Editorial

Subclinical Atherosclerosis in Systemic Lupus Erythematosus

Accelerated atherosclerosis is now recognized as a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE). Urowitz, *et al*[1] were the first to observe this, and in the last 3 decades there has been significant accumulated evidence to confirm the association. The incidence of coronary heart disease (CHD) in patients with lupus is roughly 1.3–1.5% per annum, and in women aged 35–44 years the rate of onset of myocardial infarction has been estimated to be 50-fold greater in SLE than in control populations[2]. The cumulative prevalence of CHD was 8.9% and 8.3% in 2 different series[3,4], and the average age of presentation with the first event is 48–50 years[2,5], i.e, in the perimenopausal phase. These clinical and epidemiological observations are no longer in dispute. The next step is to begin to unravel the etiology and pathogenesis of accelerated atherosclerosis in SLE.

There is considerable debate surrounding this question. As in the general population, the etiology is likely to be multifactorial and will be an interaction of traditional CHD risk factors with additional disease and therapy-related factors. In the clinical studies to date, dyslipidemia, hypertension, and older age of SLE diagnosis were the most frequently cited "traditional" factors associated with the development of CHD[5]. It is known that patients with SLE have a significantly higher prevalence of certain classic risk factors, especially hypertension and diabetes mellitus, compared to population controls[6], and that hypercholesterolemia, especially if sustained, is strongly predictive of future CHD events[7].

Even after adjustment for classic risk factors there is still an excess risk of CHD in patients with SLE[8]. Many other factors are likely to be implicated. Patients with SLE also have higher homocysteine, triglycerides, and very-low-density lipoprotein cholesterol compared to controls[6], and the impact of these on subsequent CHD risk needs to be explored. Disease-related factors also need to be considered. These are especially important since dissecting out the inflammatory origins of atherosclerosis in SLE may provide clues to etiology of atherosclerosis in the general population.

One limitation of studies to date has been that in case-control studies using CHD events as the outcome, the number of affected cases has been relatively small, thereby limiting the power to detect all but the strongest associations. Ideally, in order to better understand the risk factors for CHD-related events in SLE, large prospective studies involving several thousand patients are needed. Such studies are, however, demanding, on both resources and time.

Identifying subclinical atherosclerosis or vascular changes is another approach that is gaining considerable attention. This approach allows better use to be made of existing patient populations and can also be used to explore potential interventions. In the general population, detection of subclinical atherosclerosis is itself also an independent risk factor for future CHD events[9]. This is partly because subclinical disease is likely to be the integrated result of both known and hitherto unknown risk factors. The noninvasive nature of most methods employed adds to their usefulness and acceptability. The major advantage is to identify a larger number of "cases" or to quantify vascular abnormalities as a continuous variable to improve power to explore potential novel risk factors in more detail.

There are a few disadvantages to the approach of identifying subclinical changes. First, most techniques will only assess the presence of atherosclerosis *or* related vascular changes. These are not synonymous with clinical CHD and therefore risk factors for the two, while overlapping will not be identical. Second, studies to date using such techniques have tended to be cross-sectional, which again limits their power to detect important associations. Finally, their validity in SLE has yet to be demonstrated, i.e., whether they have the same predictive power for future events in SLE remains unclear. A variety of methods for measuring subclinical atherosclerosis have been developed, and newer techniques are continually being explored. As their number increases it should be remembered that some techniques are

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yet to be fully validated in the general population, therefore their use in SLE should also be approached with some caution.

Various studies have employed a variety of techniques to investigate subclinical vascular disease in SLE[10-12]. Two of the larger studies are from Pittsburgh[13] and New York[14]. Both used carotid Doppler scanning to measure atherosclerosis, and found a prevalence of atherosclerotic plaque of 40% and 39%, respectively[13,14]. Studies using other techniques such as myocardial perfusion abnormalities and coronary calcification scores have also found a comparable prevalence of subclinical changes[10,12].

A range of risk factors have been identified using these techniques; however, agreement between studies is less consistent. With regard to SLE itself, the recently published case-control study by Roman, *et al* found there was a 4-fold increase of subclinical disease in female SLE patients compared to population controls. SLE itself was an independent predictor of plaque[14]. Interestingly, carotid plaque in this study was associated with older age at diagnosis, longer disease duration, higher damage scores, less cyclophosphamide use, and absence of Smith antibodies[14].

The report of Wolak, *et al*[15] in this issue of *The Journal* is the latest case-control study that examines this problem in SLE. Their cross-sectional study, which included SLE patients and healthy controls in Israel, looked at intimal and medial changes in the common carotid artery and common femoral artery using a noninvasive technique, "ultrasonic biopsy." This novel method uses a scoring system to grade and classify plaque severity according to anatomical location and has been shown to have predictive value for future events in the general population[16]. The prevalence of plaque was 28% in the SLE group and 10% in the control group ($p = 0.02$). Within SLE, age was the only factor associated with atherosclerosis using a multivariate model.

The findings of Wolak, *et al* are in accord with many other studies on subclinical atherosclerosis in SLE. The study confirms that the problem of premature atherosclerosis in SLE patients is globally relevant, and the reported prevalence of subclinical atherosclerosis (28%) using this novel technique is comparable to many other studies. The study's major limitation is its size and consequent limited power to look at predictive factors within the SLE group. Age alone emerged as being associated with atherosclerosis development, which is not surprising since age probably summarizes the overall exposure to individual risk factors as a function of time.

We therefore now know that, compared to the general population, patients with SLE have an excess risk of clinical CHD. They also have a higher burden of atherosclerosis that can be detected by several different techniques. Several key risk factors for CHD are also present more frequently in SLE populations. We now need to explore novel mechanisms that may contribute to atherosclerosis development in SLE. The recent data suggesting that less exposure to therapy is itself a risk factor[14] needs confirmation, and may begin to shed light on the interaction of pro and antiinflammatory mechanisms in this context. We need to plan large-scale prospective studies of CHD development in SLE and clinical trials to explore potential interventions to reduce future CHD risk. The former is now under way through the Systemic Lupus International Collaborating Clinics (SLICC) collaborative group, and over the 10-year period of followup it will help to better define the role of the disease and its therapy in CHD development.

Studies of subclinical atherosclerosis nevertheless remain of enormous value. They help us refine our hypotheses of pathogenesis. They also enable us to test potential novel interventions over a shorter time scale, which will be of benefit in planning larger trials. The study by Wolak, *et al*[15] increases our appreciation of the scale of the atherosclerosis problem in SLE. Moreover, followup of these patients may shed further light on why accelerated atherosclerosis develops in SLE.

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