved life expectancy. As this multisystem autoimmune disorder progressively became a chronic disease over the last few decades, we gradually realized that this more favorable prognosis came at a price: the occurrence of comorbidities. The main comorbidities recognized in SLE patients include cardiovascular disease, osteoporosis and malignancies. As these conditions now represent a significant proportion of the morbidity and mortality associated with SLE, it is important to understand them better in order to appropriately screen for them, or even to try preventing them. We will, in this article, review the current literature on these three complications, which can be an unfortunate 'second hit' for patients suffering from an already complex illness.

"I stood outside the examining room for several minutes re-reading the result of the CT scan … trying to see if I could somehow attribute these findings to lupus … knowing that it was probably cancer, and trying to think of the best way to break the news to my patient …"

These words reflect the thoughts of a clinician faced with the development of serious comorbidity in a patient with systemic lupus erythematosus (SLE). It is an unfortunate reality that SLE patients are burdened not only by the chronic, often life-threatening disorder itself, but also by one or more 'second hits' related to comorbid diseases. Some of the most important comorbid illnesses in SLE include cardiovascular disease (CVD), osteoporosis and malignancies. In this review, we discuss recent data related to the risk of a second hit due to these diseases in SLE.

Cardiovascular disease in SLE

Risk of cardiovascular disease in SLE

Early descriptive studies brought to light the possibility that SLE patients may be at increased risk of CVD, including coronary artery disease (CAD, consisting of angina and myocardial infarction) and stroke. It was in the mid-1970s, when we started to see an important improvement in the survival of lupus patients, that Urowitz and colleagues noted that mortality early in the disease course was often a consequence of active lupus, while late mortality was more commonly associated with the presence of CAD [1]. Later cohort studies have attempted to quantify this problem, and established that lupus patients have a prevalence of symptomatic CAD ranging between 6 and 12% [2–6]. When compared with age-matched groups from the general population, SLE patients have up to a 52-fold increase in their risk of CAD [3] and are more than twice as likely to be admitted to hospital for myocardial infarction, congestive heart failure or stroke, especially in the age group 18–44 years [7]. After adjusting for all traditional CAD risk factors, the risk of a first acute myocardial infarction by a SLE patient was in fact shown to be comparable to that of a patient with diabetes mellitus (DM) [8].

Lupus investigators have also examined for the presence of subclinical CVD. First, autopsy studies assessing for the presence of CVD in lupus patients have revealed that 30–50% of cases examined had evidence of moderate-to-severe coronary atherosclerosis [9–11]. Various noninvasive techniques were used to test for the presence of asymptomatic CVD. Studies using myocardial perfusion scintigraphy have revealed that up to 40% of SLE patients show some reversible perfusion anomalies [12,13]. Other studies using carotid ultrasonography, echocardiography, or electron beam computed tomography determination of coronary calcification have found higher rates of subclinical CVD compared with the general population [14–18]. It is essential to note that in addition to being a significant comorbidity in SLE patients, CVD now also represents a major cause of mortality in this patient population [19–21].

Contributors to the increased risk of cardiovascular disease in SLE

Factors that have been hypothesized to be potential contributors to the increased risk of CVD in SLE patients include traditional 'Framingham' risk factors (**Box 1**), medications used to treat

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Box 1. Traditional CVD risk factors.

Modifiable

- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Homocysteinemia
- Obesity
- Sedentary lifestyle

Nonmodifiable

- Older age
- Male sex
- Family history

SLE, autoantibodies, the presence of chronic inflammation, or the direct effects of lupus disease activity.

An important body of literature has examined the presence of traditional Framingham risk factors in the lupus population and has shown a high prevalence for many of them, including hypertension, hyperlipidemia, smoking, DM, obesity and sedentary lifestyle [2,4,14,15,22,23]. Despite these findings, it has become clear that traditional Framingham equations [5] or a modified Framingham risk score [17] are unable to fully account for the high risk of CAD in lupus. An early study on this subject by Rahman and colleagues compared the lupus patients with premature CAD with a cohort of patients who had premature CAD in the absence of SLE [24]. This study showed that female patients from the non-SLE cohort had an average of nearly three traditional CAD risk factors, while women with SLE on average had only two recognized risk factors, implying that there may be an unrecognized SLE-associated factor. A study by Esdaile and colleagues has examined this question further in a cohort of 296 SLE patients observed over a mean follow-up duration of 8.6 years [5]. They concluded that lupus patients had a significant risk of CVD that is not fully explained by the Framingham equations, again suggesting the presence of a lupus-related factor.

The use of glucocorticosteroids has been hypothesized to play a role in the development of CVD in lupus patients, with many studies (although not all) showing an association between them [2,4,14,15,22,23,25]. The proposed mechanisms by which glucocorticosteroids may produce their effect include increased rates of hypertension, hyperlipidemia, weight gain and DM. It is, however, clear that CVD occurs in the absence of glucocorticosteroid exposure [26]. Although the effect of glucocorticosteroids on dyslipidemia is clear, it is important to note that the use of antimalarials has been shown to prevent some of these negative effects [27]. There are little data regarding the use of immunosuppressive medications and CVD, but the study by Roman *et al.* indicated a possible protective effect, with less carotid plaque in patients receiving cyclophosphamide. Although this does suggests that the control of lupus activity may be important in curtailing CVD risk, it is unknown how different aspects of the underlying disease may influence outcome; for example, if lupus activity does affect CVD risk, might severe acute illness have effects that are different from chronic smoldering inflammation?

Autoantibodies are major contributors in the pathophysiology of many lupus manifestations. With regards to CVD, however, this mechanism does not appear to play a major role. Despite their association with valvular disease (mitral regurgitation, valve nodules or valve thickening), antiphospholipid antibodies (anticardiolipins, anti-β_2 microglobulin 1 and lupus anticoagulant) are not associated with CAD [28]. In fact, it is clear that CAD in lupus patients is not associated with focal thrombosis or vasculitis, but rather a process that is mainly related to accelerated atherosclerosis [25,29]. Anti-Ro/SSa antibodies have the potential to induce rhythm abnormalities and third-degree atrioventricular block in a subset of newborns with the neonatal lupus syndrome [30]. These antibodies have also been associated with rhythm anomalies, mostly QT prolongation, in adult SLE patients [31–33], but an association with CVD has not been established at this time.

With many observations pointing toward the possibility that a SLE-related factor may be implicated in the development of premature CVD in these patients, many investigators have examined measures of lupus disease activity and severity for possible associations. Studies of lupus disease activity, as measured by commonly used disease activity indices such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), have shown no association with the presence of symptomatic or asymptomatic CVD [6,12,14–16,18]. In addition, the association between CVD and markers of inflammation, such as high sensitivity C-reactive protein, erythrocyte sedimentation rate and fibrinogen, was evaluated in SLE patients with no conclusive result [15,34–38]. On the other hand, cumulative damage measured by the Systemic Lupus International Collaborating

Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) was shown to be strongly associated with CVD [6,12–16,18]. Although cumulative damage is recognized as a good marker of lupus disease severity, its association with disease duration, age, glucocorticosteroid use and other comorbidities precludes any conclusion regarding the role of SLE severity in the development of CVD.

Osteoporosis in SLE

Risk of abnormal bone mineralization

When compared with healthy peers, patients with SLE have a lower bone mineral density (BMD) and are at increased risk for fractures. By some estimates, the frequencies of osteopenia and osteoporosis in SLE are as high as 50.8 and 23%, respectively [39,40]. Early work demonstrated that compared with normal controls, premenopausal women with longstanding SLE and glucocorticosteroid exposure have significantly lower BMD at the lumbar spine and hip [41]. Another study, using BMD measurements of the lumbar spine and femur, detected osteoporosis in 22.6% of 84 premenopausal female SLE patients [42]. Pineau and colleagues studied 205 women with SLE and showed rates of 48.8 and 18%, respectively, for osteopenia and osteoporosis [43]. This study also highlighted the fact that subjects enrolled in these studies generally have more traditional risk factors for osteoporosis and more severe SLE.

Interestingly, some investigators have observed reduced BMD even early in the course of SLE. In one study, a group of 20 premenopausal women with SLE duration of less than 1 year were found, when compared with healthy women of a similar age, to have significantly lower BMD at the lumbar spine (although no group differences were seen at the femoral neck) [44].

There are very few longitudinal investigations of bone mass among SLE patients. In a 3-year prospective study, Kipen and colleagues [45] evaluated BMD changes in 32 premenopausal women with SLE and found significant changes in BMD at the lumbar spine only in women taking at least 7.5 mg of glucocorticosteroid per day. In a similar longitudinal study, Jardinet and coworkers studied 35 premenopausal women with SLE [46]; they found significantly lower baseline BMD at both the lumbar spine and hip, compared with healthy age-matched women. Over an average of 21 months, the SLE patients experienced significant decline in their lumbar spine BMD (1.22% per year), although not at the hip. One difference in the two study populations was a somewhat longer SLE duration in the Jardinet study.

Bone loss in SLE is heterogenous in terms of anatomical regions affected, as was shown in a 2-year longitudinal study of 48 women with SLE [47]. In women exposed to glucocorticosteroids, the greatest bone loss occurred at trabecular-rich sites, such as the lumbar spine, while sites of cortical-rich bone, such as the distal forearm, sustained the least bone loss. Over the course of the study, bone loss at the lateral lumbar spine, total hip and forearm were 5.5, 3.6, and 0.3%, respectively. Although data suggest glucocorticosteroid exposure to be a major contributor to bone loss in SLE, it has been difficult to identify other determinants, especially since glucocorticosteroid-naive patients comprise only a small proportion of all subjects assessed longitudinally.

Of course, BMD data need to be correlated with fracture occurrence, and only a few studies have addressed this important issue in SLE. In a large (n = 702) population-based female SLE cohort, 12.3% of women reported sustaining at least one fracture unrelated to severe trauma since the time of SLE diagnosis [48]. When compared with general population fracture rates from the US 1994 National Health Interview Survey, almost a fivefold increased fracture risk was observed in women with SLE. Furthermore, this elevated risk was seen even in relatively young women; SLE patients in the 25–44 year-old age group had more than three times the number of fractures expected to occur in the age- and sex-matched general population [48].

In a cross-sectional study of 242 SLE patients [39], fragility fractures occurred in 9.1% of all patients; of those with fractures, 81.8% were postmenopausal, and 90.9% had low BMD, (31.8% with T-scores in the osteoporotic range). Another study of vertebral radiographic findings in 107 SLE patients [49], found at least one vertebral fracture in 20% of the sample. Interestingly, 40% of the total sample were potential candidates for osteoporosis medications, but only 16% were using bisphosphonates.

With respect to ethnicity, Caucasian and Asian ethnicities are established traditional risk factors for osteoporosis, whereas African–American ethnicity is associated with comparatively higher peak bone mass in the general population. However, in a recent cross-sectional study of 77 African–American and 221 White women with SLE, African–American

ethnicity was associated with low BMD at the lumbar spine after accounting for relevant clinical factors [50]. Thus, the traditional relationship between ethnicity and BMD may be altered in the context of SLE.

Contributors to the increased risk of osteopenia & osteoporosis in SLE

Multiple factors contribute to reduced bone mass in SLE; likely both traditional osteoporosis risk factors (**Box 2**) [51] and SLE-related factors play key roles. Published studies have found a relationship between the factors mentioned in **Box 2** and decreased BMD [43,52–55]; of primary importance are age, Caucasian and Asian ethnicity, post-menopausal status, body weight and low levels of physical activity.

As indicated earlier, exposure to glucocorticosteroids is a major risk factor for osteoporosis [42–44,52,53,55–59], although not all studies have shown the expected association between glucocorticosteroids and osteoporosis in SLE patients [43,54,60–63]. In the second largest study (n = 205) of osteoporosis SLE, Pineau and coworkers [43] were unable to demonstrate an association between decreased BMD and use, mean dose or cumulative dose of glucocorticosteroids. In this study, the major determinants of low BMD were higher age and cumulative damage, as measured by the SLICC/ACR DI. Similarly, two studies by Becker *et al.* [54,63], a cross-sectional study of 64 and a longitudinal study of 86 SLE patients, were unable to demonstrate a link between mean or cumulative glucocorticosteroid dose and low BMD. Gordon *et al.* [59] were also unable to demonstrate an association between fractures and glucocorticosteroid use in SLE. These studies have to be interpreted with caution, since none of them had sufficient power to definitely establish an association between low BMD and glucocorticosteroid use.

The potential role of lupus disease activity and cumulative damage has been examined; one early study showed that SLE patients not exposed to glucocorticosteroids had a lower BMD than normal controls, thus suggesting that SLE alone is a risk factor [44]. No study to date has been able to definitely link lupus disease activity to osteoporosis, although Petri *et al.* [64] demonstrated a correlation between a surrogate of lupus disease activity, low serum complement level (C4) and osteoporotic fractures. There are on the other hand many studies that demonstrate an association between bone loss and cumulative damage [42,43,52,62,65] as measured by the SLICC/ACR DI. The damage index does itself correlate with lupus disease severity, and its association with bone loss (even after adjusting for glucocorticosteroid use) supports the hypothesis that lupus-specific factors potentially contribute to low BMD.

Box 2. Major and minor risks for the development of osteoporosis.

Major

- Female sex
- Age over 65 years
- Vertebral compression fracture
- Fragility fracture
- Osteopenia on plain film
- Family history of osteoporotic fracture
- Malabsorption syndrome
- Hyperparathyroidism
- Hypogonadism
- Menopause before age 45 years
- Glucocorticoids for >3 months
- Caucasian or Asian race

Minor

- Hyperthyroidism
- Chronic anticonvulsant use
- Chronic unfractionated heparin use
- Low dietary calcium
- Smoking
- Excessive alcohol or caffeine use
- Weight <57kg
- Weight reduction >10%
- Rheumatoid arthritis

Malignancy in SLE

Recent data regarding cancer occurrence in SLE

Data indicate a small increase in SLE regarding the incidence of all cancers combined, but a greatly elevated risk for hematological malignancies, particularly for non-Hodgkin's lymphoma (NHL). For example, in a recent international multicenter SLE cohort study of cancer risk, compared with the general population, the standardized incidence ratio (SIR) for hematological cancer was 3.64 (95% confidence interval [CI]: 2.63, 4.93) [66]. In addition, the study confirmed an increased risk of lung cancer (SIR: 1.37; 95% CI: 1.05, 1.76), and hepatobiliary cancer (SIR: 2.60; 95% CI: 1.25, 4.78). The histology of the lung cancer cases in that study resembled that of the general population, where adenocarcinoma predominates. The study did not focus on cervical dysplasia, but an increased risk of dysplasia in SLE has been established (especially after exposure to immunosuppressives) [67–70].

The same group examined the mortality risk due to malignancy in the international SLE cohort; an increased risk of death was seen for both NHL (standardized mortality ratio [SMR]: 2.8; 95% CI: 1.2, 5.6) and lung cancer (SMR: 2.3; 95% CI: 1.6, 3.0) [71].

The question of NHL incidence and autoimmune disease has been further studied in a case–control study of more than 3000 NHL cases from the general population [72]. Of these NHL cases, eight had a prior history of SLE, compared with two of the matched cancer-free controls; the adjusted odds ratio (OR) for SLE and NHL was 4.6 (95% CI: 1.0, 22). A recent meta-analysis suggests that, as well as an increase in NHL, Hodgkin's lymphoma (HL) is increased in SLE versus the general population; the pooled SIR estimate was 3.16 (95% CI: 1.63, 5.51) in that study [73]. An increased risk of HL in SLE was also documented in a study of administrative data from the general population of Denmark and Sweden [74]; here the OR for HL, given a past history of SLE, was 5.8 (95% CI: 2.2, 15.1).

Regarding other hematological malignancies, a recent case–control study did not identify a history of SLE as one of the risk factors for multiple myeloma [75], although other work has suggested that a family history of SLE increases multiple myeloma risk (OR: 2.66; 95% CI: 1.12, 6.32) [76].

There is a growing body of information concerning the histology and clinical presentation of lymphomas in SLE. More than one study has indicated that the association between SLE and NHL seems most apparent for the diffuse large B-cell lymphoma subtype [72,77,78].

Some data suggest a tendency for the lymphomas in SLE to present in extranodal sites, which is a marker of poor lymphoma prognosis in general. This is compatible with two recent analyses of lymphoma in autoimmune rheumatic diseases, including SLE, indicating a tendency to present extranodally and/or in advanced stages [79,80]. Analyses in these studies corroborate previous suggestions that Epstein–Barr virus does not appear to be the major force driving lymphomas risk in autoimmune rheumatic disease.

Of course, there is great interest in the possible link between cancer risk and medication exposures in SLE. Two recent reviews of NHL cases in patients with SLE and other autoimmune rheumatic diseases found a relatively low prevalence of exposure to immunosuppressive agents [79,80]. A population-based study of NHL indicated that of the eight persons with SLE who had developed NHL, only one had been treated with immunosuppressants prior to the cancer [72].

A recent case-cohort study based on a large multicenter lupus sample studied 246 SLE cancer cases and 538 SLE subjects without cancer [81]. The adjusted hazard ratio (HR) for overall cancer risk after any immunosuppressive drug (cyclophosphamide, azathioprine or methotrexate) was 0.73 (95% CI: 0.45, 1.18). Multivariate models suggested that age 65 years and above, and the presence of nonmalignancy damage, were associated with overall cancer risk in SLE. For lung cancer, smoking was also a prominent risk factor. When looking at hematological cancers specifically, there was the suggestion of an increased risk of malignancy after immunosuppressive drug exposures, particularly when these were lagged by a period of 5 years (adjusted HR: 2.31; 95% CI: 1.03, 5.20). Thus, although immunosuppressive therapy may not be the principal driving factor for overall cancer risk in autoimmune diseases such as SLE, it may contribute to an increased risk of some hematological malignancies.

Early data had indicated a potential association, in the general population, between NHL and exposures to glucocorticosteroids and/or NSAIDs; a recent meta-analysis provided little evidence that glucocorticosteroid or NSAID exposures are themselves risk factors for NHL [82]. In the case-cohort study mentioned above, there was a trend towards decreased cancer risk in SLE subjects exposed to NSAIDs, which may reflect in part the beneficial effects of these agents on solid cancers (e.g., lung, breast, etc.).

One group has suggested that antimalarial agents play a protective role against solid malignancies [83], but these findings may (at least in part) reflect methodological issues. In this study, a Cox proportional hazards model was used, where exposure to antimalarials was classified dichotomously as any use during the cohort follow-up, not accounting for time. This approach misclassifies person-time in terms of exposure history, and can lead to the false suggestion of a protective effect in exposed individuals [84]. Other data have not supported a role of antimalarial agents on cancer risk in SLE [79,81].

To summarize then, there have been interesting developments regarding cancer risk in SLE. There remains important work to do; one key question remains regarding the relative roles of

medication exposures versus lupus disease activity in lymphoma risk. Work in progress will hopefully elucidate this issue.

Conclusion

It is now well accepted that patients with SLE have an increased incidence of CVD, osteoporosis and malignancy, thus, unfortunately, patients suffering from an already complex illness are at risk for a second hit. Although these three comorbidities are very different, it is interesting that in all cases SLE activity has been postulated as a risk factor. Unfortunately, in the case of each of these comorbid diseases, establishing the specific effects of lupus activity versus treatment is difficult, given the correlation of these two factors. This is likely to remain a challenge for years to come and may only be resolved with the development of finer markers of lupus disease activity, and with a better understanding of the pathophysiology of SLE at the molecular level. Regardless, the clinician caring for lupus patients should have a heightened awareness of those potential comorbidities and should maintain an aggressive attitude towards screening for risk factors and for risk reduction.

To address the increased risk of CVD, SLE patients should be screened for traditional risk factors on a regular basis. This includes counselling on weight loss, exercise and smoking cessation, aggressive treatment of hypertension and screening for DM. Fasting lipid levels should be carried out annually, and given the high risk of CAD in SLE, many lupus clinicians should treat to a target low-density lipoprotein cholesterol below 115 mg/dl. Finally, physicians should have a high index of suspicion for the presence of CVD and should investigate and refer appropriately. Prophylaxis against CAD, with low-dose aspirin, is a strategy employed in DM; it is unknown whether this approach might also be valuable in SLE.

Similarly, regarding osteoporosis, regular BMD measurements should be considered, especially in patients with risk factors for osteoporosis (e.g., glucocorticosteroid exposure, postmenopausal status, etc.). Informing patients of the potential lifestyle changes that may benefit their bone health (e.g., weight-bearing exercise), and ensuring adequate calcium and vitamin D intake are essential, especially in patients with multiple risk factors. Finally, with glucocorticosteroid therapy, calcium and vitamin D supplementation are particularly important, and additional osteoporosis prophylaxis, such as bisphosphonate therapy, should be considered with long-term glucocorticosteroid use. However, since the safety of bisphosphonates in pregnancy is not established, these agents should be avoided during pregnancy, or in women planning pregnancies.

Regarding malignancy risk in SLE, some drug exposures are known to be associated with certain cancers (e.g., cyclophosphamide and leukemia or bladder cancer). Thus, patients exposed to these agents should be followed carefully; for example, those who have received cyclophosphamide will need lifelong periodic urinalyses (and careful workup of hematuria) so that an occult bladder cancer may be detected. Monitoring for cervical cancer in SLE (with pap testing as per established guidelines [85]) is also important, especially after exposures to immunosuppressive therapies. Measures such as smoking cessation are beneficial for many reasons, including curtailing lung cancer risk.

Future perspective

As mentioned previously, a focus of research activity currently involves establishing the specific effects of lupus activity versus treatment in the development of CVD, osteoporosis and cancer. Another important research focus is the development of therapeutic agents that are effective for steroid-sparing and maintaining disease remission, without increasing the risk of adverse events such as malignancies. As one example, mycophenolate mofetil has shown much promise as a steroid-sparing agent for lupus nephritis, and may in some cases allow patients to avoid excessive exposures to more toxic drugs, such as cyclophosphamide.

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Executive summary

Comorbidities in systemic lupus erythematosus

- There has been a great improvement in the overall prognosis of patients with systemic lupus erythematosus (SLE).
- Comorbidities can be a 'second hit' in SLE, and may have an increasingly important impact on the duration and quality of life in these patients.
- Cardiovascular disease (CVD), osteoporosis and malignancies are the comorbidities that have received the most attention in recent studies.

Cardiovascular disease in SLE

- Lupus patients have a significant increased risk of cardiovascular events.
- This increase in risk is related to an increased number of traditional risk factors (hypertension, hyperlipidemia, etc.), but lupus-related factors (e.g., glucocorticosteroid exposure and SLE activity) may also be important.
- Because lupus patients are at high risk of CVD, they should have regular screening for the presence of traditional risk factors, and aggressive risk reduction.

Osteoporosis & SLE

- A high prevalence of osteoporosis and osteopenia is present in SLE.
- Although part of this increase in risk is due to recognized risk factors (glucocorticosteroid use, decreased physical activity, decreased sun exposure, etc.), lupus activity may also play a role.
- Screening for osteoporosis with bone mineral densitometry should be considered in all SLE patients, especially in the presence of osteoporosis risk factors.
- Early and aggressive measures for bone preservation should be considered in all patients treated with glucocorticosteroids.

Malignancy & SLE

- SLE is associated with an increased risk of malignancies, particularly lymphoma and lung cancer.
- Although immunosuppressive therapy may not be the principal driving factor for overall cancer risk in autoimmune diseases such as SLE, it may contribute to an increased risk of some hematological malignancies.
- Lymphoma risk in SLE may in part be driven by disease activity, but work in progress aims to differentiate the effects of lupus treatment from lupus activity.

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