Lupus (2000) 9, 166–169
0961-2033/00 $15.00
www.nature.com/lup

REVIEW

Epidemiology of cardiovascular disease in systemic lupus erythematosus

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Awareness of the impact of cardiovascular disease on the late morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE) is increasing. Clinical events secondary to accelerated atherosclerosis have been documented in lupus cohorts across the globe. We review the history and epidemiology of cardiovascular disease in patients with SLE.
Lupus (2000) **9,** 166–169

Keywords: systemic lupus erythematosus; coronary artery disease; atherosclerosis

Cardiovascular disease secondary to accelerated atherosclerosis is increasingly recognized as a cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Although the etiology and pathophysiology of this phenomenon is poorly understood, the epidemiology is well documented and accepted by the rheumatologic community. This article will review the history and the epidemiology of accelerated atherosclerosis in SLE.

The early era (1970s–early 1980s) was characterized by awareness of coronary artery disease in patients with SLE. Initial observations in the form of anecdotal reports described patients with SLE who had suffered myocardial infarctions, many of which were fatal.[1–4] These individuals were primarily young women who had had lupus for a number of years, ranging from 6 to more than 20 years.

Urowitz and his colleagues were among the first to recognize the significance of coronary artery disease in the late clinical course of patients with SLE.[5] Analysis of the 11 deaths in their cohort at the University of Toronto revealed a bimodal distribution of mortality. Early deaths occurred within the first year after diagnosis. These patients died with active lupus. The late deaths (comprising 45% of all deaths) were attributed to myocardial infarction, emphasizing the importance of coronary artery disease in the late clinical course of this lupus cohort.

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Several other cohorts documented death from myocardial infarction during this time.[6–8] In contrast to the impact observed by Urowitz, these cohorts reported mortality at a significantly lower and very consistent rate of 3–4% of total deaths.

Two autopsy studies confirmed the histologic presence of coronary artery disease with and without myocardial infarctions in young women with lupus. The histology was remarkable for the absence of inflammatory changes or vasculitis and showed coronary artery narrowing secondary to atherosclerosis. Bulkley and Roberts published an uncontrolled autopsy study of 36 SLE patients[9] in 1975. These patients were young (with a mean age of 32 years), female (33 of 36) and had all been treated with steroids. 21% had greater than 50% narrowing of at least one coronary artery and pathology in four of the autopsy cases demonstrated the presence of a myocardial infarction. A second autopsy study by Haider and Roberts[10] subsequently published in 1981 included 22 SLE patients as well as matched controls. Ten of these 22 young (age ranged from 16–37) patients exhibited coronary artery narrowing greater than 75% while the other 12 patients had lesser degrees of narrowing, similar to that seen in the matched controls.

The increased risk for clinical coronary artery disease conferred by SLE in comparison to the general population was first described in a small but stable lupus population in Sweden in 1989. Compared to the age matched general population the risk of coronary artery disease was 9-fold greater for the 81 lupus patients identified.[11]

The latter part of the 1980s and through the past decade has been characterized by a renewed interest in the burden of atherosclerosis in SLE. Not only has mortality secondary to atherosclerosis again been noted with higher mortality rates than initially noted (6–16%, 12–15) but the larger issue of morbidity from atherosclerosis in SLE has been addressed. Thus published reports in the current period include the incidence/prevalence of nonfatal MI's or symptomatic angina and peripheral vascular disease. Several lupus centers have begun to screen their populations for subclinical atherosclerotic disease by newer and more sophisticated techniques. Furthermore, by searching for clinical associations and for the risk factors associated with accelerated atherosclerosis in these populations, investigators are attempting to understand the pathophysiology of this condition.

Urowitz and colleagues identified 8.9% of 507 SLE patients with coronary artery disease manifested as angina or a myocardial infarction. Mean age of lupus onset was 43 y with a mean disease duration of 7.5 y. Previous cardiac manifestations of SLE such as pericarditis or myocarditis were risks for coronary artery disease. Other risks included hypertension, high cholesterol or triglycerides, diabetes or congestive heart failure. There was no increased risk with corticosteroid therapy.[16]

The prevalence of cardiovascular events including myocardial infarction, cardiac sudden death or angina was reported as 8.3% in 229 patients in the Baltimore Lupus Cohort[17] and comprised 30% of all lupus deaths. Angina was experienced in 15.8% of patients with coronary artery disease. Traditional risk factors for atherosclerotic events included a higher mean serum cholesterol, hypertension or use of antihypertensive medications. Corticosteroid use was not significantly associated with atherosclerotic events although the duration of prednisone use did predict for coronary artery disease.

The SUNY Health Science Center at Brooklyn retrospectively examined a subset of our SLE cohort. 15% of 200 consecutively followed patients were found to have coronary artery disease.[18] This subset was 96% female, with a mean age at onset of SLE of 29.8 y and a mean duration of disease of 13.9 y. Myocardial infarction was clinically diagnosed in 13 (6.5%) of patients; angina confirmed by abnormal stress test, stress thallium test, or coronary angiography in 24 (12%) of patients. Significant risk factors for coronary artery disease included hypertension, postmenopausal status and age. The mean age of onset of coronary artery disease was 47.5 y. Raynaud's phenomenon, cutaneous vasculitis, pericarditis and myocarditis, nephrotic syndrome, a GFR $< 50\%$ or diabetes mellitus were not statistically different between patients with and without coronary artery disease. No features of steroid therapy (cumulative steroid dose or maximal steroid dose or duration) were significantly associated with coronary artery disease. In fact, patients without coronary artery disease received a significantly higher peak dose of steroids. Although the duration of steroid therapy was virtually the same in both groups, patients without coronary artery disease had a significantly longer total duration of SLE.

Age-specific incidence rates of manifestations of coronary artery disease, i.e. (myocardial infarction and angina) for 498 patients from the SLE Cohort at Pittsburgh, were contrasted to age-specific rates in controls.[19] The controls were 2208 women from the Framingham Offspring Study followed during the same time period. These investigators reported that female lupus patients in the 35–44 age group were over 50 times more likely to have an MI than controls (rate ratio = 52.4%). The mean age of the 33 women presenting with angina or myocardial infarction was 48 y (range 22–72). Risk factors for cardiovascular events included older age (at diagnosis), longer disease duration, longer corticosteroid use, hypercholesterolemia and postmenopausal status.

Recently using age-matched controls, the risk of hospitalization for atherosclerotic events was demonstrated to be greater in lupus patients than in nonlupus hospitalized controls in California, USA.[20] The risk of hospitalization for an acute myocardial infarction was 2.27 times greater for lupus patients between 18 and 44 years than in nonlupus controls. When adjusted for age, race, socioeconomic factors as well as hypertension, diabetes and chronic renal failure, the risk (the proportionate morbidity ratio) for acute myocardial infarction remained significant at 1.94 in this age bracket. Although Ward did not show an increased risk for myocardial infarction in other age groups (45–64 or $\geq$ 65 years of age), the risk of hospitalization for congestive heart failure, even after adjusting for the above factors, remained significant for each age group (3.01, 1.39 and 1.33 respectively). The risk of hospitalization for a cerebrovascular accident was 2.03 times greater for lupus patients aged 18–44 y. Extrapolation of this data to generate prevalence rates in SLE relative to the general population suggests that hospitalizations in women 18–44 y old due to acute myocardial infarction are 8.5 times more common, 45–64 y, 2.8 times and $\geq$ 65 y 0.7 times as common.

Similarly, analysis of data from a Canadian lupus population (89% female with a mean age of 38 ± 14 y), revealed the overall risk for myocardial infarction conferred by SLE after controlling for the Framingham risk factors (male, age, systolic BP and diastolic BP, smoking, diabetes, cholesterol and left

ventricular hypertrophy) was estimated to be an 8.3 fold increase.[21] The risk of stroke was increased 6.7 fold in patients with SLE.

Detection of asymptomatic subclinical narrowing is important as it more accurately reflects the true prevalence of atherosclerosis. Detection of asymptomatic disease also offers an opportunity to intervene when a potential for reversibility may still be present and it additionally provides the ability to identify and follow CAD during the early stages of the process facilitating investigation of the pathogenic mechanisms.

Routinely available clinical tests used to detect early atheromatous disease are often either to invasive (coronary angiography) or unreliable in this patient population of young women who often have other cardiopulmonary or musculo-skeletal abnormalities which may prevent accurate testing. Nevertheless, ischemic heart disease documented by electocardiogram or echocardiogram was reported in 16% of Mexican women with SLE.[22] Abnormal thallium perfusion studies suggestive of ischemia occurred in 25% of 16 female lupus patients followed in Brooklyn and in 38 of male and female SLE patients.[23,24] Dual-isotope myocardial perfusion abnormalities were seen in 40% of 60 female patients at the University of Toronto.[25]

Newer techniques to detect subclinical atherosclerotic disease continue to be developed. Two methods, high resolution measurement of carotid artery intima media thickness (IMT) and electron beam CT, have been applied to groups of patients with SLE. Using ultrasonographic techniques, the carotid artery intima media thickness can be measured; plaque can also be detected. The IMT measurement correlates with angiographic measures of carotid artery roughness and coronary artery stenosis. It has also been shown to be a good prognostic indicator for subsequent myocardial infarction.[26] Previous reports suggest that cardiovascular events are rare in subjects with mean IMT measurements below 0.6 mm.[27] Ultrafast computed tomography or electron beam CT can noninvasively measure coronary artery calcification. Coronary artery calcification is a marker for asymptomatic coronary atherosclerosis and is associated with atheromatous plaque[28] as well as with coronary artery stenosis. A calcium score can be generated for any or all of the coronary vessels. There has been one preliminary report of electron beam CT in a small group of lupus patients ages 33–48[29]. Thirteen patients with 2 known traditional risk factors for coronary artery disease underwent the study. Calcification in the 70th percentile of age-matched controls (without CAD) was present in 2 of the 13 patients and calcification in the 90th percentile of age matched controls (without CAD) was present in 3 patients with SLE.

Reports of subclinical disease detected by carotid IMT measurements in lupus have varied. Focal plaque was observed in 40% of 175 lupus patients from the Pittsburgh lupus cohort.[30] This cohort is 87% white with a mean age of 45 years. Fifteen percent had experienced previous clinical atherosclerotic events. A history of a prior clinical event did prove to associate with the presence of plaque. After removing these patients from analysis, variables associated with carotid plaque included older age, elevated systolic blood pressure, higher LDL and longer use of prednisone. Similarly, plaque was detected in 42% of patients with lupus or antiphospholipid syndrome reported by Roman in New York City.[31] In marked contrast, only 8% of 97 patients from the Baltimore Lupus Cohort[32] exhibited plaque on ultrasound of the carotid vessels. Differences in techniques as well as inherent differences in the patient populations (the Baltimore Cohort is 50% African-American) may account for some of these discrepancies. The mean carotid artery intima media thickness of women from the Pittsburgh lupus cohort was 0.71 mm.[30] Analysis of those patients without clinical disease revealed that age, pulse pressure and lupus damage (measured by SLICC and modified to exclude damage secondary to atherosclerosis) significantly associated with higher IMT measurements. At SUNY-HSC at Brooklyn the mean IMT measurement in 72 women was 0.70 mm, similar to that observed in Pittsburgh.

In summary, clinical events secondary to atherosclerosis are increasingly recognized as a contributing factor of late morbidity and mortality in patients with SLE. The true prevalence of subclinical disease is not yet certain but appears to affect a significant percentage of patients with SLE. Although conventional risk factors for atherosclerosis are common in lupus patients, lupus specific risk factors are hypothesized given the young age of these individuals at clinical presentation as well as the increased risk for atherosclerotic events that remains after controlling for conventional risk factors.

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