Chapter 17

Peripheral Vascular Disease and Diabetes

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SUMMARY

Lower extremity arterial disease (LEAD) is clinically identified by intermittent claudication and/or absence of peripheral pulses in the lower legs and feet. These clinical manifestations reflect decreased arterial perfusion of the extremity. With the use of doppler technology and blood pressure measurements of the extremity, LEAD can be identified noninvasively before clinical manifestation. X-ray of the extremities can detect arterial calcification that is indicative of arterial disease with or without an occlusive component. Ultrasound with duplex scanning can also detect occlusive LEAD noninvasively, while angiography remains the gold standard for identification and diagnosis of LEAD.

The incidence and prevalence of LEAD increase with age in both diabetic and nondiabetic subjects and, in those with diabetes, increase with duration of diabetes. Many elderly diabetic persons have LEAD at the time of diabetes diagnosis. Diabetes is an important risk factor for LEAD. Hypertension, smoking, and hyperlipidemia, which are frequently present in patients with diabetes, contribute additional risk for vascular disease. LEAD in diabetes is compounded by the presence of peripheral neuropathy and by susceptibility to infection. These confounding factors in diabetic patients contribute to progression of LEAD to foot ulcerations, gangrene, and ultimately to amputation of part of the affected extremity. Diabetes accounts for ~50% of all nontraumatic amputations in the United States. A secondary amputation within several years after the first is exceedingly common.

Mortality is increased in patients with LEAD, particularly if foot ulcerations, infection, or gangrene occur. Three-year survival after an amputation is <50%. Prevention is an important component of LEAD management. By the time LEAD becomes clinically manifest, it may be too late to salvage an extremity, or it may require more costly resources to improve the circulatory health of the extremity.

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DEFINITION AND ASSESSMENT

LEAD manifests itself by decreased arterial perfusion to the lower extremities. This decreased perfusion results in diminution or absence of peripheral pulses and may lead to intermittent claudication (pain on walking, relieved promptly by rest), proneness to infection, ulcerations, poor healing of sores and ulcers, gangrene, and ultimately to amputation. Intermittent claudication is indicative of clinical occlusive LEAD. LEAD is associated with increasing age and duration of diabetes.

Assessment of peripheral vascular disease in diabetes was addressed by an international workshop in 1992[1]. Palpation of peripheral pulses has been used as a clinical tool to assess occlusive LEAD in diabetic and nondiabetic patients, particularly when intermittent claudication is present. However, it is sometimes difficult to interpret the significance of diminished peripheral pulses when symptoms are not present. Ambient temperature, anatomic variation, and expertise in palpating peripheral pulses may contribute to variation in the clinical examination. Absence of pulses remains a significant clinical finding. Absent posterior tibial, popliteal, or femoral pulses with or without bruits that persist on repeated examination are clinically significant and indicate significant occlusive LEAD whether intermittent claudication is present or not. However, clinical findings such as diminution or absence of peripheral pulses and presence of bruits are more meaningful of occlusive disease in the context of clinical symptoms such as intermittent claudication. Because of anatomic variation, absence of the dorsalis pedis pulse alone may not indicate LEAD. The Rose

questionnaire[2] for identifying significant LEAD has a high frequency of false negatives in our experience and that of others and does not allow assessment of whether one or both legs are involved. The questionnaire should be revised to correct these deficiencies[1].

Measurement of the ankle-brachial index (ABI), which represents the systolic blood pressure at the posterior tibial or dorsalis pedal level compared with brachial blood pressure, can be used to define clinically significant occlusive LEAD. An index of <0.9 is suggestive of occlusive LEAD, particularly if symptoms or clinical findings such as bruits or absent pulses are present. ABI levels ≤0.8 indicate LEAD regardless of symptoms. The lower the ABI, the more significant the occlusion whether symptoms are present or not. It is highly unlikely that symptoms would not be present in patients whose ABI is <0.5. The ABI may be more sensitive with exercise, and a 5-minute exercise period with measurement of the ABI post-exercise may indicate significant occlusive LEAD before the resting ABI becomes abnormal[1,3,4]. The post-exercise ABI helps differentiate the etiology of exercise-induced leg pain[1].

X-ray of the extremities will identify calcified arteries that may be associated with high ABI levels, indicating noncompressible arteries. It is more difficult to identify occlusive LEAD in these patients because of the high ABI levels and the continued presence of peripheral pulses. Velocimetry with continuous-wave Doppler technique may be able to identify occlusive LEAD in the presence of noncompressible vessels[1]. Also, the toe systolic blood pressure index (TSPI) may be helpful in identifying occlusive LEAD in this circumstance. Otherwise, the first symptoms of occlusive LEAD in these patients may be related to gangrene or ulceration.

Measurement of toe pressures has received a great deal of attention because of their predictability in defining individuals at high risk of gangrene, ulceration, and infection associated with occlusive arterial disease, even in patients with noncompressible vessels. Reduced toe pressures are highly associated with progression of LEAD to gangrene, ulceration, and the need for amputation[1].

Velocimetry with continous-wave Doppler alluded to above provides a qualitative measure of occlusive LEAD, but the ABI and TSPI are the definitive quantitative diagnostic indices for occlusive disease in compressible arteries[1].

Ultrasonic duplex scanning adds a new dimension to assessment of LEAD. This technology is still evolving and may help localize occlusive disease and determine appropriate intervention strategies. There is no role for duplex scanning at this time in screening or establishing the diagnosis of LEAD. Screening and diagnosis of LEAD are best accomplished with measurement of ABI and TSPI[1]. Transcutaneous oxygen measurement (Po_2) may help assess the healing of ischemic skin lesions. The measurement is not useful for screening or diagnosis of LEAD[1].

Angiography remains the gold standard for identifying occlusive LEAD and the areas of occlusion in the arterial system. Patients being considered for amputation because of occlusive LEAD should have angiography performed to determine whether revascularization may be effective in salvaging the limb or in lowering the level of amputation.

PREVALENCE

The prevalence of LEAD is higher in diabetic than nondiabetic patients in population-based and clinic-based studies[1,3-21]. Because of selection in referral, however, the prevalence of LEAD in patients seen at secondary and tertiary medical centers is higher than in diabetic patients in the general community (Table 17.1). Using pulse deficits as the criterion for LEAD, 8% of the Rochester, MN diabetic population diagnosed in 1945-69 had LEAD at the time of initial diagnosis of diabetes. Among the prevalent diabetic patients on January 1, 1970, 10.5% had LEAD and 3.2 per 1,000 Rochester residents had both diabetes and LEAD on that date[8]. Using pulse deficits as the criterion, 9.9% of prevalent diabetic patients in Kristianstad, Sweden, had LEAD; the comparable figure for the nondiabetic population was 2.6%[5]. In the Kristianstad study, when the indicator of moderate or marked arterial calcification was used, LEAD was detected in 16.4% of patients with diabetes of short duration (mean duration 1.5 years) and 38.7% of patients with diabetes of long duration (mean duration 20 years). The comparable figure for the nondiabetic population was 12.2%. The prevalence of LEAD in Mexican Americans in San Antonio, TX is discussed in Chapter 32.

In the physician's examination of a probability sample of U.S. adults in the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II), pulse deficits were determined. Prevalence of diminished or absent pulsation of the dorsalis pedis artery was found in 16.2% of adults with diagnosed diabetes age 35-54 years and 23.5% of those age 55-74 years (Table 17.2). These rates were considerably higher than those for nondiabetic subjects.

Table 17.1
Prevalence of Lower Extremity Arterial Disease in Diabetic Patients in Population-Based and Clinical Studies

Ref.	Type of study	Measurement	No.	% with LEAD
Population-Based Studies				
5	Kristianstad, Sweden	Pulse deficits	374	9.9
8	Rochester, MN	Pulse deficits	724	10.5
17	Randomly selected newly diagnosed diabetic males, Finland	Intermittent claudication	70	8.8
		Absent foot pulses	70	30.1
		Ankle-arm blood pressure ratio <0.9	70	7.3
Clinical Studies				
7	UGDP subjects within 1 year of diabetes diagnosis	Arterial calcification	997	16.1
		Pulse deficits	1,018	13.1
		Intermittent claudication	1,011	5.1
9	Diabetic volunteers	History, physical exam, physiologic tests	430	28.6
10	Hospital outpatients	Doppler ultrasound	623	15.9
11	Diabetic volunteers	Physiologic tests	426	30.8
14	Diabetic volunteers	Doppler and plethysmography	514	38.9

UGDP, University Group Diabetes Program.

Source: References are listed within the table

Data for LEAD from the 1989-91 National Hospital Discharge Survey (NHDS) for diabetic and nondiabetic patients are shown in Table 17.3. The data are based on diagnoses listed on the hospital discharge record. The specific criteria for the diagnoses are not provided. These data therefore have the inherent bias of what the clinician judged or classified as LEAD. In addition, the completeness of recording LEAD and diabetes is unknown. Nevertheless, LEAD occurs more frequently in diabetic than nondiabetic patients on the basis of these data. LEAD is listed in ~3% of diabetic hospitalizations versus 0.6% of nondiabetic hospitalizations. LEAD is associated with an increased frequency of hospitalization in males versus females in patients with and without diabetes.

Table 17.2
Prevalence of Diminished/Absent Pulsation of Dorsalis Pedis Artery, U.S., 1976-80

Diabetes status	No.	Percent
Age 35-54		
Medical history of diabetes	92	16.2
Newly diagnosed diabetes	29	0.0
Nondiabetic	959	8.6
Age 55-74		
Medical history of diabetes	425	23.5
Newly diagnosed diabetes	154	16.5
Nondiabetic	1,482	13.7

Medical history of diabetes determined by interview; newly diagnosed diabetes and nondiabetic determined by 75-g 2-hour oral glucose tolerance test using World Health Organization criteria; IDDM were excluded based on age <30 years at diagnosis, lack of obesity, and continuous insulin use since diagnosis; data were collected during a physician's examination.

Source: 1976-80 Second National Health and Nutrition Examination Survey

INCIDENCE

In the Rochester, MN population-based cohort of diabetic patients, the cumulative incidence of LEAD, measured by pulse deficits, was 21.3 per 1,000 person-years of diabetes for men and 17.6 per 1,000 person-years for women. The actuarially estimated cumulative incidence of LEAD was 15% at 10 years after the initial diagnosis of diabetes and 45% after 20 years. If the 8% of patients who already had LEAD at the time of initial diagnosis of diabetes were included, the overall cumulative incidence would be higher. Using a history of intermittent claudication as the criterion for LEAD, the Framingham, MA study identified a lower incidence of LEAD in diabetic persons in that population (12.6 per 1,000 person-years for men and 8.4 per 1,000 person-years for women)[6]. Values for individuals without diabetes in the Framingham population were 3.3 and 1.1 per 1,000 person-years for men and women, respectively. Sixteen years after the diagnosis of diabetes, 18.8% of Framingham diabetic subjects had developed intermittent claudication. In both the Rochester and Framingham studies, incidence of LEAD was higher in men than in women. Incidence in Framingham of abnormal peripheral arterial findings increased with age in both diabetic and nondiabetic subjects[18]. Much of the excess risk associated with diabetes was found in those age <70 years.

Table 17.3

Hospital Discharges Listing Diabetes and Lower Extremity Arterial Diseases, U.S., 1989-91

ICD9-CM code, race, and sex	Hospitalizations with diabetes		Hospitalizations without diabetes	
	Average annual no. (thousands)	% of total DM discharges	Average annual no. (thousands)	% of total non-DM discharges
Diabetic peripheral circulatory diseases, 250.7				
Total	81.6	2.8		
White	51.7	2.5		
Black	15.7	3.5		
Other/not stated	14.3	3.2		
Male	42.8	3.4		
Female	38.8	2.3		
Atherosclerosis of the extremity, 440.2				
Total	40.4	1.4	80.0	0.25
White	30.3	1.5	58.3	0.27
Black	5.9	1.3	9.9	0.27
Other/not stated	12.5	2.8	11.9	0.19
Male	22.3	1.8	49.7	0.38
Female	18.1	2.0	30.3	0.16
Peripheral vascular disease, 443.89, 443.9				
Total	97.3	3.3	188.6	0.59
White	73.4	3.6	144.0	0.66
Black	10.7	2.4	15.8	0.43
Other/not stated	13.2	3.0	28.8	0.45
Male	53.7	4.3	113.9	0.87
Female	43.6	2.6	74.8	0.40
Chronic leg ulcer, 707.1				
Total	80.3	2.7	62.0	0.20
White	56.3	2.8	43.3	0.20
Black	11.7	2.6	9.3	0.25
Other/not stated	12.3	2.7	9.4	0.15
Male	41.6	3.3	30.9	0.24
Female	38.7	2.3	31.2	0.17
Gangrene, 785.4				
Total	50.9	1.7	65.4	0.21
White	30.2	1.5	44.3	0.20
Black	10.3	2.3	12.0	0.32
Other/not stated	10.5	2.3	9.1	0.14
Male	26.8	2.1	37.5	0.29
Female	24.1	1.4	27.9	0.15

Percent of total refers to the percent of all discharges in the race or sex group. DM, diabetes; non-DM, no diabetes mentioned on the hospital discharge. Total average annual number of discharges (in thousands) with any diabetes diagnosis in 1989-91 were age <17 years, 40.9; age 18-44 years, 346.8; age 45-64 years, 855.0; age ≥65 years, 1,682.4; all ages, 2,925.1. ICD9-CM codes used to identify diabetes hospitalizations were 250.00-250.92, 251.3, 357.2, 362.00-362.02, 366.41, 648.00-648.04, and 775.10 as any diagnosis listed on the hospital discharge record.

Source: 1989-91 National Hospital Discharge Surveys

The progression of LEAD was investigated in age- and sex-matched cohorts of control subjects, subjects with LEAD without diabetes, and subjects with diabetes with and without LEAD[4]. Incidence rates for development or progression of LEAD are shown in Table 17.4. The rates of progression of LEAD in patients with LEAD at baseline were similar for those with and without diabetes. It thus appears that diabetic subjects with LEAD do not have a greater progression rate than nondiabetic subjects with LEAD. Even when severity of the baseline LEAD was taken into account, there was no significant difference in progression between diabetic and nondiabetic subjects with LEAD.

Many patient studies that are not population-based also indicate the increased frequency of intermittent claudication, LEAD, foot ulcers, gangrene, and amputations in diabetic versus nondiabetic subjects. Data from patients enrolled in the University Group Diabetes Program (UGDP) study of adult-onset diabetes

Table 17.4
Incidence of Lower Extremity Arterial Disease (LEAD), Rochester, MN

Cohort	No. per 1,000 person-years	95% confidence interval
No diabetes, no LEAD	2.6	0.1-14.0
Diabetes, no LEAD	25.1	15.1-35.0
Diabetes, with LEAD	71.7	49.0-98.5
No diabetes, with LEAD	77.4	54.2-100.6

Peripheral occlusive arterial disease was assessed by clinical criteria and non-invasive testing, including post-exercise ankle/brachial systolic blood pressure ratio. Diabetes was determined by clinical criteria.

Source: Reference 4

indicate a variable risk for LEAD, depending on the diagnostic criteria employed. By 13 years after the start of the study in 1961, the actuarially estimated cumulative incidence of arterial calcification was 61% among men and 32% among women[16]. The cumulative incidence of pulse deficits was ~35%, while the cumulative incidence of intermittent claudication was >30%. In a separate study using a variety of more sophisticated physiologic indicators, LEAD was found in 7% of a group of diabetic patients free of the disorder 2 years earlier[14].

RISK FACTORS

Age, sex, diabetes, hyperlipidemia, hypertension, and cigarette smoking are significant risk factors for LEAD[3,11-13,20,22]. In patients with diabetes, vascular disease, ABI, current smoking, and arm systolic blood pressure were identified as significant independent risk factors for LEAD[20]. Surprisingly, serum lipid levels, platelet function measures, platelet factor 4, and platelet survival were not associated with progression of LEAD. However, the platelet-derived specific protein, beta-thromboglobulin, was associated with progression of vascular disease, suggesting that platelet activation has a role in disease progression, but the mechanism(s) of platelet activation was not apparent from the other platelet studies performed. The study corroborated the long-standing clinical impressions that smoking, hypertension, and presence of LEAD are associated with progression of vascular disease in diabetes.

MORBIDITY

The morbidity of LEAD includes intermittent claudication, foot ulcers, gangrene, and amputation. The subject of amputations is discussed in Chapter 18. Foot ulcers and gangrene are frequent comorbid conditions with LEAD and are discussed below. Concurrent peripheral neuropathy with impaired sensation make the foot susceptible to trauma, ulceration, and infection.

The progression of LEAD in diabetes is compounded by such comorbidity as peripheral neuropathy and insensitivity of the feet and lower extremities to pain and trauma. With impaired circulation and impaired sensation, ulceration and infection occur. Progression to osteomyelitis and gangrene may necessitate amputation. Revascularization procedures have assisted with improving perfusion and flow to the lower extremities but have apparently not decreased the frequency of amputation[23,24]. Arterial calcification on X-ray of the extremities identifies a group of individuals who have developed significant LEAD, but these patients may or may not have occlusive LEAD. Foot ulcers or gangrene or both, with or without infection, may be the initial manifestation of occlusive LEAD in these patients (see Definition and Assessment section for techniques to identify such patients at risk of occlusive LEAD).

DIABETIC FOOT ULCER

Diabetic foot ulcers may occur not only in conjunction with LEAD but also may be associated with neuropathy, venous insufficiency (varicose veins), trauma, and infection. LEAD contributes to these other conditions in producing or precipitating foot ulcers. Foot ulcers do not necessarily represent progression of LEAD, as they may occur in the presence of adequate clinical peripheral arterial perfusion. Patient-based studies indicate an increased risk of foot ulceration in diabetic patients who have peripheral neuropathy and a high plantar foot pressure[25].

The prevalence of a history of ulcers or sores on the foot or ankles was 15% of all diabetic patients in the population-based study in southern Wisconsin[15]. The prevalence was higher for diabetic individuals diagnosed at age <30 years, was slightly higher in men (16%) than in women (13%), and was greater in insulin-treated diabetic patients (17%) than in patients not taking insulin (10%). The prevalence increased with age, especially in diabetic patients diagnosed at age <30 years.

In patient studies from Europe, prevalence of foot ulcers in diabetic patients was 3% in those age <50 years[26], 7% in those age ≥60 years[27], and 14% in those age ≥80 years[28]. Prevalence was greater in males than

in females at age ≥70 years[28].

Data related to chronic ulcer of the leg from hospital discharge summaries are shown in Table 17.3. Hospitalization for this diagnosis is more frequent in discharges listing diabetes in all ethnic categories compared with nondiabetic discharges. In addition, ulcers were more frequent in discharges of diabetic males than diabetic females. Approximately 3% of diabetic hospitalizations in 1989-91 listed chronic ulcer of the leg as a diagnosis.

GANGRENE

Gangrene is defined as focal or extensive necrosis of the skin and underlying tissue. However, this definition presents difficulties. There are several etiologies for gangrene, as there are for foot ulcers. One is LEAD of the large or small vessels, but infection and neuropathy may also play a role. Gangrene is better correlated with LEAD than is foot ulcer. The demonstration of clinical or subclinical LEAD is essential if gangrene is to be considered a manifestation of the progression of LEAD in the individual patient.

In the Rochester, MN population-based study[8], the incidence of new episodes of gangrene in diabetic residents who were initially free of any LEAD was 4.5 per 1,000 person-years of study. In patients with LEAD, the incidence of gangrene was much higher, being 29.6 per 1,000 person-years in men and 37.1 per 1,000 person-years in women. In the Rochester, MN study, the prevalence of gangrene in diabetic patients was 0.8%. The prevalence of gangrene is greater in selected diabetic patient populations than in the general community. However, prevalence is not a satisfactory indicator of the importance of gangrene in diabetes, compared with incidence, because of the poor survival experience of these patients and their consequent loss from the prevalent population.

Risk factors for gangrene have not been adequately quantified for diabetic patients. They include LEAD, peripheral neuropathy, infection, trauma, and delayed healing. Hospitalization data for gangrene in the 1989-91 NHDS are shown in Table 17.3 for discharges in which diabetes was and was not listed. Approximately 2% of diabetic discharges listed gangrene versus 0.2% in nondiabetic patients. Hospitalization for gangrene was more common in males than females in both diabetic and nondiabetic discharges. Revascularization procedures such as lower limb endarterectomy (*International Classification of Diseases, 9th Revision* (ICD-9) code 381.8) and aorto-iliac-femoral bypass (ICD-9 code 392.5) were listed in ~0.3% of diabetic hospitalizations versus 0.1% in nondiabetic hospitalizations in the 1989-91 NHDS.

MORTALITY

There is increased mortality in patients with LEAD, particularly in those with progressive disease and following amputation. This mortality is increased both in population-based studies and in patient-based studies. In Rochester, MN residents with diabetes and LEAD, ~14% were alive 13 years after the diagnosis of diabetes, compared with an expected 42.5% survival rate in the general community. These rates indicate a threefold excess death rate for diabetic patients. However, LEAD per se increases the mortality rate even in the absence of diabetes. The mortality rate in Framingham, MA residents with intermittent claudication without diabetes was 39.4 per 1,000 person-years for men and 20.4 per 1,000 person-years for women, which was 1.9 and 2.9 times greater than expected, respectively[29]. Similarly, in the UGDP, mortality was 70%-80% greater in diabetic subjects with nonpalpable peripheral pulses at entry to the study than in diabetic individuals with palpable pulses[16]. Medial artery calcification is an independent risk factor for cardiovascular mortality in patients with non-insulin-dependent diabetes mellitus (NIDDM)[30].

In the Rochester, MN cohort with diabetes and gangrene, survival was poor with only 39% alive after 2 years, which was 45% of the expected survival rate[8]. Gangrene was listed on U.S. death certificates in 1950-67 20 times more often in diabetic than nondiabetic individuals[15]. In 1978, 41% of all death certificates in Louisiana that listed gangrene also listed diabetes[15].

PREVENTION

LEAD represents a major chronic complication of diabetes and a major health care delivery problem for diabetic patients. Preventive measures at the primary and secondary prevention levels are essential if morbidity, mortality, and health care costs are to be reduced. Primary prevention of LEAD in diabetic patients consists of control of risk factors including obesity, hyperglycemia, hyperlipidemia, smoking, and hypertension. Secondary prevention after LEAD has been clinically recognized consists of correction of these risk factors in hope of delaying progression of LEAD. The Diabetes Control and Complications Trial (DCCT) showed a beneficial trend of glycemic control on vascular disease in insulin-dependent diabetes

mellitus (IDDM), but this trend was not statistically significant[21]. Perhaps with longer followup the beneficial effect on vascular disease could be demonstrated.

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