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Risk factors for chronic ulceration in patients with varicose veins: A case control study

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Background/Objective: **Identifying which patients with varicose veins are at risk of progressing to more severe forms of chronic venous disease could help in assigning clinical priorities and targeting appropriate treatments. The aim of this study was to determine, in subjects with varicose veins, the characteristics of venous disease and other factors associated with an increased risk of ulceration.**

Methods: **One hundred twenty subjects with varicose veins and an open or healed venous leg ulcer were compared with 120 controls with varicose veins and no history of venous ulcer on this case control study. Subjects were recruited from hospital settings and primary care. Each subject completed a questionnaire on lifestyle and medical history and underwent an examination comprising of clinical classification of venous disease (CEAP), duplex scanning, quantitative digital photoplethysmography, and measurement of dorsiflexion. Multiple logistic regression analyses and calculation of receiver operating characteristic (ROC) curves were performed to identify the combination of factors which most accurately predicted which patients with varicose veins will develop leg ulcers.**

Results: **An increased risk of ulceration was associated with the severity of clinical venous disease, especially with the presence of skin changes ($P < .0001$). Other significant risk factors included history of deep vein thrombosis (DVT) ($P = .001$), higher body mass index (BMI) ($P = .006$), smoking ($P = .009$), and reflux in the deep veins ($P = .0001$). Ulceration was associated with reduced volume of blood displaced as reflected by photoplethysmography and a limited range of ankle movement (not wholly due to the effects of an active ulcer) (both $P < .05$). Multivariate analyses showed that skin changes including lipodermatosclerosis (odds ratio [OR] 8.90, 95% confidence interval [CI] 1.44-54.8), corona phlebectatica (OR 4.52, 95% CI 1.81-11.3) and eczema (OR 2.87, 95% CI 1.12-7.07), higher BMI (OR 1.08, 95% CI 1.01-1.15), and popliteal vein reflux (OR 2.82, 95% CI 1.03-7.75) remained independently associated with increased risk of ulceration while good dorsiflexion of the ankle (OR 0.88, 95% CI 0.81-0.97) and an effective calf muscle pump (OR 0.96, 95% CI 0.92-0.99) remained protective factors. ROC curve analyses indicated that a model based on clinical observation of skin changes, duplex scanning for popliteal reflux, and calf muscle pump tests would be the most accurate in determining which patients with varicose veins develop leg ulcers.**

Conclusions: **The results of this study confirm that, in patients with varicose veins, those with skin changes of chronic venous insufficiency and deep vein incompetence are at greatly increased risk of ulceration. However, the risks may also be increased in those who smoke, are obese, and have restricted ankle movement and reduced calf muscle pump power. (J Vasc Surg 2009;49:1490-8.)**

Varicose veins occur commonly in the general population with 36% of people in the United Kingdom affected.[1] A major complication of varicose veins is venous ulcer, which accounts for over 75% of all chronic leg ulceration. Venous ulcers affect around 1% of the population during their lifetime, are notoriously difficult to heal, and cause considerable morbidity and diminished quality of life.[2,3] In the United Kingdom, venous leg ulceration alone has been estimated to cost the National Health Service (NHS) $575 million dollars a year.[4] It has been estimated that the treatment of venous ulceration accounts for around 3% of the total expenditure on health care.[5] Given the high cost of treating ulcers, strategies aimed at preventing leg ulceration would have compelling economic rationale.

Attempts to improve the healing rates of venous ulcers by conventional treatments in the community have not been successful, as shown in the Scottish Leg Ulcer Project.[6] Greater attention needs to be given to prevention of leg ulceration if the community burden is to be reduced. NHS expenditure on treating varicose veins has been curtailed by most health authorities. There is a strong case for targeting available expenditure on the high risk fraction of the varicose vein population. As yet, there is little good scientifically validated evidence on which clinical and other factors increase the risk of ulceration. A few cross-sectional and case control studies have compared risk factors in ulcer patients with the population as a whole[7-10] and several hospital based studies of ulcer patients have de-

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scribed the frequency of certain clinical characteristics.[8-10] However, such studies have tended to be observational case series, and there is a lack of controlled studies comparing risk factors in those varicose vain patients who develop ulceration with those who do not. Furthermore, since the etiology of venous ulceration is undoubtedly multifactorial, there is a need to identify high risk profiles for potential prevention strategies. Most studies have not investigated combinations of possible risk factors nor adequately accounted for confounding factors.

The aim of this study was to determine, in subjects with varicose veins, the characteristics of venous disease and other factors associated with an increased risk of ulceration.

METHODS

Study design. A case control study was conducted on 240 subjects with varicose veins. Subjects were recruited from the register of venous patients scanned at the Vascular Laboratory, Royal Infirmary of Edinburgh, and also from general practices within the Lothian area. Both hospital and primary care settings were used as sources of recruitment in order to encompass a typically diverse distribution of severity of venous disease within the study population. Approval from each subjects' general practitioner was obtained prior to inviting the subject to take part. This study was approved by the Lothian Research Ethics Committee, and each subject gave informed written consent to participate in the study.

Cases were selected to comprise 120 men or women of any age with C_2 trunk varicose veins (defined using the CEAP classification[11]) and an open or healed venous leg ulcer. The ulcer must have been active for at least 8 weeks in order to exclude acute leg ulcers. Patients with ulcers in their feet were also excluded to rule out arterial and diabetic ulcers. The control group was selected to comprise 120 subjects with C_2 varicose veins, but no history of leg ulcer.

With 120 subjects in each group, the study had 80% power to detect the following absolute differences between cases and controls in the important clinical characteristics of valvular incompetence: superficial reflux only (17%), deep reflux only (12%), combined superficial and deep reflux (16%) at the two-sided 5% significance level.

Clinical examination. All subjects underwent a clinical examination at the Vascular Laboratories at the Royal Infirmary of Edinburgh and Glasgow Royal Infirmary. Subjects had their standing height measured to the nearest 5 mm without shoes using a free standing stadiometer. Weight, without shoes or outdoor clothes, was measured to the nearest 100 g on a digital Soehnle scale. Body mass index (BMI) was calculated (kg/m^2). We defined subjects with a BMI of 25 to <30 as "overweight" and subjects with a BMI of 30 or more as "obese", in accordance with the World Health Organization's criteria.[12] For all cases, pre-ulcer weight was also recorded and based on the patient reporting their weight before developing an ulcer. Blood pressure in the right arm was measured using a stethoscope and sphygmomanometer. Measurement of ankle-brachial pressure index (ABPI) was made using a hand-held continuous wave Doppler ultrasound and sphygmomanometer. Any subject with a pressure index <0.8 did not proceed further with the examination and was excluded due to possible peripheral arterial disease.

Assessment of the site and severity of venous disease was made according to the International Consensus Committee protocol based on Clinical, Etiological, Anatomical and Pathophysiological data (CEAP).[11] Subjects stood on a raised platform with their feet in two standard positions and were asked to remain standing for a minimum of 2 minutes to allow blood to pool in their legs, prior to classification of their veins. Limbs were classified as: C_0 no visible or palpable signs of venous disease, C_1telangiectases or reticular veins, C_2 varicose veins, C_3 edema and corona phlebectatica, C_4 skin changes ascribed to venous disease (pigmentation, venous dermatitis, and lipodermatosclerosis), C_5 skin changes ascribed to venous disease as above with healed ulceration, and C_6 skin changes ascribed to venous disease as above with active ulceration. Within the C_1 and C_2 categories, each of these groups was further subdivided into grades of severity 1 to 3, determined according to the degree and extent of the tortuosity and prominence of the veins based on the Basle classification.[11] Observer variations were minimized by use of standardized training and regular quality control checks of inter-rater reliability throughout the study. For the ulcer group, the index leg was defined as the leg with the ulceration or if bilateral ulceration was present, the leg with the more severe ulcer. For control subjects, the index leg was the leg with the more severe varicose veins. Duplex scanning of the deep, superficial, and perforator systems of the index leg was carried out using an ultrasound scanner with a 5 MHz probe. The scans were carried out by one of four experienced vascular technologists using a standard protocol.

Subjects were examined on a tilting couch in a reversed 15-degree Trendelenburg position with their back to the couch and the leg being scanned relaxed with the knee slightly bent and weight supported on the opposite leg. In the active ulcer patients, bandaging was removed before the examination and reapplied by a specialist tissue viability nurse.

Vein segments were examined for patency and competency in the index leg in predesignated sites: (1) the common femoral vein (CFV) just proximal to the saphenofemoral junction; (2), the saphenofemoral junction (SFJ); (3) the femoral vein (FV), approximately 2 cm below the confluence with the profunda femoris vein; (4) the profunda femoris vein (PFV); (5) the popliteal vein (POP); (6) the saphenopopliteal junction (SPJ); (7) the great saphenous vein (GSV) just distal to the saphenofemoral junction; (8) the small saphenous vein (SSV) just distal to the saphenopopliteal junction; (9) posterior tibial veins (PTV); (10) anterior tibial veins (ATV); (11) peroneal veins (PER); and (12) perforating veins. Venous reflux was defined as the presence of reversed blood flow greater than 0.5 seconds following the release of a firm manual calf compression.[13-15]

Two measurements of maximal, voluntary dorsiflexion in the supine, non-weightbearing position were taken in both legs from a neutral 90° position using a portable goniometer. Subjects were instructed to push as hard and fast as possible throughout the movement. Digital photoplethysmography was conducted to measure the effectiveness of the calf muscle pump in the index leg. This test was performed with the subject in a sitting position with their knee at an angle of 110° and the sensor placed 10 cm above the medial malleolus. The subject executed 10 dorsal extensions of their index foot to the sound of a metronome over a 15-second period. In a normal subject, activation of the calf muscle pump results in reduction of venous pressure and dermal blood volume. The efficacy of the calf pump depends on the percentage of displacement of initial blood volume. Displacement of blood is reduced or restricted in patients with venous valvular disease.[16] The photoplethysmography test provides information on the venous refilling time(s) and venous pump power expressed as percentage of blood displaced (%).

A questionnaire was administered to gather information on patient demographics, previous treatment for venous disease, medical history, smoking status, physical exercise, and daily activity. When responding to questions concerning medical history, all subjects were asked to report whether a medical professional had ever told them that they had the specified condition. Physical exercise and daily activity levels were ascertained for the past year and also when the subject was aged 35 to 45 years, which in most cases would be prior to development of ulceration. Physical exercise was evaluated in four categories: none, light, moderate, and strenuous assigned according to reference activities. Daily activity was also evaluated in four categories: prolonged sitting, standing, prolonged standing, and heavy work.

Statistical analysis. Information from the recording forms and questionnaires was checked, coded, and double entered by two independent researchers onto the University mainframe computer system. Statistical analysis was performed with SPSS-X software (SPSS Inc, Chicago, Ill). Univariate statistical analyses were conducted to compare the risk factor levels between cases and controls using the *t* test, χ^2 test, or their nonparametric equivalent. Risk factors that were statistically significant on univariate analyses were entered into a stepwise logistic regression model to determine which factors were independently associated with increased risk of venous leg ulcer. Receiver operating characteristic (ROC) curves were plotted and areas under the curve for each model were compared to identify which factors were the most predictive in determining those subjects with varicose veins who were most likely to develop chronic leg ulceration. A *P* value of $\leq .05$ was used to denote statistical significance.

RESULTS

To recruit 120 cases with venous ulcer and 120 controls without ulcer, 381 patients with varicose veins who fulfilled the inclusion criteria and deemed suitable by their general practitioners were invited to participate. Of these, 141(38 cases and 103 controls) did not respond or refused to participate giving a response rate of 63%. Eighty-one percent (81%) of cases and 67% of controls were recruited consecutively from the hospital register of patients scanned within the previous year. The remaining subjects were recruited from primary care settings.

The majority of subjects (n = 224) had C_2 varicose veins. Ten cases and six controls had moderate to severe reticular veins only. This was not ascertained until after the detailed clinical examinations had been conducted and since they only represented a small proportion of subjects, were retained in the study. The reported mean (SD) age of developing varicose veins was 38.1 (13.4) years in the ulcer group and 37.1 (11.7) years in controls ($P = .41$); 55% of cases and 43% of controls were male ($P = .07$). The mean (SD) age of ulcer patients was 64.1 (13.4) years and of controls was 59.9 (11.7) years ($P = .01$). There was no significant difference in level of education or social class between (data not shown).

The 120 cases consisted of 39 active ulcers and 81 healed ulcers; 24 had had previous varicose vein surgery. The mean (SD) age of first developing an ulcer was 56 (15.5) years and the median (interquartile range [IQR]) number of active episodes was 2 (1-3) with a mean (SD) duration of each of 7 months (13). The reported principal cause of the ulceration was poor circulation (43.2%), knock or trauma (25.4%), scratching (11.0%), and unknown (20.3%).

The classification and severity of venous disease in the cases and controls is shown in Table I. Forty-nine per cent of ulcer subjects had more severe varicose veins (grade III) compared with 33% of controls, and the former were significantly more likely to have skin changes, including corona phlebectatica (66% vs 28%), hyperpigmentation (90% vs 51%), eczema (67% vs 23%), and lipodermatosclerosis (26% vs 4%). No significant differences were found in the prevalence of telangiectases, grade of reticular varices, or proportion with edema or atrophie blanche.

Of the 110 cases with varicose veins, 63 were in the great saphenous vein only, 26 in the small saphenous vein only, and the remaining cases had varicosities affecting both the great and the small saphenous vein. Of the 114 controls with varicose veins, 72 were in the great saphenous vein only, 22 in the short saphenous vein only, and the remaining 20 controls had varicosities affecting both the great and small saphenous veins.

A history of a deep vein thrombosis or pulmonary embolism was significantly more common in ulcer patients (28%) than controls (8%) ($P = .001$), but other clinical conditions which might conceivably increase the risk of ulceration did not reach statistical significance, namely phlebitis (37% vs 28%), leg fracture (18% vs 11%), and arthritis (40% v 35%). Table II shows some differences in lifestyle and related factors. Although ulcer subjects did not differ in average height from controls, they were more obese (mean [SD] body mass index 31.7 [8.4] vs 29.1 [6.4]

Table I. Classification and severity of venous disease in ulcer cases and controls

CEAP classification	*Venous disease*	*Cases (n = 120) % (n)*	*Controls (n = 120) % (n)*	P *value*	*Odds ratio (95% CI)*[a]
C1	Telangiectases	60.0 (72)	61.7 (74)	.89	0.90 (0.53-1.53)
C1	Reticular veins grade[b]			.08	
	- I	17.5 (21)	24.2 (29)		0.69 (0.36-1.32)
	- II	45.0 (54)	31.7 (38)		1.62 (0.94-2.77)
	- III	20.8 (25)	18.3 (22)		1.26 (0.65-2.44)
C2	Varicose veins grade[b]			.03	
	- I	13.3 (16)	25.8 (31)		0.45 (0.22-0.91)
	- II	29.2 (35)	36.7 (44)		0.63 (0.36-1.11)
	- III[c]	49.2 (59)	32.5 (39)		2.28 (1.32-3.94)
-	Corona phlebectatica	65.8 (79)	27.5 (33)	<.0001	5.30 (3.00-9.37)
C3	Edema	50.8 (61)	42.5 (51)	.24	1.56 (0.92-2.65)
C4a	Hyperpigmentation	90.0 (108)	50.8 (61)	<.0001	7.87 (3.89-15.90)
C4a	Dermatitis	66.7 (80)	23.3 (28)	<.0001	6.15 (3.45-10.97)
C4b	Lipodermatosclerosis	25.8 (31)	4.2 (5)	<.0001	8.77 (3.19-24.10)
C4b	Atrophie blanche	5.8 (7)	2.5 (3)	.33	2.05 (0.50-8.45)
C5	Healed ulcer	67.5 (81)			
C6	Active ulcer	32.5 (39)			

[a]Age and sex adjusted odds ratio of risk of ulceration.
[b]Grade based on Basle classification.
[c]Includes 24 cases that had had surgery on varicose veins but developed an ulcer postsurgery.

Table II. Lifestyle and related factors in ulcer cases and controls

	Cases (n = 120)	*Controls (n = 120)*	P *value*	*Odds ratio (95% CI)*[a]
Anthropometry				
Height (m)	1.67 (0.11)	1.67 (0.10)	.74	0.54 (0.02-19.41)
Weight (kg)	88.97 (24.28)	80.93 (19.76)	.006	1.02 (1.01-1.03)
Body mass index (kg/m^2)	31.74 (8.36)	29.08 (6.42)	.006	1.06 (1.02-1.10)
Blood pressure (mm Hg)				
Systolic	138.89 (21.35)	136.00 (20.89)	.29	1.00 (0.99-1.02)
Diastolic	78.82 (11.16)	75.94 (10.42)	.04	1.03 (1.00-1.05)
Smoking % (n)				
Ever smoked	63.60 (75)	45.60 (52)	.009	1.99 (1.16-3.42)
$\sqrt{\text{pack years}}$	4.47 (3.16-6.32)	4.10 (2.45-5.48)	.28	1.08 (0.90-1.29)
Physical exercise				
Past year % (n)			.07	
- Nil	28.8 (34)	14.9 (17)		
- Light	35.6 (42)	42.1 (48)		0.44 (0.21-0.91)
- Moderate	28.2 (34)	36.8 (42)		0.43 (0.20-0.93)
- Strenuous	6.8 (8)	6.1 (7)		0.70 (0.20-2.41)
Aged 35-45 years % (n)			.74	
- Nil	15.3 (18)	14.0 (16)		
- Light	28.0 (33)	28.9 (33)		0.86 (0.37-2.01)
- Moderate	39.8 (47)	44.7 (51)		0.76 (0.34-1.68)
- Strenuous	16.9 (20)	12.3 (14)		1.29 (0.48-3.49)
Daily activity				
Past year % (n)			.006	
- Sitting	35.6 (42)	17.5 (20)		
- Walking	48.3 (57)	60.5 (69)		0.43 (0.22-0.82)
- Light loads	7.6 (9)	15.8 (18)		0.29 (0.11-0.77)
- Heavy work	8.5 (10)	6.1 (7)		0.99 (0.29-3.35)
Aged 35-45 years % (n)			.87	
- Sitting	16.1 (19)	14.9 (17)		
- Walking	47.5 (56)	44.7 (51)		1.09 (0.49-2.41)
- Light loads	14.4 (17)	18.4 (21)		0.79 (0.31-2.03)
- Heavy work	22.0 (26)	21.9 (25)		0.86 (0.35-2.10)

Values are mean (SD) or % (n).
[a]Age and sex adjusted odds ratio of risk of ulceration.

kg/m^2) (P = had higher mean blood pressure, especially diastolic (mean [SD] 78.8 [11.2] vs 76.0 [10.4] mm Hg) and a higher proportion of cases had a history of ever smoking (64% vs 46%) although lifetime smoking as measured by pack years did not differ significantly. During the past year, the ulcer group had lower levels of physical exercise (P = .07) and were more sedentary in their daily activity (P = .006). However, very similar levels of physical

Table III. Reflux on duplex scanning by venous system in index leg[a] in ulcer cases and controls

System reflux	*Cases (n = 120)*	*Controls (n = 120)*	P *value*	*Odds ratio (95% CI)*[a]
Any deep reflux	48.3 (57)	18.5 (22)	<.0001	3.43 (1.85-6.35)
Any superficial reflux	89.6 (103)	92.5 (111)	0.43	1.45 (0.58-3.61)
Combined reflux	42.7 (50)	16.8 (20)	<.0001	3.85 (2.11-7.03)

Values are % (n) patients with reflux ≥ 0.5 seconds.
[a]Age and sex adjusted odds ratio.

Table IV. Reflux on duplex scanning by venous segments in index leg[a] in ulcer cases and controls

Venous segment	*Cases (n = 120)*	*Controls (n = 120)*	P *value*	*Odds ratio (95% CI)*[b]
Deep System				
Common femoral	28.2 (33)	21.8 (26)	.33	1.69 (0.90-3.16)
Profunda femoris	10.3 (12)	2.5 (3)	.03	4.16 (1.11-15.54)
Femoral	38.7 (46)	13.4 (16)	<.0001	4.17 (2.14-8.12)
Popliteal	42.9 (51)	14.3 (17)	<.0001	4.27 (2.24-8.16)
Junctions				
Saphenofemoral	59.8 (61)	67.5 (79)	.58	0.78 (0.44-1.38)
Saphenopopliteal	32.1 (36)	21.6 (25)	.09	1.74 (0.94-3.20)
Paired calf veins				
Posterior tibial 1	5.4 (6)	1.7 (2)	.16	3.65 (1.69-19.33)
Posterior tibial 2	6.4 (7)	1.7 (2)	.09	3.68 (0.72-18.89)
Anterior tibial 1	0.0 (0)	0.0 (0)		—
Anterior tibial 2	0.0 (0)	0.0 (0)		—
Peroneal 1	8.6 (9)	0.0 (0)	.001	—
Peroneal 2	7.8 (8)	1.7 (2)	.05	5.38 (1.08-26.90)
Perforators				
Above knee	17.6 (21)	15.8 (19)	.84	1.05 (0.52-2.11)
Below knee	64.7 (77)	69.2 (83)	.55	0.84 (0.48-1.46)
Superficial system				
Proximal great saphenous	71.1 (81)	76.7 (92)	.41	0.69 (0.38-1.28)
Distal great saphenous	69.4 (77)	74.2 (89)	.51	0.75 (0.42-1.35)
Small saphenous	38.5 (45)	37.0 (44)	.92	1.04 (0.60-1.78)

Values are % (n) patients with reflux ≥ 0.5 seconds.
[a]Index leg in cases is the leg with ulcer (or more severe ulcer if bilateral) and in controls is the leg with varicose veins (or more severe veins if bilateral).
[b]Age and sex adjusted odds ratio.

exercise and daily activity at age 35 to 45 years were reported.

In the tests for ankle range of movement and calf muscle pump, dorsiflexion at the ankle in the index leg was more limited in ulcer cases, mean (SD) degree of movement was 13.3° (5.0) vs 16.9° (5.3), respectively ($P <$ .0001). A significant, but less marked difference was found in the non index leg, mean (SD) degree of movement 14.3° (5.2) vs 16.3° (5.5) ($P = .01$). The digital photoplethysmography test showed no significant difference in venous filling time, median (IQR) 10.0 (6.0-14.0) seconds vs 10.7 (7.0-16.0) seconds ($P = .15$) but the venous pump power, defined as the percentage volume of blood displaced, was significantly diminished in the index leg of the ulcer group, 11.0% (95% confidence interval [CI] 7.3-16.3) vs 17.3% (95% CI 11.6-28.0) ($P = .004$).

Table III presents the results of reflux by venous system. Deep system reflux was significantly more frequent in the ulcer group with 48% of cases found to have reflux in any deep vein compared with 18% of controls. Superficial system reflux was no significantly different ($P = .43$) whilst combined deep and superficial reflux affected 43% of cases and 17% of controls ($P < .001$).

The results for reflux in specific venous segments are displayed in Table IV. The most marked differences were the femoral (39% vs 13%) and popliteal veins (43% vs 14%) (both $P < .001$). Of the 51 cases with popliteal reflux, 39 had popliteal reflux combined with femoral reflux while the remaining 12 cases had popliteal reflux only. Of the 17 controls with popliteal reflux, 12 had popliteal reflux combined with femoral reflux and five had popliteal reflux only. Evidence of a previous thrombus in the refluxing popliteal vein was found in nine cases and two controls. Reflux occurred in around 8% of peroneal veins in cases and almost never in controls. Twenty-one cases had incompetent perforating veins above the knee and 77 had incompetent perforating veins below the knee. There were no significant differences in reflux in the superficial system, at the saphenofemoral and saphenopopliteal junctions, and in above and below knee perforators. Evidence of previous thrombosis on duplex scanning was uncommon but in the

Table V. Results of stepwise logistic regression analyses of clinical venous disease categories, lifestyle factors, and calf muscle pump tests on risk of ulceration

	Multiple adjusted odds ratio (95% CI)
Clinical signs of venous disease	
Lipodermatosclerosis	8.90 (1.44-54.8)
Corona phlebectatica	4.52 (1.81-11.3)
Dermatitis	2.87 (1.12-7.07)
Lifestyle related factors	
Body mass index	1.08 (1.01-1.15)
Duplex scanning	
Popliteal vein reflux	2.82 (1.03-7.75)
Calf muscle pump tests	
Dorsiflexion – index leg	0.88 (0.81-0.97)
Venous pump power (% volume of blood displaced)	0.96 (0.92-0.99)

Adjusted for age, sex, and all variables univariately related significantly to ulceration.

Table VI. Area under the receiver operating characteristic (ROC) curves for each combination of risk factors

	Area under ROC curve (95% CI)
Each group of risk factors separately	
Clinical signs of venous disease	0.82 (0.77-0.87)
Lifestyle related factors	0.54 (0.46-0.61)
Duplex scanning	0.71 (0.64-0.78)
Calf muscle pump tests	0.74 (0.68-0.81)
Combined groups of risk factors	
Clinical signs + duplex scanning	0.85 (0.80-0.89)
Clinical signs + calf muscle pump	0.86 (0.81-0.91)
Clinical signs + calf muscle pump + duplex scanning	0.87 (0.82-0.91)

Clinical signs of venous disease = skin changes (lipodermatosclerosis, corona phlebectatica, and dermatitis).
Lifestyle related factors = BMI.
Duplex scanning = popliteal vein reflux.
Calf muscle pump tests = dorsiflexion in index leg and percent volume of blood displaced.

superficial system was more frequent in ulcer subjects than controls: proximal long saphenous (10% vs 1%, $P = .01$), distal long saphenous (8% vs 1%, $P = .02$) and short saphenous (5% vs 0%, $P = .01$).

Using multiple logistic regression analyses, age and sex were force entered into the model and then those variables, which were significantly associated with ulceration on univariate analysis, were allowed to enter using a forward stepwise procedure (Table V). For those factors in the "clinical signs of venous disease" group, each of the skin changes of lipodermatosclerosis, corona phlebectatica, and dermatitis were independently related to risk of ulceration, but the presence of more severe varicose veins (grade III) did not remain statistically significant. An elevated body mass index was the only lifestyle factor that remained a significant predictor of the risk of ulceration. Of the venous segments, only popliteal reflux remained a statistically significant predictor of risk of ulceration. Among the calf muscle pump tests, both good dorsiflexion of the index leg and a higher percentage of volume of blood displaced remained potential protective factors.

Table VI shows that of each group of risk factors separately, the clinical signs of venous disease in the form of skin changes, had the highest area under the ROC curve (0.82, 95% CI 0.77-0.87). The addition of lifestyle factors, ie, BMI, to skin changes made no positive impact on the area under the ROC curve (0.80, 95% CI 0.75-0.86). Further addition of duplex scanning, ie, popliteal reflux and calf muscle pump tests each had similar effects, area under ROC curve (0.85, 95% CI 0.80-0.89) and (0.86, 95% CI 0.81-0.91) respectively. As expected, a model including clinical signs of venous disease, duplex scanning and calf muscle pump tests gave the highest area under the curve (0.87, 95% CI 0.82-0.91).

DISCUSSION

To our knowledge, this is the first case control study carried out in varicose vein patients comparing potential risk factors in those with venous ulceration and those with no venous ulceration.

The results of our study confirm that in patients with varicose veins, those with skin changes of chronic venous insufficiency and deep vein incompetence are at greatly increased risk of ulceration.

This study also confirmed that reflux in the deep veins is associated with venous ulceration. In particular, popliteal vein incompetence was an independent risk factor for venous ulceration. This is supported by previous findings, which have emphasized the importance of the popliteal segment in the pathogenesis of venous ulceration.[17-22] Stuart et al[20] studied 233 patients with venous disease and found that a history of open or healed ulceration was strongly associated with reflux in the popliteal vein with 49% of subjects with ulceration having reflux in their popliteal vein compared with only 15% of subjects with varicose veins ($P = .002$). Welch et al[21] also found that the frequency of reflux in the popliteal vein increased as the clinical symptoms progressed, with a significant increase in class III ulcerated limbs when compared with nonulcerated limbs.

Reflux in the superficial veins was not significantly associated with increased risk of ulceration. Given that venous ulcers typically involve reflux in the deep and superficial systems, and that our control group were selected on the basis that they had visible varicose veins, we expected similar numbers of our cases and controls to have superficial reflux (71% of cases and 77% of controls).

In the current study, ulcer subjects showed reduced dorsiflexion of the ankle in the index leg compared with controls (13° in cases compared to 17° in controls). The normal non-weightbearing range of dorsiflexion of the ankle joint has been reported to be 7 to 15°.[23] To ascertain the effect that active ulcers might have on restricting movement, we compared the dorsiflexion measures in subjects

with active vs healed ulcers. Those with an active ulcer had a lower range of movement at 12.5° compared with 13.6° those with healed ulcers, but both were significantly lower than in controls. This finding suggests that only part, but not all, of the difference between ulcer subjects and controls may have been due to an active ulcer restricting dorsiflexion. Several studies have documented that ankle range of movement decreases with age.[24-26] Given that our analysis was adjusted for age, this is unlikely to have accounted for the differences observed. Furthermore, after adjusting for venous pump action, which requires the subject to dorsiflex their foot, range of ankle movement remained significantly associated with ulceration.

It is acknowledged that inactivity is a likely contributor to decreased range of movement in patients with chronic venous insufficiency. Prolonged inactivity and bed rest can lead to muscle atrophy, contracture, and degenerative joint disease. Muscles particularly affected by resting the leg are the gastrocnemius soleus and the anterior tibialis, which acts as a dorsiflexor.[27] Our ulcer group did report lower levels of daily activity in the year prior to taking part in the study. However the Lothian and Forth Valley Leg Ulcer Study[28] found that 45% of leg ulcer patients showed restricted mobility, which was not attributed to the ulcer.

We used photoplethysmography to assess venous function. This test has been widely used as it is a noninvasive and simple technique. Activation of the calf muscle pump results in a reduction of venous pressure and dermal blood volume. Displacement of blood is reduced or restricted in patients with venous valvular or venous obstructive disease. Normal venous refilling time has been reported to range from 18 to 40 seconds but, in the presence of valvular incompetence in the superficial or deep veins, venous reflux reduces the refilling time.[16]

Several studies have reported that patients with chronic venous disease have a measurable deficiency in the calf muscle pump.[29-31] Our findings were comparable in that a better functioning pump appeared to be protective against venous ulceration. It has been proposed that, rather than the calf muscle impairment resulting from chronic venous insufficiency, the poor calf muscle itself may be responsible for calf muscle pump failure in some patients with chronic venous insufficiency and leg ulceration.[31] However, the precise relationship between calf muscle pump and venous disease cannot be determined from this study.

Results from our univariate analysis support the current evidence that previous DVT increases the future risk of developing venous ulceration.[32-34] We relied on the subjects' reporting whether a DVT had ever been diagnosed by a doctor. This is the only method of ascertaining a possible previous DVT because in many patients, recanalization would have occurred so that the thrombus would not have been detected by later duplex scanning. However, our study did show that a higher proportion of the ulcer group than controls had evidence of previous thrombosis. A prospective study conducted by Nelzen et al followed up 355 DVT patients for 13 years and found that a high proportion, 30%, developed severe venous insufficiency including ulceration.[32]

We found that, in patients with established venous disease, obesity was a significant risk factor for ulceration, even after adjusting for age, sex, blood pressure, and smoking. To gauge the importance of body mass index on the risk of venous ulceration, we assessed pre-ulcer weight in all cases and found no significant difference between pre-and post-ulcer weight (data not shown). However, this finding does not prove causality and must be interpreted with caution because we relied on subjects reporting their weight before developing an ulcer. Evidence on the association between obesity and ulceration is conflicting[1,8,10,34,35] and thus further research is required to clarify this relationship.

Cigarette smoking was associated with an increased risk of ulceration after adjusting for age and sex. Subjects who had ever smoked cigarettes were almost twice as likely to develop an ulcer compared with subjects who had never smoked. Few studies have examined the association between smoking and the risk of ulceration and, as such, evidence is lacking. Gourgou et al conducted a case control study and estimated that those who smoked between 10 and 19 cigarettes a day were 1.8 times more likely (95% CI 1.4-2.2) to develop chronic venous insufficiency than those who did not smoke.[36]

It has been suggested for many years that subjects who stand for prolonged periods of time are at increased risk of developing venous disease, although the evidence is not conclusive.[8,35,37] Our univariate analysis showed that in the year prior to taking part in the study, cases were more sedentary in their daily activity and had lower levels of physical exercise. This could have been a consequence of the debilitating effects of ulceration. However, we compared typical daily activity and physical exercise at age 35 to 45 years and found no significant difference between cases and controls. Furthermore, daily activity and physical exercise were no longer significant risk factors after adjusting for other factors. The potential benefit of exercise is that using the calf muscle pump reduces the ambulatory venous pressure. However, evidence concerning exercise levels and daily activity must be interpreted with caution as they are based solely on patient reporting and thus may be prone to recall bias.

The results of our ROC curve analysis showed that several different combinations of clinical characteristics could be used to identify individuals at high risk. In particular, classification of venous disease to diagnose skin changes had a high predictive value. This is to be expected given that skin changes are involved in the pathogenesis of venous ulceration. However, using other combinations of risk factors improved the prediction further. Using the calf muscle pump tests or duplex scanning with skin changes had a similar effect with an increase in area under the curve. The calf muscle pump tests are less resource intensive than duplex scanning and may be advantageous. They have been widely used in venous research and could potentially be an important clinical tool.

CONCLUSION

This study successfully identified single and combined clinical characteristics that were predictive of the risk of ulceration in patients with varicose veins. Our results indicated that a clinical examination to identify skin changes combined with duplex scanning to confirm popliteal reflux and calf muscle pump tests may be a useful model to best predict venous ulceration in patients with varicose veins. However, these findings need to be confirmed in longitudinal studies. Many patients with chronic venous insufficiency are referred late, when the tissue change of lipodermatosclerosis and chronic ulcer are long established, cure is difficult and intervention frequently unsuccessful. The long- term goal must be to identify high risk patients at an early stage and initiate appropriate preventive measures which have been properly evaluated.

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AUTHOR CONTRIBUTIONS

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