How to predict subclinical atherosclerosis in systemic lupus erythematosus

Does non-invasive imaging hold the key?

Autoimmunity and atherosclerosis (ATS) are linked: ANA positivity is associated with decreased carotid elasticity in women [1]. Subclinical ATS is an asymptomatic but highly prevalent condition of vascular disease [2] and, in patients with SLE, may develop at an early age due to inflammatory and immune-mediated mechanisms, oxidative stress and endothelial dysfunction [3].

An early diagnosis of subclinical ATS in young patients with SLE is preferable for a more effective immunosuppressive treatment that may reduce the development of major cardiovascular complications and improve the outcome of the disease. Assessment of endothelial dysfunction, vascular stiffness and intima-media thickness (IMT) are powerful tools in the evaluation of subclinical ATS [4]. Endothelial dysfunction has shown predictive value in the long-term progression and cardiovascular event rates of ATS [5].

The pathophysiology of ATS includes endothelial dysfunction and inflammation that act on the vascular wall affecting its permeability, increasing its stiffness and, eventually, its thickness. Before ATS develops, all these mechanisms are activated and favour an increased autoantibody production and deposition of immune complexes in the vascular wall: oxLDL forms complexes with Fc receptor promote foam cell formation leading to the development of fatty streaks in the arterial wall that may eventually evolve into atherosclerotic plaques [6]. Chronic activation of the immune system supports the pro-inflammatory state and the damaged endothelium is unable to maintain physiological vascular wall conditions, thus opening the window of opportunity that leads to the development of clinical ATS.

Therefore, endothelial dysfunction and vascular stiffness precede the increase in IMT, as has been observed in interesting studies on carotids of children and adults with ATS and familial hypercholesterolaemia [4, 7]. To predict subclinical ATS in SLE better, evaluating lupus-related factors is necessary; indeed, they are better associated with carotid ATS than traditional risk factors alone. Endothelial dysfunction and vascular stiffness, associated with lupus-related factors such as chronic inflammation, immune system activation, metabolic and genetic alterations, large use of CSs and SLE disease activity and duration, may predict subclinical ATS, an asymptomatic but potentially dangerous condition.

Several invasive and non-invasive imaging techniques may be useful in assessing endothelial dysfunction and arterial stiffness. Unfortunately, while wide variation in reproducibility is reported in endothelial function measurements, due to both differences in technical protocols and the impact of physiological factors on flow-mediated dilation, this variation is considerably less when measuring IMT. We prefer to use non-invasive techniques, such as sonography-based techniques (equipped with an internal ECG monitor), because they are less expensive, easy to use and easily tolerated by patients.

We showed the presence of increased stiffness parameters in SLE patients with normal IMT (<0.6 mm) by means of an M-Mode ultrasonography with synchronous ECG measuring the major increase and reduction in the vessel diameter of the common carotid artery during heart cycles, applying the equations shown in Fig. 1.

Clinical ATS (change in plaque echogenicity and plaque progression) is efficiently revealed and monitored by sonography and pulse-wave Doppler sonography, respectively. However, to prevent clinical ATS, strategies should rely on identification of subclinical ATS through the screening of early established markers of cardiovascular risk such as endothelial dysfunction, vascular stiffness and IMT.

Monitoring of carotid IMT excellently evaluates risk stratification in hypertensive patients, pharmacological efficacy in clinical trials and rate of progression of ATS before the formation of plaque. A meta-analysis showed that IMT significantly increased in populations with SLE disease compared with age- and sex-matched healthy controls [8]. IMT is a surrogate marker for atherosclerotic disease when deciding therapeutic strategies in lupus-mediated atherogenesis [9].

However, a debatable point is that SLE and control subjects may show similar values of carotid IMT, which is reported in several studies [10]. Moreover, a significantly lower mean IMT but a higher prevalence of plaque in SLE compared with control subjects was observed.

On the basis of physiopathology and according to some authors [4, 7], endothelial dysfunction and vascular stiffness precede the increase of IMT in subclinical ATS; they may be viewed as important predictors of subclinical ATS...
in SLE. Therefore, because subclinical ATS develops at an earlier age in patients with SLE than in controls, endothelial dysfunction and vascular stiffness should also be evaluated together with IMT. The aim to improve the management of SLE while preventing major vascular involvement would be a promising perspective, but would only be possible if the clinicians were able to recognize ATS when it is still in a subclinical form.

The clinical impact of an early diagnosis of subclinical ATS in SLE is so far unknown; however, the possibility of regulating immunomodulatory and immunosuppressive treatments and modifying lifestyle, as well as treating the classical cardiovascular risk differently, might reduce the adverse effects of ATS on clinical outcomes, preventing or delaying the development of major vascular complications. The need to reduce treatment costs caused by vascular complications that affect SLE patients is another reason to improve strategies that prevent them.

The use of non-invasive imaging techniques may have a great effect in predicting subclinical ATS through the evaluation of endothelial dysfunction, vascular stiffness and IMT, and may represent a correct approach available today to prevent and better manage vascular complications in SLE. The lack of reproducibility and agreement between the different techniques is a clear limitation and suggests their combined use in prospective cohorts.

New randomized controlled trials are needed to prove the best methods revealing these predictors of subclinical ATS, to choose the optimal interval to screen SLE patients and suggest guidelines on treatment recommendations.

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References


Sonography–based technique

**Vascular stiffness indexes**

- **vascular strain**
  \[
  \frac{\text{maxDIA} - \text{minDIA}}{\text{minDIA}}
  \]

- **vascular distensibility**
  \[
  \frac{2^{\text{vascular strain}}}{\text{sBP} - \text{dBP}}
  \]

- **vascular stiffness**
  \[
  \frac{\text{sBP} - \text{dBP}}{\text{vascular strain}}
  \]

- **pressure-strain elastic modulus**
  \[
  \frac{k(\text{sBP} - \text{dBP})}{\text{vascular strain}}
  \]

**FIG. 1** Measurement of carotid vascular wall excursions over three heart cycles. Right (→) indicates minimum diameter and left (←) maximum diameter. maxDIA: maximum common carotid diameter; minDIA: minimum common carotid diameter; sBP: systolic blood pressure; dBP: diastolic blood pressure; k: conversion factor from mmHg to Pa (k = 7 × 10^{-3}).

