# Distribution of macrovascular disease in scleroderma

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**Abstract**

***Objective*—Macrovascular disease in scleroderma has recently been described in two comparative studies. The aim of this study was to map its anatomical distribution.**

***Methods*—In a retrospective cohort study of 20 scleroderma patients, the results of Doppler studies of arteries in the limbs, neck, and abdomen were compared with those from 20 cohort negative patients. The latter were matched for age, sex, and the presence/absence of hypertension, hyperlipidaemia, smoking, and diabetes status. Arteries were compared quantitatively using a body surface area adjusted measurement of intraluminal diameter, and qualitatively using descriptive characteristics of the arterial walls. The latter were binomially categorised under three non-exclusive headings—thickening, stenosis, and calcification.**

***Results*—The ulnar arteries in scleroderma patients were significantly narrower than those of the negative cohort. The arterial walls were also characterised by smooth thickening along their entire length. The characteristics of the other arteries, including those of the lower limbs, were not significantly different from those of the negative cohort.**

***Conclusion*—The ulnar artery seems to be specifically targeted in patients with scleroderma. Assessment of the ulnar artery should be considered in these patients by means of a modified Allen's test or Doppler sonography especially in the presence of digital gangrene.**

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Vascular lesions are crucial in determining the prognosis of patients with scleroderma. Clinical manifestations include renal disease, gangrene, and pulmonary hypertension. More widespread pathology has been reported however, including skin, lung, heart, pancreas, muscle, synovium, and central nervous system.[1 2]

Most attention has focused on small vessel disease, where the small arteries characteristically show concentric intimal fibrosis, and less frequently medial thickening, fibrosis, and abnormal telangiectasia of the vasa vasorum in the tunica adventitia.[2–4]

Small descriptive studies have reported large vessel disease, often leading to lower limb amputation.[5–10] The results of the first comparative study on this finding demonstrated an increased prevalence of peripheral vascular disease in women with limited scleroderma, but no significant difference in coronary or cerebrovascular disease.[11] The former was supported by a study demonstrating an increased reporting of claudication in scleroderma.[12] The latter is supported by earlier findings of D'Angelo and colleagues who described no increased incidence of coronary atheroma in necropsy specimens.[4]

The apparent association of macrovascular disease in scleroderma led to this study. The aim was to map its anatomical distribution.

## Methods

The study was a retrospective cohort study design in which the prevalence of macrovascular disease was compared in 20 scleroderma patients and 20 matched controls.

All 20 scleroderma patients were chosen at random from the Prince of Wales and Prince Henry Hospitals data base, which comprised both private patients of one of the authors JB, and public hospital patients. Patients were chosen without regard to their macrovascular disease status. All satisfied either the ARA Preliminary Classification Criteria[13] or the Le Roy criteria.[14]

Cohort negative patients were 1:1 matched with scleroderma patients for age (± 5 years), sex, smoking, diabetes, and hypertension. These patients were randomly selected patients with a rheumatological diagnosis from the above mentioned hospitals, but excluded patients with lupus or vasculitis.

All patients underwent physical examination that included blood pressure, height, weight estimates, and assessment of scleroderma status. Blood was examined for blood sugar level, HBA1C, cholesterol, triglycerides, high density lipoprotein, antinuclear antibodies, ENA, and anticardiolipin antibodies. Outcome measures of macrovascular disease were sought using an ATL ultramark 9 HDI duplex Doppler ultrasound. The 3mHz, 7–4 mHz and 10–5 mHz probes were used for visualising abdominal, carotid and lower limb vessels, and the arm vessels respectively. Common, internal and external carotid; subclavian; brachial; radial; ulnar; aorta; common and external iliac; superficial femoral; popliteal; anterior and posterior tibial and dorsalis pedis arteries were examined prospectively to determine intraluminal size, wall characteristics, and signs of stenosis. Intraluminal diameters were measured at specific sites. The character of the vessel wall was assessed using the entire length, where possible, and was performed by one author (JG) who could not be blinded to the patients' cohort status.

*Table 1 Characteristics and distribution of potential confounders for vascular disease among positive and negative cohort*

| *Confounder* | *Positive cohort* | *Negative cohort* | *Relative risk (95% CI)/ p value* |
|---|---|---|---|
| Male sex | 2 | 2 | RR=1.0 |
| Age (median) | 64 | 66 | |
| BSA* | 1.61 | 1.71 | p=0.19 |
| Diabetes | 1 | 1 | RR=1.0 |
| Hypertension | 4 | 6 | RR=0.58 (0.11, 3.06) |
| Smoking | 8 | 6 | RR=0.64 (0.14, 2.87) |
| Hyperlipidaemia | 11 | 11 | RR=1.0 |
| Anticardiolipin antibody | 10 | 6 | RR=2.33 (0.53, 10.55) |

*Positive cohort includes three patients whose BSA was reduced secondary to amputations.

*Table 2 Distribution of increased anticardiolipin antibody concentration in positive and negative cohorts*

| | *Positive cohort* | *Negative cohort* | *Probability* | *Relative risk (95% CI)* |
|---|---|---|---|---|
| IgM LP | 5 | 2 | p=0.41 | 3.0 (0.4, 26.5) |
| IgG MP | 2 | 1 | p=1.0 | 2.1 (0.1, 64.7) |
| IgG LP | 1 | 0 | p=1.0 | |
| IgG MP | 0 | 1 | p=1.0 | |
| IgM LP + IgG LP | 0 | 1 | p=1.0 | |
| IgM MP + IgG LP | 2 | 0 | p=0.49 | |
| IgM MP +IgG MP | 0 | 1 | p=1.0 | |

LP = low positive, MP = moderately positive.

*Table 3 Frequency of vessel wall abnormalities for each artery stratified by cohort status and character of the abnormality*

| | *Irregular thick* | | *Smooth thick* | | *Calcified* | |
|---|---|---|---|---|---|---|
| | *C+* | *C−* | *C+* | *C−* | *C+* | *C−* |
| Common carotid | 4/20 | 5/20 | 1/20 | 3/20 | 0/20 | 0/20 |
| Internal carotid | 9/20 | 10/20 | 5/20 | 4/20 | 0/20 | 3/20 |
| External carotid | 4/20 | 2/20 | 0/20 | 0/20 | 0/20 | 0/20 |
| Subclavian | 0/20 | 0/20 | 0/20 | 0/20 | 0/20 | 0/20 |
| Brachial | 0/20 | 0/20 | 0/20 | 0/20 | 0/20 | 0/20 |
| Ulnar† | 0/19 | 0/20 | 10/19 | 0/20* | 1/19 | 1/20 |
| Ulnar‡ | | | 7/16 | 0/20** | | |
| Radial | 0/20 | 0/20 | 2/20 | 0/20 | 0/20 | 1/20 |
| Abdominal aorta | 2/20 | 2/20 | 3/20 | 2/20 | 3/20 | 1/20 |
| Common iliac§ | 5/20 | 2/19 | 1/20 | 3/19 | 2/20 | 0/19 |
| External iliac | 4/20 | 1/20 | 1/20 | 0/20 | 2/20 | 1/20 |
| Superficial femoral | 1/20 | 5/20 | 3/20 | 0/20 | 2/20 | 5/20 |
| Popliteal | 2/19 | 5/20 | 3/19 | 1/20 | 1/19 | 4/20 |
| Ant tibial | 2/19 | 3/20 | 6/19 | 3/20 | 1/19 | 6/20*** |
| Post tibial | 1/19 | 1/20 | 7/19 | 8/20 | 1/19 | 6/20*** |
| Dorsalis pedis | 2/19 | 3/20 | 0/16 | 2/20 | 1/19 | 6/20 |

*p<0.0001, **p=0.001, ***p=0.02. All other probability values were >0.05. C+ = cohort positive, C− = cohort negative. †Because one positive cohort had non-patent ulnar artery grafts she was therefore excluded from the ulnar artery denominator. ‡Ulnar arteries from amputees excluded. §One negative cohort common iliac arteries could not be visualised.

Two outcome measures were used. The first was a quantitative assessment of intraluminal diameter (for paired arteries the mean was recorded), which was adjusted for body surface area (BSA), a major predictor of physiological intraluminal diameter. The second was a qualitative assessment of the vessel wall, which was categorised by the presence or absence of: calcification, stenosis, and either irregular or smooth thickening none of which was mutually exclusive.

### STATISTICS

Comparison of qualitative data was made using relative risk estimates, with Taylor's series 95% confidence intervals. Quantitative data were compared using either paired or unpaired *t* test, where appropriate, after data normalisation.

Arterial wall abnormalities were treated binomially. As the character of an arterial wall could not be considered independently of its pair, statistical comparison of arterial wall character between both cohorts was performed using the person, not the artery, as the denominator. A label of "abnormal" was applied when either one or both arteries was abnormal. Statistical comparison was performed using comparison of proportions. Because 48 tests were performed, a prior probability value of p<0.01 was accepted as the level required for statistical significance.

Local ethics committee approval was gained for the study.

## Results

The scleroderma patients comprised of 18 with limited and two with diffuse disease. The median time between first disease symptom onset and study participation was 15 years. Three had limb amputations—one with a unilateral below knee amputation, one with bilateral below knee amputations, and one with a unilateral above knee amputation. The indications for surgery could not be reliably ascertained nor was histopathology available on the amputated vessels.

The negative cohort comprised six patients with osteoarthritis, six with rheumatoid arthritis, three with fibromyalgia, two with osteoporosis, one with each osteomyelitis, epiphysial dysplasia, and lower back pain. No cohort negative patients had limb amputations.

Table 1 denotes the adequacy of matching by potential confounders. Eighteen of the patients were perfectly matched for sex, age, diabetes, and hyperlipidaemia, while two had the same quantity but a different combination of risk factors (smoking and hypertension respectively).

The mean body mass index (BMI) and BSA were lower in the cohort positive group and were related, at least in part, to the four lower limb amputations. Despite this disparity, the difference in the mean BMI and BSA did not reach statistical significance (p=0.07 and p=0.19 respectively).

As the presence of increased anticardiolipin antibody concentrations was a potential confounder for vascular occlusion, their distribution in both cohorts was investigated (table 2). While the frequency of increased concentrations was in general higher in the cohort positive group, this did not reach statistical significance.

A history of claudication or night pain, or both, was noted more commonly in the scleroderma patients (three and four patients respectively), while none of the cohort negative patients reported symptoms.

Table 3 shows the frequency and distribution of vessel wall abnormalities. This demonstrates abnormalities in the character of the blood vessels ranging from 0% in both the positive and negative cohorts' subclavian arteries to 55% in the positive cohort's ulnar arteries and 50% in the negative cohort's internal carotid arteries.

Qualitative and quantitative assessment of macrovascular disease (tables 3 and 4) demonstrates similar results—the positive cohort's ulnar arteries were characteristically smoothly thickened (p<0.0001) and significantly narrower (p=0.002) than those of the negative cohort. The 10 cohort positive patients with smoothly thickened ulnar arteries included

*Table 4 Comparison of vessel intraluminal diameters adjusted for BSA*

| Vessel | Median diameter × 10/BSA (cm/m²) | | |
|---|---|---|---|
| | C+ | C− | Probability |
| Common carotid | 43.3 | 44.8 | 0.7 |
| Internal carotid | 35.5 | 35.6 | 0.6 |
| External carotid | 27.6 | 24.6 | 0.2 |
| Subclavian | 42.6 | 39.6 | 0.4 |
| Brachial | 24.1 | 22.4 | 0.7 |
| Ulnar | 9.7 | 12.8 | 0.002 |
| Radial | 13.3 | 13.5 | 0.8 |
| Abdominal aorta | 94.4 | 92.1 | 0.7 |
| Common iliac | 52.8 | 53.6 | 0.4 |
| External iliac | 42.8 | 45.1 | 0.7 |
| Popliteal | 32.5 | 32.2 | 0.9 |
| Post tibial | 9.6 | 11.4 | 0.7 |
| Ant tibial | 10.7 | 14.0 | 0.8 |
| Dorsalis pedis | 12.1 | 9.0 | 0.1 |

For paired arteries mean intraluminal diameter is quoted.

three amputees, all with limited disease. Assuming a worst case scenario—that the amputations had been performed because of underlying macrovascular disease—these three patients were then excluded from further analysis. Despite their exclusion, ulnar artery disease characterised by smoothly thickened walls remained significantly more frequent in the positive cohort (p=0.001). The positive cohort's anterior and posterior tibial arteries were less commonly calcified than those of the negative cohort (p=0.02) but did not reach the a priori determined level of statistical significance. The other arteries were similar with respect to arterial intraluminal diameter and vessel wall characteristics.

Vascular occlusion of three smoothly thickened ulnar arteries was noted in two patients with limited disease, in addition to postoperative occlusion of ulnar artery grafts in a patient with limited disease. Ulnar artery disease occurred in both limited and diffuse disease subtypes—in nine of 17 (53%) patients with limited disease (the patient with ulnar artery graft was excluded), and one of two patients with diffuse disease. The arterial wall thickening was bilateral in 6 of 10 affected patients. The frequency of occurrence of potential confounders for macrovascular disease—age, sex, and the presence of diabetes, hypertension, hypercholesterolaemia, smoking or increased anticardiolipin concentrations—was comparable in the positive cohort both with and without smoothly thickened ulnar arterial walls (table 5). While the range and mean estimates of disease duration were higher in those scleroderma patients with ulnar artery disease (mean 22.1 years and range 9–64 years versus mean 18.1 years and range 1–33 years), this did not reach statistical significance (p=0.53). Nor did the presence of anticentromere antibody confer an increased risk of ulnar artery disease in scleroderma patients (relative risk = 1.8; 90% CI 0.32, 10.32).

*Table 5 Frequency of occurrence of risk factors for macrovascular disease in the scleroderma cohort with and without smooth thickened ulnar arteries*

| | Positive cohort with regular thickened ulnar arteries (n=10) | Positive cohort without regular thickened ulnar arteries (n=9) | Probability |
|---|---|---|---|
| Limited disease | 9 | 8 | |
| Male | 1 | 1 | |
| Mean age | 65.1 | 60.1 | p=0.54 |
| Duration disease | 22.1 | 18.1 | p=0.53 |
| Anticardiolipin Ab | 5 | 5 | |
| Smoking | 4 | 3 | |
| Hyperlipidaemia | 5 | 5 | |
| Hypertension | 1 | 2 | |
| Diabetes | 1 | 0 | |

One patient with limited disease and occluded ulnar artery grafts was excluded from the analysis, because the indication for ulnar artery grafting was not apparent.

## Discussion

The most significant finding from the study is the specific targeting of the ulnar artery in patients with scleroderma. This occurred in an unexpectedly high proportion of patients and in both disease subtypes. The ulnar artery disease was not uniformly bilateral, and although it occurred more commonly in those patients with longer disease duration, this temporal relation did not reach statistical significance. The ulnar artery disease occurred in or before a mean disease duration of approximately two decades. With the possible exception of the anterior and posterior tibial arteries, which seemed to be less commonly calcified in scleroderma patients, all other arteries examined showed similar characteristics and Doppler abnormalities in the two groups.

Ulnar artery abnormalities were documented by ultrasound proximal to the wrist and were described as "smoothly thickened". In the only report of scleroderma ulnar artery pathology, findings were those of severe medial thickening with circumferential luminal narrowing and occlusion by acellular material but with no evidence of atherosclerosis.[10] Although it is unclear whether these findings consistently reflect characteristic ulnar artery changes in scleroderma, the ultrasonographic findings of smooth thickening concur with this pathology. Although atheroma may also appear as "smooth thickening", (especially in areas adjacent to arterial branching) the usual sparing of the upper limbs from atheroma argues against its presence as the underlying pathology in the scleroderma patients' ulnar arteries.[15]

Ulnar artery disease has previously been described in the hypothenar hammer syndrome, where vascular occlusion occurs often in association with repetitive trauma to the hypothenar eminence.[16–18] Most of these arteries showed wall thickening or thrombosis over the hamate bone, although arterial involvement at the wrist has also been noted.[19] Interestingly one study described hypothenar hammer syndrome and concurrent Raynaud's phenomenon associated with vibrating tool use.[19] Three factors argue against the ulnar artery pathology in our patients being ascribed to hypothenar hammer syndrome (a) the distribution of the ulnar artery pathology proximal to the wrist, (b) its presence in a cohort of predominantly older women presumably spared the risk of repetitive trauma to the hypothenar eminence, and (c) the even distribution between hands (not favouring the dominant hand).

The possibility was entertained that selection bias may have accounted for these results. While patient selection was independent of macrovascular disease status, the possibility could not be excluded that generalised macrovascular disease contributed to limb amputations in three of the

cohort positive patients. For this reason data analysis was performed both including and excluding these three patients' ultrasound results. However, the conclusions remained unchanged. The negative cohort was also chosen at random, blinded to their macrovascular disease status. Because the latter largely comprised hospital inpatients, this group may have conceivably had rates of macrovascular disease higher than the general community from which they were derived, leading to underestimation of the difference in macrovascular disease rates.

While this study demonstrates increased frequencies of ulnar artery disease in scleroderma patients, it cannot determine whether disease itself or confounders such as treatment relating to the disease or Raynaud's phenomenon was causal. Raynaud's phenomenon was a symptom in all scleroderma patients but in none of the negative cohort. Although the cooccurrence of Raynaud's and ulnar artery disease has been reported,[20–22] these have not previously been causally linked. Studies investigating this possibility are currently in progress. The mechanisms by which ulnar artery occlusion occurred was also investigated but could not be attributed to increased anticardiolipin concentrations, anticentromere antibody or other risk factors for macrovascular disease.

A negative finding from this study was the apparent lack of association between scleroderma and lower limb ischaemia. An association between peripheral vascular disease and scleroderma was first demonstrated by our group in 1995[11] and later confirmed independently by Veale and others.[12] One possible explanation for the lack of association lies in the random selection of scleroderma patients including three patients who between them had four lower limb amputations. The blood vessels of these amputated limbs were not available for retrospective histopathology or inclusion in the analysis for this study and it is possible that macrovascular disease contributed to the limb disease, which ultimately resulted in limb amputation. Assuming an association between peripheral vascular disease and scleroderma, the distribution of macrovascular disease in the lower limbs of scleroderma patients therefore remains to be determined.

This comparative study highlights both the frequency of occurrence and distribution of macrovascular disease localised to the ulnar artery in scleroderma patients. Because the ulnar artery is usually the dominant arterial supply to the hand, assessment of the ulnar artery status in scleroderma assumes importance in the assessment of reversible (Raynaud's) or irreversible digital ischaemia. This may be reliably estimated either clinically by means of the modified Allen's test[23] or by Doppler ultrasonography. The latter also allows assessment of the more distal vasculature in the hand. This also highlights the potential risk to the hand's viability when arterial blood gas samples are taken from the radial or brachial arteries.

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