Peripheral Arterial Disease in Diabetic and Nondiabetic Patients

A comparison of severity and outcome

EDWARD B. JUDE MD, MRCP
SAMSON O. OYIBO, MRCP
NICHOLAS CHALMERS, FRCR
ANDREW J.M. BOULTON, MD, FRCP

OBJECTIVE — The aim of this study was to quantify the distribution of peripheral arterial disease in the diabetic and nondiabetic population attending for angiography and to compare severity and outcome between both groups of patients.

RESEARCH DESIGN AND METHODS — Randomly selected lower-extremity angiograms were examined according to the Bollinger system. Patient demographics and medical history were recorded and case notes were examined to determine which patients later underwent a revascularization procedure or amputation and which patients had died.

RESULTS — A total of 136 arteriograms obtained between 1992 and 1996 were analyzed. The age (mean ± SD) of the patients was 64.7 ± 10.8 years. Diabetic patients (43%) and nondiabetic patients were of similar age (63.9 ± 10.4 vs. 65.3 ± 11.1 years, $P = 0.43$), with a similar history of smoking (81.0 vs. 76.9%, $P = 0.26$), ischemic heart disease (41.4 vs. 37.2%, $P = 0.54$), and hypercholesterolemia (24.4 vs. 30.8%, $P = 0.48$). However, there were a greater proportion of hypertensive patients in the diabetic group (63.8 vs. 39.7%, $P = 0.006$). Diabetic patients had greater severity of arterial disease in the profunda femoris and all arterial segments below the knee ($P = 0.02$). A greater number of amputations occurred in the diabetic group: diabetic patients were five times more likely to have an amputation (41.4 vs. 11.5%, odds ratio [OR] 5.4, $P < 0.0001$). Mortality was higher in the diabetic group (51.7 vs. 25.6%, OR 3.1, $P = 0.002$), and diabetic patients who died were younger at presentation than nondiabetic patients (64.7 ± 11.4 vs. 71.1 ± 8.7 years, $P = 0.04$).

CONCLUSIONS — In patients with peripheral arterial disease, diabetic patients have worse arterial disease and a poorer outcome than nondiabetic patients.

Diabetes Care **24:1433–1437, 2001**

Peripheral arterial disease is characterized by a gradual reduction in blood flow to one or more limbs secondary to atherosclerosis (1). The prevalence of peripheral arterial disease is ~2–6% for men and women younger than 50 years of age, increasing to >7% in those older than 70 years of age (2,3). Diabetes, smoking, hypertension, and hyperlipidemia are important risk factors for peripheral arterial disease (4).

Patients with peripheral arterial disease often have coexisting cerebrovascular disease and/or coronary artery disease and therefore have poor prognosis and reduced life expectancy (5,6). Coronary heart disease accounts for half of the total mortality, whereas vascular disease in general accounts for almost two-thirds of the total mortality (7). Renal artery stenosis has also been demonstrated in >40% of the patients with peripheral arterial disease (8). Peripheral arterial disease is also an important risk factor for lower-extremity amputation in diabetic patients with chronic foot ulcers (9).

Few studies have compared the severity and mortality of peripheral arterial disease among diabetic versus nondiabetic patients. Strandness et al. (10) reported that diabetic patients had more infrapopliteal disease, whereas King et al. (11) found greater involvement of the profunda femoris in diabetic patients. A recent study in the U.K. showed that the cost of revascularization procedures was more in diabetic patients than in nondiabetic patients with peripheral arterial disease (12).

The aim of this study was to quantify the distribution of peripheral arterial disease in the diabetic and nondiabetic population attending for angiography and to compare severity and outcome between both groups of patients.

RESEARCH DESIGN AND METHODS

Study population and procedure

The patients included in the study were those referred for peripheral angiography. From the register of ~600 patients who attended for angiography in 1996, 150 patients were randomly selected. For each individual, the first angiographic examination performed between 1992 and 1996 (i.e., before any vascular or surgical intervention) was selected for analysis. Demographic data and indications for angiography are given in Table 1. Angiograms were examined by a radiologist, who was blinded to indication for angiography and diabetic status.

The Bollinger scoring system (13) was used to assess the severity of arterial disease. In this system, each arterial segment is assigned a number corresponding with disease severity. The minimum score is 0, indicating a normal segment; the maximum score is 15, indicating total occlusion extending for more than half the length of a segment.

Patient demographics (i.e., age and sex, smoking history, and history of hy-

From the Department of Medicine, Manchester Royal Infirmary, Manchester, U.K.
Address correspondence and reprint requests to Edward Jude, MD, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, U.K. E-mail: ejude@dc.cmht.nwest.nhs.uk.
Received for publication 21 November 2000 and accepted in revised form 12 April 2001.
Abbreviations: OR, odds ratio.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Downloaded from http://diabetesjournals.org/care/article-pdf/24/8/1433/643666/1433.pdf by guest on 28 May 2024

Table 1—*Demographics, smoking history, follow-up duration, and indications for arteriography in diabetic and nondiabetic patients*

	Diabetic patients	Nondiabetic patients	*P* value
n	58	78	
Age (years)	63.83 ± 10.4	65.31 ± 11.11	0.43
Men (%)	34 (59.7)	47 (61.8)	0.42
Smokers* (%)	47 (81.0)	60 (76.9)	0.26
Duration of follow-up (years)	4.47 ± 1.25	4.52 ± 1.23	0.85
Indications for arteriography			
Intermittent claudication	50 (86.2)	64 (82.1)	0.25
Rest pain	2 (3.5)	9 (11.5)	0.04
Foot ulcer	24 (41.4)	7 (8.9)	<0.0001
Foot gangrene	7 (12.1)	2 (2.6)	0.01
Number of amputations	24 (41.4)	9 (11.5)	<0.0001
High level	18	9	
Low level	6	0	

Data are *n* (%) or means ± SD. *This includes current smokers and ex-smokers.

pertension, ischemic heart disease, nephropathy, hypercholesterolemia, and peripheral vascular disease) were taken from the case notes. Ischemic heart disease was diagnosed if there was clinical evidence of angina, changes on electrocardiography, or history of a myocardial infarction or coronary revascularization procedure. Hypertension was defined according to the previous World Health Organization criteria (systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg) or if the patient was on current antihypertensive treatment. Nephropathy was diagnosed if a patient had microalbuminuria (20–200 μg/min), macroalbuminuria (>200 μg/min), or a serum creatinine level >140 μmol/l.

Case records were also examined to assess which of these patients later underwent revascularization procedures (vascular reconstruction, angioplasty, or stent placement), multiple revascularization procedures, or lower-extremity amputations and which patients had died during the years following their angiographic procedure (up until 1999). The level of amputation was defined as high level if proximal to the midfoot and low level if distal to the midfoot.

Statistical analysis

The two-sample *t* test was used to assess differences in the mean values for age and cholesterol levels. The one-tailed test for proportions was used to confirm or refute any apparent differences in proportions (e.g., demographics, medical history, vascular risk factors, revascularization procedures and amputations, etc.) between diabetic and nondiabetic patients. χ^2 test with odds ratios (ORs) were used to determine the association between diabetes and amputations, between diabetes and mortality, and between amputation and revascularization. This test was also used to determine the associations between total arterial occlusion (Bollinger score ≥13) and a history of symptoms, ischemic heart disease, hypertension, amputation, and mortality. Fisher's exact test was used as appropriate. χ^2 test for trend (χ^2trend) was used to determine the association between number of amputations and arterial occlusion score. The Mann-Whitney *U* test was used to determine differences in the arterial disease scores between diabetic and nondiabetic patients. The 95% CI was calculated as appropriate, and statistical significance was accepted when the *P* value was <0.05.

RESULTS — Of 150 patients selected, 136 patients whose case notes could be traced were included in this study. Their age (mean ±SD) was 64.7 ± 10.8 years. A total of 58 patients (43%) had diabetes, with a duration of 13.0 ± 11.1 years. There were no significant differences in age and sex distribution, smoking history, incidence of intermittent claudication, and the duration of follow-up after angiography between diabetic and nondiabetic patients. However, although diabetic patients had more foot ulcers and gangrene than nondiabetic patients, rest pain was less common in diabetic patients. This is summarized in Table 1.

Medical history and vascular risk factors

Diabetic and nondiabetic patients had the same proportion of patients with a history of ischemic heart disease (41.4 vs. 37.2%, $P = 0.62$). In 105 patients (41 diabetic) with recorded cholesterol levels, there was no difference in the proportion of patients with hypercholesterolemia (24.4 vs. 30.8%, $P = 0.52$). There was also no difference in the mean total cholesterol levels (5.4 vs. 5.6 mmol/l, $P = 0.5$) between diabetic and nondiabetic patients. However, there was a greater proportion

Table 2—*Differences in median arterial occlusion score between diabetic and nondiabetic patients*

	Median interquartile range additive occlusion score		
Arterial segment†	Diabetic patients	Nondiabetic patients	*P* value
Aorta	3 (3–4)	3 (3–3.5)	0.50
Common iliac	3 (2–3)	3 (2–3)	0.76
External iliac	2 (0–3)	3 (2–3)	0.15
Internal iliac	3 (0–6)	3 (0–4)	0.51
Profunda femoris	3 (0–5)	0 (0–2)	0.02
Superficial femoral	8 (4–13)	7 (2–9)	0.10
Popliteal	7 (3–10)	3 (0–4)	0.02
Anterior tibial	13 (4–15)	3 (0–13)	0.002
Peroneal	5 (0–15)	0 (0–6)	0.001
Posterior tibial	15 (0–15)	4 (0–14)	0.001

Data are *n* (interquartile range). *Because arterial segment disease was bilaterally similar, only one side (left) is used for analysis.

Downloaded from http://diabetesjournals.org/care/article-pdf/24/8/1433/643666/1433.pdf by guest on 28 May 2024

Table 3—*Levels of revascularization performed in diabetic and nondiabetic patients*

	Diabetic patients	Nondiabetic patients	*P* value
n	35 (60.3)	48 (61.5)	0.90
Iliofemoral region	8 (22.9)	11 (22.9)	0.98
Femoropopliteal region	27 (77.1)	34 (70.8)	0.52
Peroneal tibial region	0 (0)	3 (6.3)	0.07

Data are *n* (%).

of diabetic patients with hypertension (63.8 vs. 39.7%, $P = 0.006$).

Arteriographic findings

The Bollinger scoring system was used to assess the distribution and severity of disease in the aorta and lower limb arteries (Table 2). A total of 111 patients (82%) had at least one completely occluded arterial segment (Bollinger score ≥13). There was no association between the presence of completely occluded arterial segments and the presence of symptoms ($P = 0.2$) or a history of ischemic heart disease ($P = 0.3$), hypertension ($P = 0.12$), or mortality ($P = 0.32$). Diabetic patients had greater severity of disease than nondiabetic patients in the profunda femoris, popliteal, anterior tibial, peroneal, and posterior tibial arterial segments, but there was no difference in severity of arterial disease between the aorta or the iliac and superficial femoral arterial segments.

Revascularization procedures

Table 3 shows the number of patients who underwent a revascularization procedure as well as the level at which the procedure was performed. Between the diabetic and nondiabetic groups, there was no difference in the proportion of patients that underwent some form of revascularization procedure (60.3 vs. 61.5%, $P = 0.9$). There was also no difference in the levels of revascularization performed between the two groups. Additionally, there was no difference in the proportion of patients who underwent more than one revascularization procedure in the period following the angiographic procedure (20.7 vs. 21.8%, $P = 0.9$).

Amputations

A total of 33 patients (24 diabetic) underwent amputation of the lower limb during the follow-up period. The greater the arterial occlusion scores, the greater the number of amputations performed (χ^2 trend 16.2, df = 1, $P < 0.0001$). Diabetic patients were five times more likely than nondiabetic patients to have undergone an amputation (41.4 vs. 11.5%, OR 5.4, 95% CI 2.3–12.9, $P < 0.0001$). Most amputations (75% of the diabetic amputations and 100% of the nondiabetic amputations) were high level (Table 1). There was a trend toward diabetic patients having more foot-preserving amputations (distal to the midfoot) and more repeat amputations.

A total of 18 patients (55%) who underwent amputation had previously undergone revascularization: 12 of these patients were diabetic. These do not all represent failures of revascularization; in some cases, revascularization was performed with the aim of limiting the extent of amputation and promoting wound healing after amputation. However, there is no clear evidence from this series that revascularization reduces the risk of amputation.

Mortality

During a mean follow-up of 4.5 years, 37% of the patients died. These patients were slightly older (67.3 vs. 63.2 years, $P = 0.03$) and had higher prevalence of ischemic heart disease at referral (50 vs. 33%, $P < 0.05$) than patients who survived. There was a significantly higher proportion of deaths in the diabetic group compared with the nondiabetic group (51.7 vs. 25.6%, OR 3.1, 95% CI 1.5–6.4, $P = 0.002$). Additionally, the diabetic patients who died were significantly younger than the nondiabetic group who died during the same period (64.7 ± 11.4 vs. 71.2 ± 8.7 years, $P = 0.04$). However, there was no difference in the proportion of revascularization procedures only (33.3 vs. 40%, $P = 0.32$), amputations only (30.0 vs. 15%, $P = 0.11$), or the proportion of patients who had both amputation and revascularization (23.3 vs. 20.0%, $P = 0.39$) between diabetic and nondiabetic patients who had died (Table 4).

Mortality in the diabetic group. The diabetic deceased group included a significantly greater number of patients who had total arterial occlusions, a history of hypertension, and amputations compared with the patients who survived. This trend was also seen in the nondiabetic group. In deceased diabetic patients, there was also a slight trend toward more microvascular complications, namely retinopathy and neuropathy, a history of ischemic heart disease, and more high-level amputations (81 vs. 63%, $P = 0.16$), compared with those who survived, but these trends did not reach statistical significance. Additionally, more deaths occurred in the patients who had undergone amputation only, compared with the patients who had undergone revascularization only (75 vs. 43%, $P = 0.04$), but there were no significant differences between the patients who had undergone both procedures and those who had undergone either amputation or revascularization only ($P = 0.2$).

CONCLUSIONS

— This study has confirmed that diabetic patients have worse peripheral arterial disease below the knee and are at higher risk of lower extremity amputation than nondiabetic patients. Diabetic patients with peripheral arterial disease also had higher mortality and died at a younger age than nondiabetic patients. The profunda femoris artery was the only arterial segment above the knee that showed worse disease in diabetic patients.

Previous epidemiological studies have demonstrated poor survival in patients with peripheral arterial disease compared with the general population (6) and a higher incidence of peripheral arterial disease and poorer prognosis in diabetic patients compared with nondiabetic patients (14,15). Similar to our study, previous studies have also shown worse profunda and infrapopliteal arterial disease in diabetic patients (10,11). Faglia and colleagues also observed a positive trend between severity of arterial disease and amputation rate in diabetic patients (16), as demonstrated in this study.

We did not find any difference in the symptom of intermittent claudication between the two groups. This is similar to a previous study, which also did not report any difference in the frequency of symptoms between diabetic and nondiabetic subjects with peripheral vascular disease

Downloaded from http://diabetesjournals.org/care/article-pdf/24/8/1433/643666/1433.pdf by guest on 28 May 2024

Table 4—*A comparison between diabetic and nondiabetic patients who died and diabetic and nondiabetic patients who survived*

	Diabetic patients			Nondiabetic patients		
	Survivors	Deceased	*P*	Survivors	Deceased	*P*
n	28	30		58	20	
Age (years)	62.9 ± 9.2	64.7 ± 11.4	0.51	63.3 ± 11.2	71.2 ± 8.7	0.005
Men	17 (59.7)	17 (61.8)	0.38	34 (58.6)	13 (65.0)	0.31
Smokers	23 (82.1)	24 (80.0)	0.41	44 (75.9)	16 (80.0)	0.35
Duration of diabetes (years)	10.4 ± 9.8	15.5 ± 11.8	0.08	—	—	—
Retinopathy	10 (35.7)	16 (53.3)	0.09	—	—	—
Neuropathy	12 (42.9)	16 (53.3)	0.21	—	—	—
Nephropathy	6 (21.4)	7 (23.3)	0.43	—	—	—
Hypertension	14 (50.0)	23 (76.7)	0.02	24 (41.4)	7 (35.0)	0.31
Ischemic heart disease	10 (35.7)	14 (46.7)	0.19	18 (31.0)	12 (60.0)	0.01
Total occlusion	13 (46.4)	24 (80.0)	0.004	28 (8.2)	15 (75.0)	0.02
Total amputations	8 (28.6)	16 (53.3)	0.03	2 (3.4)	7 (35.0)	0.001
Amputations only	3 (10.7)	9 (30.0)	0.04	0 (0)	3 (15.0)	0.001
Revascularization only	13 (46.4)	10 (33.3)	0.15	34 (58.6)	8 (40.0)	0.07
Both procedures*	5 (17.9)	7 (23.3)	0.30	2 (3.4)	4 (20.0)	0.01

Data are means ± SD or *n* (%). *Patients who had revascularization and amputation.

(17). However, in that study (17), the evidence of vascular disease was based on the presence or absence of pulses in the lower limb and not radiological assessment. It may be possible that symptoms did not occur as frequently as expected in the diabetic patients (who had worse disease) due to the presence of diabetic neuropathy, which could have masked the pain of intermittent claudication. Therefore, these patients may present later than if they had normal sensation.

Even though diabetic patients in this study had more severe arterial disease, we did not observe any difference in the rate of arterial revascularization procedures performed between both diabetic and nondiabetic patients. This could be due to a number of reasons. First, the more severe arterial disease seen below the knee in the diabetic patients may have precluded arterial reconstruction; second, the performance of extreme distal revascularization procedures, even when technically feasible, may not always be performed because of the risk of high failure rate (18).

In conclusion, this is the first study that compares angiographic findings between diabetic and nondiabetic patients with peripheral arterial disease. This study has revealed that in a group of patients referred for angiography of the lower extremity, diabetic patients have worse angiographic findings, more amputations, and higher mortality than nondiabetic patients. Furthermore, and in keeping with previous studies (19), there is no convincing evidence that revascularization is effective in preventing amputation. Additional studies are required to determine whether earlier diagnosis and intervention may prevent amputation.

References

1. Ross R: The pathogenesis of atherosclerosis: an update. *N Engl J Med* 314:488–500, 1986
2. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ: Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 20:384–392, 1991
3. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA: The prevalence of asymptomatic and unrecognised peripheral arterial occlusive disease. *Int J Epidemiol* 25:282–290, 1996
4. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV: Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edingburgh Artery Study. *Am J Epidemiol* 135:331–340, 1992
5. Dormandy J, Heeck L, Vig S: The natural history of claudication: risk to life and limb. *Semin Vasc Surg* 12:123–137, 1999
6. Cheng SW, Ting AC, Lau H, Wong J: Survival in patients with chronic lower extremity ischemia: a risk factor analysis. *Ann Vasc Surg* 14:158–165, 2000
7. Verhaeghe R: Epidemiology and prognosis of peripheral obliterative arteriopathy. *Drugs* 56 (Suppl. 3):1–10, 1998
8. Missouris CG, Buckenham T, Cappuccio FP, MacGregor GA: Renal artery stenosis: a common and important problem in patients with peripheral vascular disease. *Am J Med* 96:10–14, 1994
9. Reiber GE, Pecoraro RE, Koepsell TD: Risk factors for amputation in patients with diabetes: a case control study. *Ann Intern Med* 117:97–105, 1992
10. Strandness DE, Priest RE, Gibbons GE: Combined clinical and pathological study of diabetic and non-diabetic peripheral arterial disease. *Diabetes* 13:366–372, 1964
11. King TA, DePalma RG, Rhodes RS: Diabetes mellitus and atherosclerotic involvement of the profunda femoris artery. *Surg Gynecol Obstet* 159:553–556, 1984
12. Panayiotopoulos YP, Tyrrell MR, Arnold FJL, Korzon-Burakowska A, Amiel SA, Taylor PR: Results and cost analysis of distal (crural/pedal) arterial revascularization for limb salvage in diabetic and nondiabetic patients. *Diabet Med* 14:214–220, 1996
13. Bollinger A: Semi-quantitative assessment of lower limb atherosclerosis from routine angiographic images. *Atherosclerosis* 38: 339–346, 1981
14. Pyorala K, Laakso M, Unsitupa M: Diabetes and atherosclerosis: an epidemiologic view. *Diabetes Metab Rev* 3:463–524, 1987
15. Donahue RP, Orchard TJ: Diabetes mellitus and macrovascular complications: an epidemiological perspective. *Diabetes Care* 15:1141–1155, 1992
16. Faglia E, Favales F, Quarantiello A, Calia P, Clelia P, Brambilla G, Rampoldi A, Morabito A: Angiographic evaluation of peripheral arterial occlusive disease and

Downloaded from http://diabetesjournals.org/care/article-pdf/24/8/1433/643666/1433.pdf by guest on 28 May 2024

its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. *Diabetes Care* 21:625–630, 1998
17. Walters DP, Gatling W, Mullee MA, Hill RD: The prevalence, detection, and epidemiological correlates of peripheral vascular disease: a comparison of diabetic and non-diabetic subjects in an English community. *Diabet Med* 9:710–715, 1992
18. Mercer KG, Berridge DC: Peripheral vascular disease and vascular reconstruction. In *The Foot in Diabetes*. 3rd ed. Boulton AJM, Connor H, Cavanagh PR, Eds. Chichester, U.K., Wiley, 2000, p. 215–234
19. Tunis SR, Bass EB, Steinberg EP: The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. *N Engl J Med* 325:556–562, 1991

Downloaded from http://diabetesjournals.org/care/article-pdf/24/8/1433/643666/1433.pdf by guest on 28 May 2024