Macrovascular disease in systemic sclerosis: the tip of an iceberg?

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This mini review evaluates mortality in SSc and provides a literature review concluding that premature death does occur in this population. However, there has been a changing spectrum of cause of death over the past three decades, with interstitial lung disease now being the commonest cause of SSc-related mortality. Cardiovascular (CV) mortality and events also contribute to the premature mortality seen in these patients, and this contention is supported by epidemiological studies, and further underpinned by a plethora of increased biomarkers for CV disease and events. Thus, macrovascular disease does occur in these patients, and is likely to contribute to mortality. It remains to be seen whether addressing conventional risk factors will attenuate CV disease in this population.

KEY WORDS: Systemic Sclerosis, Atherosclerosis, Macrovascular disease.

Premature mortality

The disease of SSc is a broad-based challenge to the physician, which includes the clinical aspects of diagnosis, assessment of disease severity and particularly treatment. It is usually described as a generalized disorder of small arteries and connective tissue, characterized by fibrosis and vascular spasm and obliteration in the skin and various internal organs. SSc can be classified as either limited (lSSc) or diffuse (dSSc). Epidemiological studies have yielded an incidence of 10 cases/million with a female prevalence. It is thus an uncommon disorder, difficult to study, but one to which there is attached a significant mortality. SSc is a multi-system disorder [1], which is associated with premature death. The 5-yr survival rates are reported to vary between 34% and 87% (mean 60%) [2] with the most recent studies showing an improved overall survival around 86% at 5 yrs and 69% at 10 yrs [3]. The authors conclude that this improvement may be due to earlier diagnosis and treatment, but it is likely also that increased sensitivity of antibody detection is leading to the diagnosis of milder forms of SSc (with better outcome), which may previously not have been recognized (Fig. 1).

The mortality rate is partially dependent on organ involvement, and in general patient survival in lSSc is greater than that in dSSc. For example, among patients with severe ventilatory restriction (forced vital capacity <50% of predicted) as a result of lSSc-related interstitial lung disease mortality is ~42% within 10 yrs after the onset of the disease [4]. A very recent study showed standardized mortality ratios (95% CI) of 3.72 (2.41–5.32) in lSSc and 6.06 (4.09–9.02) in dSSc [3]. This same study showed a worse outcome for males with SSc and worst of all for males with dSSc. In the United States, similar figures were being collected in terms of mortality, with a further increase in mortality in African Americans [5]. Death from SSc-related complications (e.g. scleroderma-related renal crisis, pulmonary artery hypertension, pulmonary fibrosis, gastrointestinal and heart defects such as arrhythmias or conduction defects) were shown to have fallen from 70% in the period 1972–76 to 50% between 1997 and 2001. However, deaths by non-scleroderma-related causes such as cancers, atherosclerotic cardiovascular (CV) disease or cerebrovascular disease increased correspondingly in that period. No matter the cause there is no doubt that there is an increased mortality conferred by the disease of SSc.

CV mortality

Whilst it was previously thought that organ insufficiency secondary to the SSc process was responsible for all deaths, this is not the current belief [7]. In the early 1980s, the common use of angiotensin-converting enzyme (ACE) inhibitors dramatically decreased the incidence of SSc renal crisis, which until then contributed significantly to the increased mortality [1]. Other causes of death now predominate within this population. Most recent studies suggest that pulmonary disease produces the highest mortality in terms of SSc-related problems [5], but CV deaths are consistently reported as being responsible for 20–30% of all premature deaths. A large inception cohort study demonstrated a 4-fold increase in mortality [6] (using standardized mortality ratios) and almost 30% of these deaths were due to CV causes. Furthermore, in the Swedish study of 2007 [3], 10/49 (20%) of deaths were from CV events. In a large recent Danish study [7], of the 160 patients who died during the study, 41 deaths (26%) were SSc related, and 48 (30%) were from CV causes (excluding CV disease directly associated with SSc, e.g. constrictive pericarditis) accounting for one-third of the excess mortality.

Cardiac disease is well-recognized in SSc and 24-h ambulatory ECG monitoring has demonstrated serious ventricular and supraventricular arrhythmias in 62% of SSc patients. Conduction defects also occur and there is left ventricular hypertrophy with impaired right and left ventricular function. While some of this cardiac pathology is undoubtedly due to the involvement of the myocardium in the SSc process it can be atherosclerotic in origin and is often asymptomatic until death [8].

Macrovascular or microvascular disease?

There is no doubt that considerable microvascular disease occurs in SSc, and this has been reviewed in mini-review no. 7. How does this impact on the development of macrovascular disease and CV events?

There is both vasospasm in the small vessels, and endothelial dysfunction. Such endothelial dysfunction has been shown to predict future CV events in many clinical situations [9] via the development of large vessel (macrovascular) atherosclerosis over time. Thus it is not surprising that premature CV mortality is being documented in a condition with such widespread endothelial abnormalities. Furthermore, the novel non-traditional CV risk factors for atherosclerosis are also present in SSc, such as increased lipoprotein (a), oxidized LDL, adrenomedullin [10] and inflammation. Moreover, markers of vascular damage like Von Willebrand Factor (vWF) and increased levels of vascular adhesion molecules are present in SSc [11], which are also linked to atherosclerosis.

Interestingly, a recent 2008 review article [12] suggests that published literature documenting clinically manifest
atherosclerosis is rare, and the authors suggest that CV involvement is most likely the result of vasospasm of the coronary arteries, and not atherosclerotic in origin. They do document endothelial dysfunction and other abnormalities as above, but indicate their belief that atherosclerosis is rarely found at autopsy. The studies they quote, however, are from the 1960s and early 1970s when cause of death was likely to be renal crisis with onset prior to atherosclerosis development, and such elderly assessments cannot be held to reflect the arteries as they may be found today. In contrast, in the recent Danish [7] and Swedish [3] studies from 1998 and 2007 there was a high level of autopsy-proven death certification (80 and 55%, respectively) where the macrovascular cause of death was either heart, cerebral or limb ischaemia in approximately one-third of the cases. Although similar rates of CV death occur in normal populations it is occurring in SSc more than a decade earlier. The 2007 US [5] study does not give exact details about autopsy-proven disease but certainly documents atherosclerotic CV disease as occurring over time.

This 2008 review [12] also indicate that the study of early atherosclerosis, as measured by intima media thickness (IMT) of the carotid artery has produced conflicting results. However, this measure is very operator dependent, and of note is the fact that two of the four negative papers were from the same group, the third had n = 20 subjects, which is underpowered for carotid IMT; (however, they did show increased IMT elsewhere in the body), and the fourth was another small study whose P-value missed significance (P = 0.067) for IMT but confirmed endothelial dysfunction using flow-mediated dilatation (FMD), a test very much used as a biomarker for future CV events [9]. In contrast, the four studies documenting increased IMT complement other positive studies in the literature. As atherosclerosis is a dynamic process small studies are likely to miss subtle changes, and the larger studies are more likely to avoid a type 2 error from under-powering.

A number of studies have documented atherosclerosis by arteriography [13], by decreased ABPI [14] (though not all studies) and by autopsy [3], and it would be surprising if this disease were indeed to be found to be very different from its rheumatological cousins, the other connective tissue disorders such as SLE and RA. However, it might be expected that in a disease where there may be less inflammation than that seen in RA and SLE, this atherosclerotic process may not be as aggressive, nor as visible in small numbers studies.

Conclusion

Recent mortality studies, aided by autopsy diagnosis, have shown that mortality in patients with SSc is both decreasing and changing in aetiology. Whereas previously patients with SSc died from renal crisis, mortality profiles show that interstitial lung disease is now the commonest SSc-associated cause of death, whereas CV events are the commonest non-SSc-associated mortality cause. These findings are underpinned by blood and vascular abnormalities which have been shown to be surrogate markers for future CV events. These include endothelial dysfunction, oxidized LDL and inflammation itself.

However, whilst there is convincing evidence supporting macrovascular disease as a clinical problem for our patients, there is no evidence, as yet, to support the contention that modifying CV risk will prevent events in this patient group. Many difficulties exist in the study of ‘Orphan Disorders’, not least their rarity at each centre; however, one of the key future trials for SSc is likely to be one of CV risk modification, which if positive, will be one of the few effective treatments against mortality in this disease!