CHAPTER 20

PERIPHERAL ARTERIAL DISEASE, FOOT ULCERS, LOWER EXTREMITY AMPUTATIONS, AND DIABETES

Edward J. Boyko, MD, MPH, Matilde Monteiro-Soares, DPM, PhD, and Stephanie G.B. Wheeler, MD, MPH

Dr. Edward J. Boyko is Professor at the University of Washington and Staff Physician at the Veterans Affairs Puget Sound, Seattle, WA. Dr. Matilde Monteiro-Soares is an Investigator at the Center for Health Technology and Services Research (CINTESIS) and an Instructor in the Department of Community Medicine Information and Health Decision Sciences (U753-FCT), Oporto Faculty of Medicine, Oporto, Portugal. Dr. Stephanie G.B. Wheeler is Associate Professor at the University of Washington and Staff Physician, Veterans Affairs Puget Sound, Seattle, WA.

SUMMARY

Peripheral arterial disease (PAD) is common among persons with diabetes, and estimates of prevalence range from 10% to 20%. The condition is often asymptomatic. Persons with diabetes are at increased risk for PAD and often have more distal vascular disease than persons without diabetes. PAD is associated with substantial morbidity, including pain and functional impairment, amputation, and higher risk of death. Diabetic foot ulcer (DFU) occurs commonly in persons with diabetes, with a lifetime prevalence estimated between 12% and 25%. Healing of DFU may take months to years, and often these lesions lead to lower extremity amputation (LEA). The leading cause of DFU is neuropathy, with contributions from multiple other risk factors, including PAD, diabetes duration and control, and self-care factors. Although diabetes accounted for the majority of all LEA in the United States in 1997, the frequency of hospitalizations for amputation among persons also coded as having diabetes fell dramatically between 1996 and 2008, from approximately 11 to 4 per 1,000 persons hospitalized. Although reduced, this rate is approximately sevenfold higher compared to persons without diabetes. PAD, DFU, and LEA have a considerable negative impact on both the functional status and survival of persons with diabetes in the United States.

PERIPHERAL ARTERIAL DISEASE

INTRODUCTION

Peripheral arterial disease (PAD) refers to partial or complete obstruction of the peripheral arteries, typically the arteries in the legs. The most common symptom of PAD is intermittent claudication, which is calf and lower extremity pain that develops with walking or other exertion and is relieved by rest. However, the majority of persons with PAD are asymptomatic. PAD is more common among persons with diabetes due to the higher risk for arterial atherosclerosis associated with this metabolic disorder.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS IN DIABETES

Diabetes is associated with an increased risk for atherogenesis and vascular inflammation, caused by hyperglycemia, excess free fatty acids, insulin resistance, and other factors. Inflammation and atherogenic activity are associated with endothelial cell dysfunction, abnormalities in vascular smooth muscle cell function, platelet abnormalities, and a hypercoagulable state (1,2,3). Nitric oxide (NO) is an important mediator of endothelial function due to its effects on vasodilation, leukocyte-vascular wall interactions, and platelet aggregation. Hyperglycemia contributes to the loss of NO homeostasis by blocking endothelial cell NO synthase (4) and increasing production of reactive oxygen species accompanied by vascular inflammation (5). Insulin resistance leads to increased free fatty acid levels, which activate protein kinase C, inhibit phosphatidylinositol-3 kinase, and increase production of reactive oxygen species. Increases in these proinflammatory factors, together with the loss of NO homeostasis and increased local oxidative stress, are associated with the transformation of leukocytes into foam cells (3). Transition to foam cells is an important early step in atheroma development. Hyperglycemia activates inflammatory mediators and reactive oxygen products that are associated with abnormal migration of vascular smooth muscle cells, so that advanced atherosclerotic lesions in diabetic patients have fewer vascular smooth muscle cells compared with lesions in those without diabetes. This can promote atherosclerotic lesion formation and plaque instability. Glucose entry into platelets is not dependent on insulin, so glucose levels in the platelet are similar to intravascular levels and can lead to changes associated with accelerated atherogenesis, including oxidative stress, increased platelet aggregation, and decreased levels of endogenous inhibitors of platelet activity. Hyperglycemia increases blood coagulability and impairs fibrinolysis through increased production of tissue factor, a potent procoagulant. Hyperglycemia also increases plasma concentrations of factor VII and

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plasminogen activator inhibitor type 1 and decreases endogenous anticoagulants, such as antithrombin III and protein C.

Differences in Pathophysiology Compared to Persons Without Diabetes

Arterial disease in people with diabetes is both morphologically and physiologically different than in persons without diabetes (6,7,8). The femoropopliteal arterial segments are most often affected, as in nondiabetic patients. However, smaller vessels below the knee, including the profunda femoris, popliteal, anterior tibial, peroneal, and posterior tibial arteries, are more severely affected in diabetic than in nondiabetic patients (2,8,9,10), with a high prevalence of diffuse rather than focal lesions. In addition, medial calcification of the tibial and peroneal arteries is more common. Diabetes is associated with a propensity to earlier arterial calcification, increased thrombogenicity, and generally poorer prognosis.

DEFINITION AND MEASUREMENT OF PAD

PAD refers to narrowing of the vascular lumen resulting in a reduction in blood supply that leads to inadequate oxygenation of the tissues of the lower extremity. The most common cause of PAD is atherosclerosis, in which the arterial lumen becomes occluded by plaque arising from the intima. This process largely affects the large and medium-sized arteries, usually at branch points and bifurcations (10,11).

Invasive Measurement

Visualization of the arterial vasculature is possible via radiographic contrast angiography, which is considered the gold standard for vascular disease diagnosis. Due to its invasive nature and the risk of kidney injury, radiographic contrast angiography is rarely used in clinical diagnosis other than in the setting of planned revascularization, where it is performed to precisely localize anatomic arterial obstructions. Magnetic resonance angiography is fast becoming an important noninvasive method for the detection of PAD.

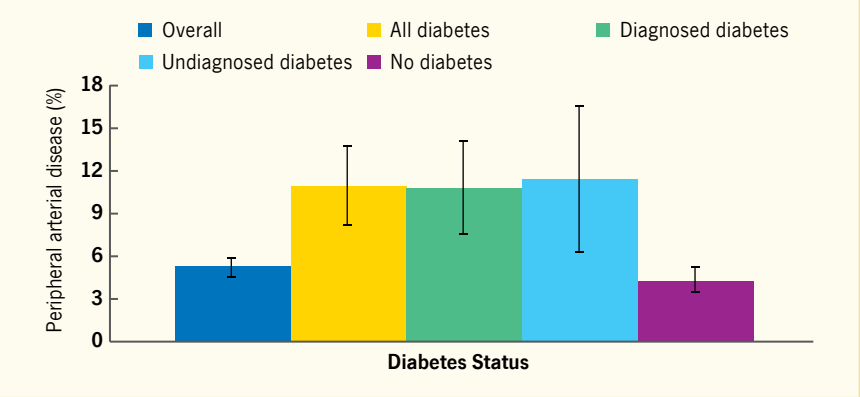
TABLE 20.1. Mean Ankle-Brachial Index Among Adults Age ≥40 Years, Overall and by Diabetes Status, U.S., 1999–2004

	MEAN (STANDARD ERROR)				
	Overall	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	No Diabetes
Right side	1.12 (0.003)	1.10 (0.005)	1.09 (0.006)	1.10 (0.012)	1.13 (0.004)
Left side	1.13 (0.003)	1.11 (0.005)	1.11 (0.006)	1.11 (0.013)	1.13 (0.003)

Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.1. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, by Diabetes Status, U.S., 1999–2004



Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* Error bars represent 95% confidence intervals. See Table 20.2 for further details. A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Noninvasive Measurement

The ankle-brachial index (ABI) is a noninvasive, simple to perform, inexpensive, and widely used method for the assessment of arterial blood flow to the lower extremity. The ABI is measured in a supine patient by obtaining the brachial and ankle systolic pressures using a 5–7 MHz handheld Doppler device. Both the posterior tibial and dorsalis pedis systolic pressures should be obtained, because adequate flow in either of these arterial beds is sufficient to perfuse the foot. The ABI is calculated by dividing the higher of the posterior tibial or dorsalis pedis systolic pressures by the higher of either of the brachial systolic pressures (12,13). The normal ABI can be defined as 0.9–1.3 (1). To account for variability in the measurement, it is generally agreed that a lower cutoff value of 0.95 is normal (10). PAD is often defined as an ABI ≤0.90, although some studies have used a cutoff of 0.80. Severe obstruction requiring vascular surgery evaluation is usually recommended for a value <0.4 or <0.5.

In persons with diabetes, calcification of the tibial and peroneal arteries may render them noncompressible and produce a falsely elevated ABI considerably greater than 1.0 (10). Symptoms of PAD may therefore occur even with an ABI >0.9, if noncompressible, calcified vessels result in falsely high readings of the ankle systolic blood pressure (14). The phenomenon of greater frequency of calcified, noncompressible arteries in diabetes may explain the similar values for mean ABI by diabetes status seen in new analyses conducted for *Diabetes in America, 3rd edition,* based on the National Health and Nutrition Examination Surveys (NHANES) 1999–2004 (Table 20.1), despite a higher prevalence of ABI <0.9 among persons with diabetes (Figure 20.1, Table 20.2).

TABLE 20.2. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Smoking Status, and Diabetes Status, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	Overall	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	No Diabetes
Overall	5.23 (0.38)	10.99 (1.40)	10.79 (1.64)	11.39 (2.55)	4.32 (0.43)
Age (years)					
40–64	2.72 (0.35)	5.68 (1.31)	5.11 (1.14)	6.88 (2.96)[2]	2.36 (0.39)
65–74	11.27 (1.43)	16.84 (3.32)	17.99 (3.67)	14.47 (6.33)[2]	9.57 (1.55)
≥75	15.27 (1.46)	22.93 (3.09)	21.88 (4.36)	25.18 (6.57)	13.40 (1.58)
Sex					
Men	4.72 (0.48)	11.40 (1.81)	11.15 (1.97)	11.85 (3.43)	3.47 (0.49)
Women	5.70 (0.56)	10.48 (1.73)	10.41 (2.01)	10.67 (3.99)[1]	5.06 (0.61)
Race/ethnicity					
Non-Hispanic white	5.13 (0.46)	12.13 (1.95)	11.83 (2.33)	12.70 (3.40)	4.18 (0.50)
Non-Hispanic black	7.99 (0.95)	14.77 (1.63)	15.68 (2.35)	12.20 (2.98)	6.30 (1.06)
All Hispanic	4.13 (1.09)	5.82 (1.72)	5.07 (1.82)	[3]	3.70 (1.03)
Mexican American	3.76 (0.79)	5.81 (1.42)	6.26 (1.13)	[3]	3.23 (0.94)
Smoking status					
Never smokers	3.41 (0.48)	5.39 (1.09)	5.97 (1.42)	4.10 (1.63)[1]	3.12 (0.54)
Former smokers	6.64 (0.77)	14.98 (2.33)	15.83 (3.19)	13.42 (4.28)[1]	5.09 (0.87)
Current smokers	6.98 (0.93)	15.74 (3.94)	12.20 (2.32)	24.46 (10.32)[2]	5.76 (0.91)

Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

An American Diabetes Association consensus statement recommended using the ABI to screen for peripheral vascular disease in persons with diabetes age >50 years (15). The issues of screening and misclassification and the limitations of the ABI were acknowledged. However, the problems were not felt to detract from the clinical usefulness of the ABI to screen for and diagnose PAD in persons with diabetes. Hallux pressures may be used in patients with medial artery calcification in whom the ABI is elevated. Calcification of the arterial media is common in persons with diabetes, but medial calcification does not extend into the digital arteries. Thus, perfusion pressure can be assessed by measuring hallux systolic pressure using either a strain-gauge sensor or photoplethysmography (16).

Symptom-Based Diagnosis

Claudication is an insensitive measure of PAD, with symptomless diminished arterial flow estimated to occur at least two to five times as frequently as symptomatic claudication (17). Multiple questionnaire instruments are available to assess the presence of claudication, including the Rose questionnaire (11), which inquires about the following features of PAD clinical symptoms: pain located in one or both calves, provocation by walking quickly or uphill, never occurring at rest, forces the subject to stop or slacken pace, disappears within 10 minutes of rest, and never disappears with continued walking. The original Rose questionnaire has only moderate sensitivity (60%–68%) in capturing persons with this clinical diagnosis (18) when physician diagnosis and ABI are used as the gold standard. The Edinburgh Claudication Questionnaire, a simplified version of the Rose questionnaire, has improved diagnostic test indices with sensitivity of 91.3% (95% confidence interval [CI] 88.1%–94.5%) and specificity of 99.3% (95% CI 98.9%–100%) (18).

Exercise Testing

Exercise testing can help with diagnosis of PAD in patients who have typical symptoms of claudication but a normal ABI or in those with atypical symptoms. Patients walk on a graded treadmill until symptoms are elicited, and ABIs are recorded immediately thereafter (10). Patients with arterial obstruction will typically have a >20 mmHg drop in ankle pressure after exercise.

Measures Suitable for Epidemiologic Research

The ABI is a valid and reproducible measurement of PAD. Compared with an assessment of pulses or a medical history, the ABI is more accurate (1). The ABI has been validated against angiography and found to be 95% sensitive and almost 100% specific (19,20). Limitations to the ABI are that it is inaccurate in patients with calcified, poorly compressible vessels and in symptomatic patients with moderate aortoiliac stenoses (1).

EPIDEMIOLOGY

Data Sources and Limitations

One general data source for this chapter includes new analyses of existing U.S. national health survey data conducted for *Diabetes in America, 3rd edition*. These surveys include self-reported data from telephone or in-person interview of participants and, in some cases, physical examination and laboratory and imaging studies. Strengths of such surveys are that they have national representation. Limitations include the inaccuracies of self-reported information and reliance on measurements other than the reference standard, due to the cost and sometimes invasive nature of such tests. Other

TABLE 20.3. Prevalence of Intermittent Claudication Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Smoking Status, and Diabetes Status, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	Overall	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	No Diabetes
Overall	14.13 (0.68)	23.21 (1.17)	27.72 (1.53)	12.80 (2.55)	12.52 (0.76)
Age (years)					
40–64	13.59 (0.83)	23.59 (2.19)	29.95 (2.84)	9.81 (2.58)	12.25 (0.89)
65–74	16.34 (1.63)	24.67 (2.48)	25.74 (2.85)	21.95 (5.44)	13.51 (2.01)
≥75	14.61 (1.44)	19.72 (2.77)	23.44 (3.28)	10.40 (3.51)[1]	13.19 (1.55)
Sex					
Men	12.26 (0.77)	19.27 (1.75)	24.93 (2.14)	8.66 (2.37)	10.84 (0.87)
Women	15.76 (1.08)	27.55 (1.78)	30.40 (2.28)	19.07 (4.36)	13.92 (1.22)
Race/ethnicity					
Non-Hispanic white	13.23 (0.86)	21.85 (1.68)	26.84 (2.29)	11.68 (2.93)	11.92 (0.91)
Non-Hispanic black	19.64 (1.83)	33.16 (2.67)	36.72 (2.98)	21.61 (6.02)	15.84 (2.18)
All Hispanic	16.96 (1.86)	23.07 (2.17)	25.49 (2.14)	15.20 (5.47)[1]	15.32 (2.36)
Mexican American	17.40 (1.29)	26.56 (2.27)	30.48 (2.24)	15.67 (4.62)	14.94 (1.63)
Smoking status					
Never smokers	11.76 (0.80)	21.04 (1.64)	26.59 (2.21)	6.95 (1.93)	10.16 (0.92)
Former smokers	13.29 (1.12)	22.59 (1.90)	25.79 (2.53)	16.13 (4.17)	11.43 (1.35)
Current smokers	21.04 (2.01)	30.37 (3.63)	34.30 (4.16)	20.21 (6.69)[1]	19.66 (2.19)

Intermittent claudication is defined as answering yes to both of the following questions: "Do you ever get pain in either leg while you are walking?" and "Does this pain include pain in your calf or calves?". Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

sources of data include published reports of investigations conducted in other population or clinical settings. Limitations of such data include limited generalization, potential selection bias, and at times, low power due to smaller sample size.

Prevalence of PAD

Estimating the prevalence of PAD is difficult, because the majority of patients are asymptomatic. Older studies used claudication symptoms to identify those with PAD, which underestimates the prevalence. Data from physicians' practices, in the Peripheral Artery Disease Awareness Risk and Treatment Program (PARTNERS), indicate that among participants with an ABI <0.9, 50% were asymptomatic, 40% had claudication, and 10% had clinical lower extremity disease (21). Estimates of the prevalence of PAD are available from the NHANES, where a modified ABI test was performed. Instead of measuring pressure in both the posterior tibial and dorsalis pedis arteries as per the usual recommendation, pressure was measured in the former location only (22). New analysis of data from the NHANES 1999–2004 showed that overall prevalence of PAD, defined as an ABI <0.9 in either leg, in persons age ≥40 years was 5.23% (Figure 20.1, Table 20.2). Unadjusted prevalence varied considerably by diabetes status, with greater than a twofold difference seen in persons with diagnosed and undiagnosed diabetes compared to those without diabetes (Figure 20.1, Table 20.2). In the NHANES 1999–2000 among adults age ≥40 years only, the prevalence of PAD was 10.8% (95% CI 3.2%–18.4%) among those with diabetes compared to 3.6% (95% CI 2.2%–5.0%) in those without diabetes (23).

The importance of using a sensitive measure of PAD rather than one based on symptoms can be seen by comparing PAD prevalence to the presence of intermittent claudication (Table 20.3). Before discussing these results, it is important to recognize that the presence of calf pain while walking was used to suggest presence of claudication and probably overestimates the prevalence of true claudication due to PAD. Diabetes was associated with an approximately twofold higher prevalence of claudication in a new analysis of NHANES 1999–2004 data. This association, though, was seen in those with known diabetes. The prevalence of claudication was similar among nondiabetic persons compared to those with undiagnosed diabetes (Table 20.3) but higher in persons with diagnosed diabetes, possibly due to longer or more severe disease leading to higher risk of atherosclerosis. This result differs when PAD is defined using ABI <0.9 (Figure 20.1, Table 20.2), where a higher prevalence of PAD is seen in both known and undiagnosed diabetes compared to nondiabetic persons.

Medical care utilization data also suggest a higher frequency of PAD among persons with diabetes, who had a fourfold higher occurrence of ambulatory care visits for PAD in the United States in 2002–2009 compared to persons without diabetes (Figure 20.2). The proportion of hospitalizations listing PAD among the discharge diagnoses was greater in persons with diabetes compared to those without diabetes during 2002–2009 (Figure 20.3, Table 20.4), regardless of age, sex, or race/ethnicity categories examined.

Other correlates of higher prevalence of PAD in the NHANES 1999–2004 were greater age, non-Hispanic white or black compared to all Hispanic race/ethnicity, and former or current smoking (Table 20.2). In each age, sex, race/ethnicity, and smoking stratum, diabetes was associated with a higher prevalence of PAD (Figures 20.4–20.7, Table 20.2).

Diabetes and PAD Risk Factors

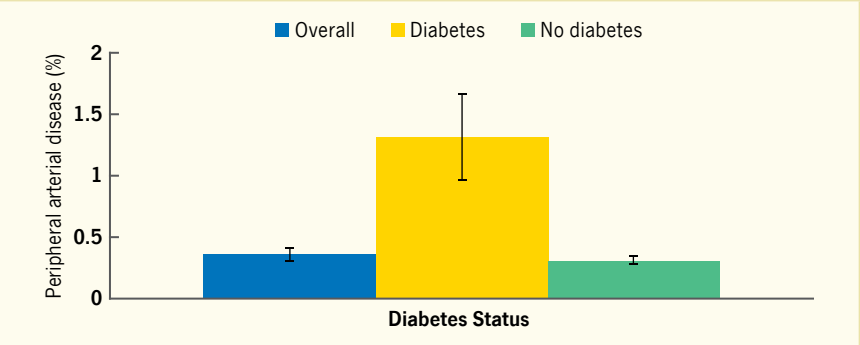
The Framingham Offspring Study examined 1,554 males and 1,759 females for PAD. In this population-based study, the odds ratio for PAD was 2.3 (95% CI 1.5–3.6) for diabetic versus nondiabetic participants (24). The Health Professionals Follow-up Study included 48,607 men followed for 12 years (25). After adjusting for cardiovascular disease (CVD) risk factors, the relative risk of developing PAD for men with diabetes compared with men without diabetes was 2.61 (95% CI 1.98–3.45).

Among patients who have type 1 diabetes, PAD is more common than among the general population. In the Pittsburgh Epidemiology of Diabetes Complications Study of childhood-onset type 1 diabetes, women who had type 1 diabetes for 30 years had a prevalence of PAD >30% compared to only 11% for men when determined by ABI <0.8 at rest or after exercise (26). The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of the Diabetes Control and Complications Trial (DCCT), evaluated outcomes associated with intensive versus conventional glycemic control and identified those patients with ABI <0.9. The EDIC study found that intensively treated participants, with an average duration of type 1 diabetes of about 14 years, had a prevalence of PAD of 8.8% among women and 4.6% among men (27). Although men have a higher risk for coronary artery disease than women, PAD was shown in a comprehensive systematic review to occur with equal frequency by sex in higher income countries and more frequently in women in low to middle income countries (28).

Greater duration of diabetes is associated with a higher risk of developing PAD. Compared with men without diabetes in the Health Professionals Follow-up Study, the relative risk for PAD was 1.39 (95% CI 0.82–2.36) for 1–5 years of diabetes, 3.63 (95% CI 2.23–5.88) for 6–10 years, 2.55 (95% CI 1.50–4.32) for 11–25 years, and 4.53 (95% CI 2.39–8.58) for >25 years (29).

Patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) had a prevalence of PAD of

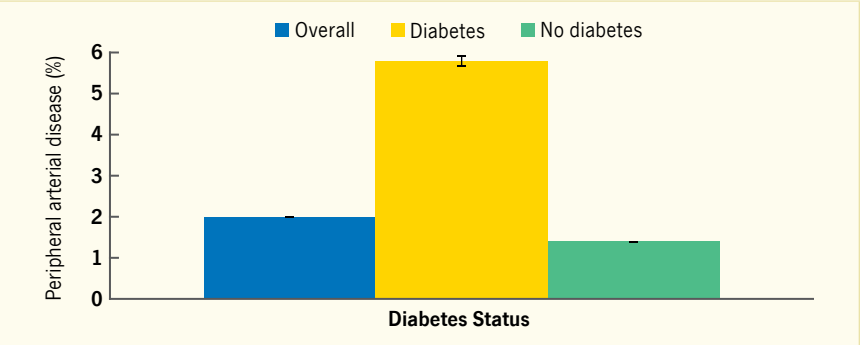
FIGURE 20.2. Percent of Outpatient Visits to a Physician Pertaining to Peripheral Arterial Disease, by Diabetes Status, U.S., 2002–2009



Peripheral arterial disease is defined based on ICD-9 codes 250.7, 440.2–440.4, 442.2, 442.3, 443.8, 443.9, 451.1, and 451.2. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Error bars represent 95% confidence intervals. ICD-9, International Classification of Diseases, Ninth Revision.
All relative standard errors ≤30%

SOURCE: National Ambulatory Medical Care Surveys 2002–2009

FIGURE 20.3. Percent of Hospital Discharges Listing Peripheral Arterial Disease, by Diabetes Status, U.S., 2002–2009



Peripheral arterial disease is defined based on ICD-9 codes 250.7, 440.2–440.4, 442.2, 442.3, 443.8, 443.9, 451.1, and 451.2. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Error bars represent 95% confidence intervals. Confidence intervals were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. See Table 20.4 for further details. ICD-9, International Classification of Diseases, Ninth Revision.
All relative standard errors ≤30%

SOURCE: National Hospital Discharge Surveys 2002–2009

TABLE 20.4. Percent of Hospital Discharges Listing Peripheral Arterial Disease, Overall and by Age, Sex, Race, and Diabetes Status, U.S., 2002–2009

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	Overall	Diabetes	No Diabetes
Overall	2.0 (0.01)	5.8 (0.07)	1.4 (0.01)
Age (years)			
<45	0.1 (0.05)	1.5 (0.09)	0.1 (0.004)
45–64	2.4 (0.03)	5.4 (0.11)	1.6 (0.03)
65–74	4.3 (0.06)	7.3 (0.15)	3.4 (0.06)
≥75	3.9 (0.04)	6.6 (0.13)	3.2 (0.05)
Sex			
Men	1.5 (0.02)	4.8 (0.08)	1.1 (0.02)
Women	2.6 (0.03)	7.0 (0.11)	1.8 (0.02)
Race			
White	2.1 (0.02)	5.8 (0.10)	1.5 (0.02)
Black	2.0 (0.04)	6.1 (0.17)	1.1 (0.03)
AIAN	1.3 (0.16)	5.2 (0.76)	0.5 (0.11)
Asian	0.9 (0.08)	3.5 (0.49)	0.5 (0.07)

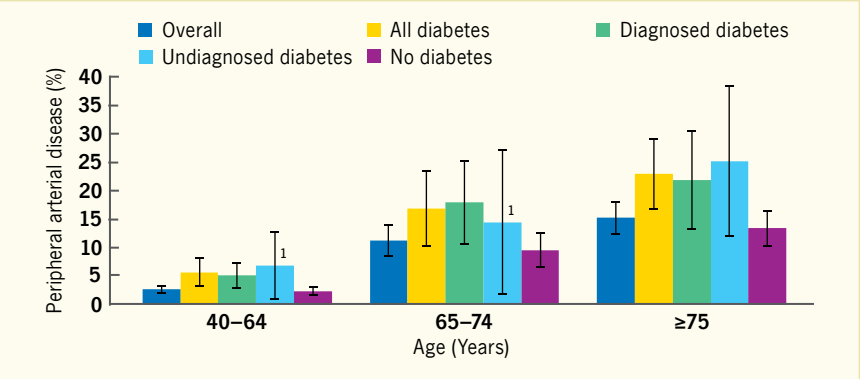
Peripheral arterial disease is defined based on ICD-9 codes 250.7, 440.2–440.4, 442.2, 442.3, 443.8, 443.9, 451.1, and 451.2. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AIAN, American Indian/Alaska Native; ICD-9, International Classification of Diseases, Ninth Revision.
All relative standard errors ≤30%

SOURCE: National Hospital Discharge Surveys 2002–2009

1.2% (95% CI 0.9%–1.5%) at the time of diagnosis of their diabetes (30). PAD in the UKPDS was defined as the presence of any two of the following: (1) ABI <0.8, (2) absence of both dorsalis pedis and posterior tibial pulses to palpation in at least one leg, and (3) claudication. At 6 years of follow-up in the UKPDS, 2.7% of participants (95% CI 2.2%–3.2%) had incident PAD according to these criteria, and 10.6% had at least one of these three abnormal measures. The prevalence of PAD increased to 12.5% (95% CI 3.8%–21.1%) in a smaller subgroup of participants followed for 18 years. In the UKPDS, each 1% increase in glycosylated hemoglobin (A1c) was associated with a 28% (95% CI 12%–46%) increased risk of PAD (30). The association with hyperglycemia was independent of other risk factors, including age, elevated systolic blood pressure, low high-density lipoprotein (HDL) cholesterol, smoking, prior CVD, peripheral sensory neuropathy, and retinopathy (30).

A1c was measured in adults age ≥40 years in the NHANES 1999–2004 with and without diabetes. According to a new analysis for *Diabetes in America*, similar mean A1c levels were seen by presence of PAD among persons with diagnosed or undiagnosed diabetes (Table 20.5). One reason for this similarity might be that persons with PAD and diagnosed diabetes were considered to be at higher risk for complications and treated more intensively than those with diabetes but without PAD. However, this assertion is not supported among persons with undiagnosed diabetes who would not have been targeted for diabetes treatment, where mean A1c was 0.51% lower among persons with PAD (Table 20.5). Among persons without diabetes, mean A1c was slightly higher in persons with PAD compared to those without, although the mean A1c in persons with PAD would be classified as normal by American Diabetes Association criteria (15). In general, A1c differences by PAD presence among persons with and without diabetes did not vary substantially when examined within age, sex, and race/ethnicity strata with the exception of the "all Hispanic" group. Among all Hispanics, a difference

FIGURE 20.4. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, by Age and Diabetes Status, U.S., 1999–2004

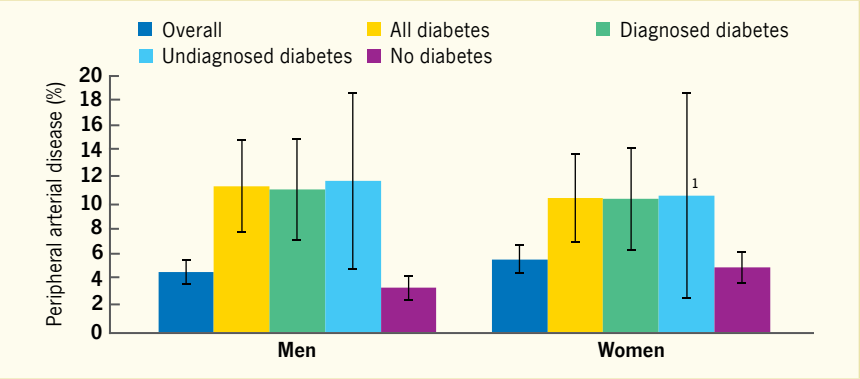


Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.2 for further details. A1c, glycosylated hemoglobin.

[1] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.5. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, by Sex and Diabetes Status, U.S., 1999–2004

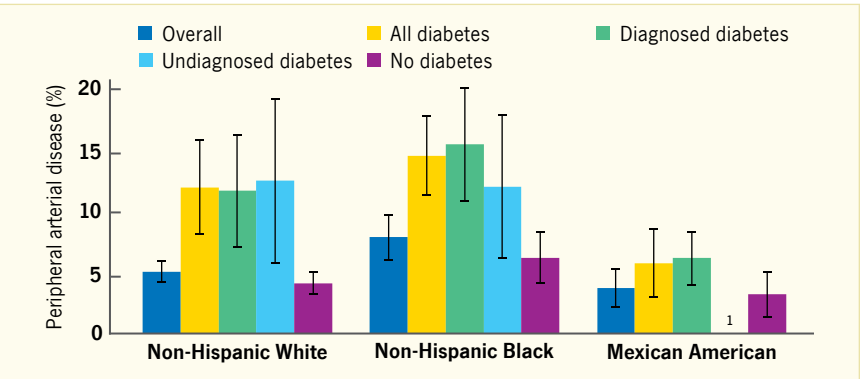


Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.2 for further details. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.6. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, by Race/Ethnicity and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.2 for further details. A1c, glycosylated hemoglobin.

[1] Estimate is too unreliable to present; ≤1 case or relative standard error >50%. All other relative standard errors ≤30%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.5. Mean A1c (%) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	7.03 (0.16)	7.24 (0.07)	7.38 (0.21)	7.43 (0.09)	6.34 (0.10)	6.85 (0.12)	5.51 (0.03)	5.36 (0.01)
Age (years)								
40–64	7.46 (0.46)	7.44 (0.09)	8.07 (0.58)	7.69 (0.12)	6.50 (0.15)	6.91 (0.18)	5.53 (0.06)	5.33 (0.01)
65–74	6.84 (0.20)	6.98 (0.13)	7.16 (0.21)	7.09 (0.15)	6.05 (0.09)	6.76 (0.19)	5.48 (0.05)	5.45 (0.02)
≥75	6.83 (0.15)	6.71 (0.10)	7.02 (0.22)	6.72 (0.10)	6.47 (0.20)	6.68 (0.19)	5.49 (0.03)	5.49 (0.02)
Sex								
Men	7.06 (0.22)	7.22 (0.11)	7.55 (0.30)	7.43 (0.14)	6.24 (0.10)	6.85 (0.15)	5.56 (0.04)	5.36 (0.02)
Women	6.98 (0.21)	7.26 (0.10)	7.17 (0.26)	7.43 (0.11)	6.52 (0.22)	6.85 (0.16)	5.47 (0.04)	5.35 (0.02)
Race/ethnicity								
Non-Hispanic white	6.84 (0.19)	6.94 (0.08)	7.20 (0.26)	7.09 (0.09)	6.22 (0.10)	6.66 (0.14)	5.49 (0.04)	5.34 (0.02)
Non-Hispanic black	7.79 (0.28)	7.74 (0.12)	8.03 (0.26)	7.96 (0.16)	6.97 (0.25)	7.20 (0.27)	5.58 (0.06)	5.43 (0.02)
All Hispanic	6.95 (0.48)	8.08 (0.20)	7.11 (0.67)	8.17 (0.27)	6.67 (0.38)	7.82 (0.24)	5.58 (0.08)	5.43 (0.02)
Mexican American	7.70 (0.52)	8.01 (0.15)	7.76 (0.71)	8.13 (0.17)	7.50 (0.06)	7.74 (0.29)	5.45 (0.09)	5.41 (0.02)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin. All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

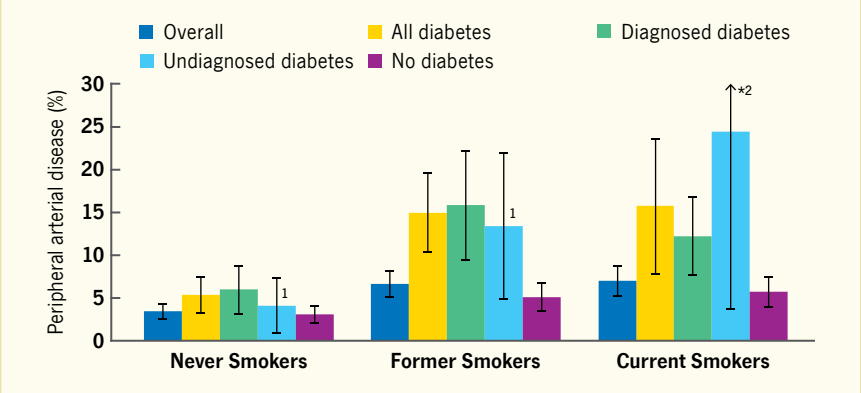
of >1% in the A1c value was seen by presence of PAD for both known and undiagnosed diabetes, with lower values seen in those with PAD in these categories (Table 20.5).

Other Risk Factors for PAD

Multiple factors other than diabetes are associated with greater risk of PAD including age, race/ethnicity, smoking, hypertension, lipid concentrations, inflammatory markers, and renal dysfunction. Greater age and non-Hispanic black race are both associated with a higher prevalence of this condition in previous publications and in the NHANES 1999–2004 data as discussed earlier (Figures 20.4 and 20.6, Table 20.2) (23,24,31,32).

The number of cigarettes smoked is strongly associated with the incidence of intermittent claudication as demonstrated in the Framingham Study, in which smoking was the strongest single risk factor for development of symptomatic PAD, regardless of sex (33). Multiple studies reported that smoking is associated with a twofold to fourfold increase in the risk of developing PAD (24,30,34,35,36,37,38,39). In the NHANES 1999–2004 data, 15.74% of current smokers with diabetes had PAD compared with 5.39% of never smokers with diabetes (Figure 20.7, Table 20.2).

FIGURE 20.7. Prevalence of Peripheral Arterial Disease Among Adults Age ≥40 Years, by Smoking Status and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* Error bars represent 95% confidence intervals. See Table 20.2 for further details. A1c, glycosylated hemoglobin.

* Upper confidence interval is 45.3%.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

The greater prevalence of PAD among smokers was seen in both the previously undiagnosed and diagnosed diabetes groups compared to persons without diabetes (Figure 20.7, Table 20.2). An overall higher prevalence of current or former smoking was seen among persons with as opposed to those without PAD in those with diagnosed or undiagnosed diabetes, as well as those without diabetes (Figures 20.8 and 20.9, Tables 20.6 and 20.7).

Hypertension was reported to be associated with a threefold increased risk of intermittent claudication at the 16-year follow-up of the Framingham Study (34). The Cardiovascular Health Study reported about a 50% higher prevalence of an ABI <0.9 associated with hypertension in a multivariate analysis adjusted for age, smoking, diabetes, and dyslipidemia (32). In a new analysis of the NHANES 1999–2004, among persons without diabetes, hypertension frequency was approximately 70% higher in those with PAD compared to

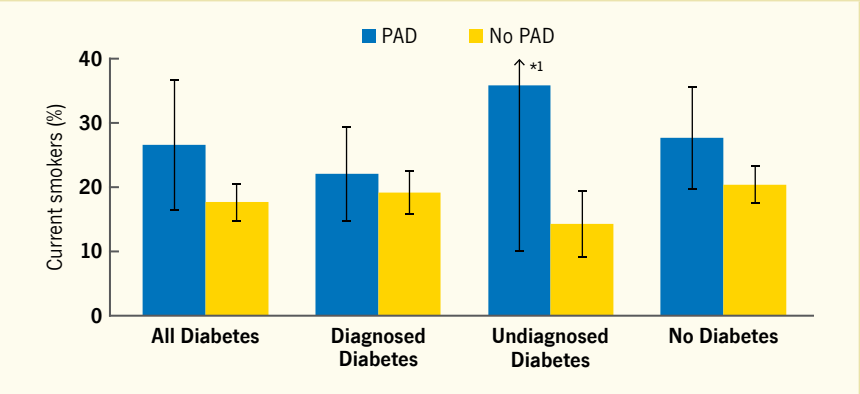
those without PAD (Table 20.8). In these data, the prevalence of hypertension in diabetes was increased, so that persons with PAD had a higher prevalence of hypertension, but the elevation compared to those without PAD was not as pronounced. Women with diabetes, in particular, had a higher prevalence of hypertension than men, with or without PAD.

The association of hypercholesterolemia with atherosclerosis of the lower extremities has been known since the 1930s (40). The prevalence of claudication in patients with serum cholesterol levels >260 mg/dL (>6.73 mmol/L) is on average over twice as high as in those with concentrations below this level. The Edinburgh Artery Study reported a higher prevalence of PAD in association with higher serum cholesterol and lower HDL cholesterol in multiple logistic regression analysis (41). The Cardiovascular Health Study reached similar conclusions among its sample of 5,084 subjects age ≥65 years, with PAD defined as an ABI <0.9 (32).

A variety of novel risk factors have been associated with a higher prevalence of PAD in several population-based studies. Higher circulating levels of homocysteine have been demonstrated with PAD (42), as have low levels of folate in red blood cells and circulating vitamin B6 (43). Higher levels of various hemostatic factors have been demonstrated in persons with low ABI, suggesting that a hypercoagulable state predisposes to the development of PAD (44,45). Increased levels of hemostatic factors, such as fibrinogen, von Willebrand factor, tissue plasminogen activator (t-PA), fibrin D-dimer, and plasma viscosity explained in part the higher prevalence of PAD in subjects with diabetes or impaired glucose tolerance in the Edinburgh Artery Study (46).

A number of studies have shown an association between various inflammatory markers and PAD. C-reactive protein and the presence of PAD, defined as ABI <0.9, were studied among 1,600 subjects with the metabolic syndrome, diabetes, or preexisting arterial disease in the NHANES 1999–2000 (47). Compared

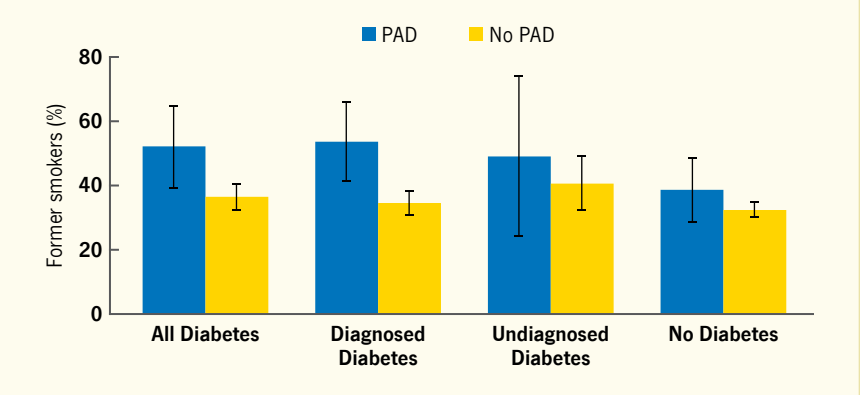
FIGURE 20.8. Prevalence of Current Smoking Among Adults Age ≥40 Years, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.6 for further details. A1c, glycosylated hemoglobin.
* Upper confidence interval is 62.1%.
[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.9. Prevalence of Former Smoking Among Adults Age ≥40 Years, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.7 for further details. A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

to those without preexisting disease and a C-reactive protein of <1 mg/L (<9.52 nmol/L), those with diabetes and an elevated C-reactive protein had an odds ratio for PAD of 8.6 (95% CI 2.2–34.0). Subjects with the metabolic syndrome and an elevated C-reactive protein also had higher odds of PAD (odds ratio 3.9, 95% CI 1.1–14.6). A new analysis of NHANES 1999–2004 data showed that among participants age ≥40 years, mean C-reactive protein concentration was higher among those with PAD compared to those without PAD among persons with diagnosed diabetes and without diabetes but not among persons with undiagnosed diabetes, where mean C-reactive protein concentration was lower (Table 20.9). The reason for the lower mean C-reactive protein in those with PAD among persons with undiagnosed diabetes is unknown. Mean C-reactive protein concentration was higher in persons with PAD among those diagnosed with diabetes when subjects were further stratified by age, sex, or race/ethnicity, with the exception of non-Hispanic black subjects (Table 20.9). An earlier report of the NHANES 1999–2002 found that inflammatory markers, including C-reactive protein, fibrinogen,

TABLE 20.6. Prevalence of Current Smoking Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	26.7 (5.1)	17.7 (1.5)	22.1 (3.7)	19.2 (1.7)	36.0 (12.9)[1]	14.3 (2.6)	27.8 (4.0)	20.5 (1.5)
Age (years)								
40–64	54.7 (8.2)	23.7 (2.0)	48.5 (11.0)	25.4 (2.2)	64.5 (20.2)[1]	20.1 (3.9)	39.6 (8.2)	23.8 (1.7)
65–74	20.6 (7.6)[1]	8.1 (1.8)	13.9 (5.7)[2]	9.5 (2.1)	[3]	[3]	29.5 (8.3)	10.5 (1.8)
≥75	[3]	5.1 (2.3)[2]	[3]	[3]	[3]	[3]	7.9 (3.7)[2]	4.7 (1.4)
Sex								
Men	30.3 (6.3)	19.7 (2.1)	27.2 (5.7)	21.9 (2.6)	35.4 (16.4)[2]	15.7 (4.1)	37.1 (7.0)	22.9 (1.9)
Women	22.0 (7.8)[1]	15.2 (2.2)	16.1 (6.0)[1]	16.4 (2.7)	[3]	12.1 (4.1)[1]	22.2 (5.5)	18.5 (1.5)
Race/ethnicity								
Non-Hispanic white	26.7 (7.1)	14.2 (2.1)	19.0 (5.0)	16.5 (2.2)	40.3 (15.6)[1]	9.7 (2.9)	27.6 (4.6)	20.1 (1.7)
Non-Hispanic black	34.3 (5.8)	26.8 (3.3)	35.8 (6.4)	25.9 (3.9)	[3]	29.1 (7.2)	21.5 (7.1)[1]	25.7 (2.8)
All Hispanic	10.0 (4.1)[2]	21.6 (3.4)	15.6 (4.3)	21.4 (4.2)	[3]	22.0 (6.2)	[3]	24.0 (3.3)
Mexican American	14.2 (6.7)[2]	21.0 (2.0)	18.7 (7.7)[2]	19.6 (2.7)	[3]	24.4 (4.7)	18.0 (6.2)[1]	20.8 (2.7)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.7. Prevalence of Former Smoking Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	52.1 (6.4)	36.5 (2.1)	53.6 (6.2)	34.5 (1.9)	49.0 (12.4)	40.7 (4.2)	38.6 (5.1)	32.5 (1.2)
Age (years)								
40–64	27.7 (8.5)[1]	31.3 (2.5)	22.8 (7.6)[1]	31.0 (2.3)	[3]	31.9 (5.0)	26.6 (7.4)	29.5 (1.4)
65–74	63.7 (8.9)	47.5 (3.4)	66.1 (8.7)	40.4 (4.0)	57.4 (22.3)[1]	61.7 (5.0)	44.3 (8.3)	43.7 (2.7)
≥75	62.1 (10.0)	41.4 (4.9)	65.5 (10.7)	41.5 (4.8)	55.7 (15.9)	41.3 (10.0)	51.0 (8.0)	43.3 (3.4)
Sex								
Men	48.9 (8.3)	45.1 (2.8)	46.9 (7.7)	44.3 (2.9)	52.4 (16.0)[1]	46.7 (5.5)	52.7 (6.9)	38.0 (1.7)
Women	56.3 (9.4)	26.0 (2.6)	61.5 (9.0)	23.9 (2.8)	43.1 (19.9)[2]	31.4 (6.1)	30.2 (5.9)	27.5 (1.5)
Race/ethnicity								
Non-Hispanic white	52.9 (8.4)	42.7 (3.3)	56.5 (8.3)	39.8 (3.1)	46.6 (14.8)[1]	48.2 (5.1)	41.5 (6.2)	34.5 (1.4)
Non-Hispanic black	43.3 (6.1)	26.9 (2.8)	45.9 (5.9)	27.4 (2.9)	[3]	25.3 (7.6)	32.7 (8.7)	21.2 (2.1)
All Hispanic	72.7 (7.6)	25.5 (3.1)	57.1 (12.6)	26.0 (4.0)	[3]	24.1 (5.2)	24.5 (11.8)[2]	25.5 (2.1)
Mexican American	53.7 (6.7)	34.1 (3.3)	39.1 (8.8)	34.2 (4.8)	[3]	33.7 (5.5)	53.7 (10.3)	23.5 (2.0)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

and leukocyte count, were independently associated with PAD among 4,787 participants age ≥40 years (48). The InCHIANTI study, a population-based Italian study that enrolled 955 men and women age ≥60 years, found that subjects with PAD had higher levels of interleukin (IL)-1 receptor antagonist, IL-6, fibrinogen, and C-reactive protein compared to subjects without PAD (49).

Other factors associated with PAD have been reported using NHANES data. Blood cadmium levels were associated with increased prevalence of PAD, as defined by an ABI <0.9, in the NHANES 1999–2000 among subjects age ≥40 years (50). The highest quartile of cadmium level compared to the lowest was associated with an odds ratio for PAD of 2.82 (95% CI 1.36–5.85). An analysis of the NHANES 1999–2000 population demonstrated that renal insufficiency, defined as a reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2), was associated with an odds ratio of 2.17 (95% CI 1.10–4.30) for prevalent PAD (23). This analysis adjusted for diabetes, coronary artery disease, stroke, hypertension, body mass index (BMI), total cholesterol, diastolic and systolic blood pressures, and smoking history. Other studies have shown similar results (30,36,51,52,53).

TABLE 20.8. Prevalence of Hypertension Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	75.9 (4.93)	65.3 (1.74)	77.8 (4.17)	64.2 (2.07)	71.7 (12.59)	67.8 (3.11)	66.2 (5.17)	38.9 (1.37)
Age (years)								
40–64	63.5 (9.55)	58.3 (2.89)	74.0 (9.46)	53.9 (3.05)	[1]	67.6 (4.40)	50.7 (8.50)	31.5 (1.57)
65–74	84.2 (5.53)	76.2 (3.54)	81.3 (6.73)	81.4 (3.41)	93.6 (6.81)	66.2 (7.87)	78.5 (6.57)	61.1 (2.61)
≥75	78.3 (6.67)	79.8 (3.93)	76.2 (7.89)	83.3 (3.65)	82.4 (15.21)	72.3 (8.04)	75.9 (6.12)	75.7 (2.44)
Sex								
Men	71.8 (7.72)	59.1 (2.52)	75.4 (5.89)	56.2 (2.85)	65.9 (17.27)	64.1 (4.51)	69.8 (6.27)	36.2 (1.93)
Women	81.5 (4.58)	72.9 (2.57)	80.5 (5.84)	72.7 (2.87)	84.6 (7.70)	73.4 (4.67)	63.9 (5.98)	41.3 (1.82)
Race/ethnicity								
Non-Hispanic white	73.5 (6.21)	67.4 (2.32)	75.9 (5.27)	65.2 (3.17)	68.8 (15.21)	71.6 (4.03)	64.3 (6.05)	38.8 (1.63)
Non-Hispanic black	80.7 (5.49)	74.5 (2.95)	83.0 (6.35)	77.2 (3.96)	71.8 (14.94)	67.6 (7.03)	72.3 (9.48)	51.7 (2.73)
All Hispanic	88.2 (4.28)	51.2 (4.84)	81.5 (6.90)	52.2 (6.06)	[1]	48.3 (8.41)	80.2 (8.59)	30.2 (2.74)
Mexican American	82.3 (4.97)	52.3 (3.12)	76.7 (8.17)	54.2 (4.18)	[1]	47.4 (6.96)	64.1 (13.03)	30.9 (2.25)

Hypertension is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.9. Mean C-Reactive Protein (mg/L) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	0.86 (0.20)	0.57 (0.03)	1.02 (0.27)	0.55 (0.04)	0.54 (0.17)[1]	0.61 (0.07)	0.69 (0.07)	0.42 (0.02)
Age (years)								
40–64	1.14 (0.55)[2]	0.62 (0.04)	[3]	0.58 (0.05)	0.39 (0.11)	0.71 (0.11)	0.79 (0.11)	0.41 (0.02)
65–74	0.67 (0.18)	0.45 (0.04)	0.64 (0.15)	0.48 (0.05)	[3]	0.39 (0.04)	0.78 (0.21)	0.51 (0.05)
≥75	0.79 (0.09)	0.56 (0.11)	0.98 (0.18)	0.57 (0.13)	0.46 (0.07)	0.52 (0.15)	0.44 (0.07)	0.44 (0.04)
Sex								
Men	0.80 (0.32)[2]	0.44 (0.03)	1.07 (0.45)[2]	0.44 (0.05)	0.34 (0.08)	0.44 (0.08)	0.71 (0.16)	0.35 (0.02)
Women	0.94 (0.15)	0.73 (0.05)	0.96 (0.17)	0.68 (0.06)	0.88 (0.36)[2]	0.87 (0.13)	0.68 (0.07)	0.49 (0.03)
Race/ethnicity								
Non-Hispanic white	0.87 (0.27)[1]	0.53 (0.04)	1.10 (0.38)[1]	0.54 (0.04)	0.49 (0.20)[2]	0.50 (0.07)	0.68 (0.09)	0.42 (0.02)
Non-Hispanic black	0.77 (0.14)	0.91 (0.14)	0.75 (0.15)	0.75 (0.08)	0.84 (0.22)	1.30 (0.38)	0.82 (0.25)	0.54 (0.05)
All Hispanic	0.97 (0.33)[1]	0.57 (0.05)	1.21 (0.59)[2]	0.54 (0.06)	0.54 (0.07)	0.66 (0.09)	0.61 (0.16)	0.42 (0.02)
Mexican American	1.29 (0.48)[1]	0.57 (0.04)	[3]	0.54 (0.04)	0.58 (0.19)[1]	0.63 (0.09)	0.45 (0.11)	0.45 (0.03)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

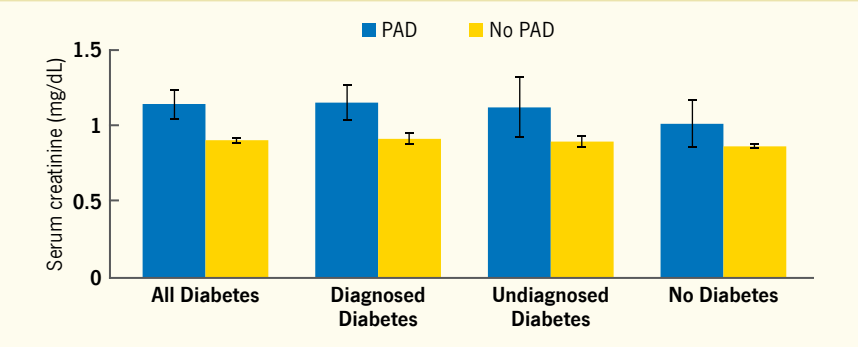
SOURCE: National Health and Nutrition Examination Surveys 1999–2004

In NHANES 1999–2004 data analyzed for *Diabetes in America*, mean serum creatinine, a marker of renal function, was higher in subjects with PAD compared to those without PAD regardless of diabetes status (Figure 20.10, Table 20.10). The same association was found when data were stratified by age, sex, and race/ethnicity for both subjects with known and undiagnosed diabetes (Table 20.10). Higher elevated serum creatinine appears as a consistent accompanying feature of PAD among persons with diabetes according to these data. Presence of albumin in the urine also reflects renal dysfunction, and a spot urine albumin-to-creatinine ratio exceeding the threshold for microalbuminuria was associated with a higher prevalence of an ABI >0.9 in the Multi-Ethnic Study of Atherosclerosis (MESA) study (54). A new analysis of NHANES data from 1999–2004 confirms a higher mean urinary albumin-to-creatinine ratio among persons with PAD for those with known diabetes and for men without diabetes (Figure 20.11, Table 20.11). Estimates of the mean among women lacked sufficient precision to permit similar comparisons (Table 20.11). A published analysis of the NHANES 1999–2004 of PAD prevalence in relation to eGFR <60 mL/min/1.73 m^2 and microalbuminuria, defined as urinary

albumin-to-creatinine ratio >30 mg/g, found the following odds ratios for the dimensions of renal function singly and in combination: microalbuminuria, 1.72 (95% CI 1.16–2.55); eGFR, 1.58 (95% CI 1.09–2.29); and both microalbuminuria and eGFR, 2.26 (95% CI 1.30–3.94) (55). NHANES 1999–2004 data showed that urinary albumin-to-creatinine ratio ≥30 mg/g was associated with PAD among persons age 40–64 years and in men only (Figure 20.12, Table 20.12). The association between PAD and renal dysfunction is not entirely understood and is explained only in part by shared risk factors (56).

According to new analyses conducted for *Diabetes in America*, persons with diabetes are more likely to have generalized and abdominal adiposity than those without diabetes, as seen in the higher mean BMI and waist circumference measurements in the NHANES 1999–2004 population by diabetes status (Appendices 20.1 and 20.2). The same direction of association is not seen within the diabetes categories by PAD presence. Instead mean BMI and waist circumference are similar or slightly lower among persons with PAD (Appendices 20.1 and 20.2). Potential explanations for this association are that adiposity is not related to risk of PAD among persons with diabetes or that adiposity is lower among persons with PAD due to higher smoking prevalence.

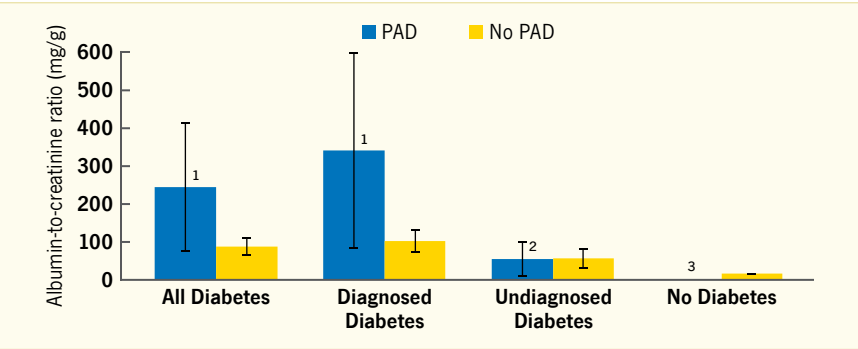
FIGURE 20.10. Mean Serum Creatinine (mg/dL) Among Adults Age ≥40 Years, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.10 for further details. A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.11. Mean Urinary Albumin-to-Creatinine Ratio (mg/g) Among Adults Age ≥40 Years, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined by A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.11 for further details. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.10. Mean Serum Creatinine (mg/dL) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	1.14 (0.05)	0.90 (0.01)	1.15 (0.06)	0.91 (0.02)	1.12 (0.10)	0.89 (0.02)	1.01 (0.08)	0.86 (0.01)
Age (years)								
40–64	0.99 (0.05)	0.85 (0.02)	1.08 (0.08)	0.86 (0.02)	0.86 (0.04)	0.83 (0.03)	0.81 (0.03)	0.85 (0.01)
65–74	1.13 (0.08)	0.97 (0.03)	1.10 (0.08)	0.98 (0.03)	1.19 (0.21)	0.93 (0.03)	1.21 (0.25)	0.87 (0.01)
≥75	1.31 (0.07)	1.04 (0.04)	1.29 (0.09)	1.01 (0.02)	1.34 (0.11)	1.10 (0.11)	1.12 (0.06)	0.97 (0.02)
Sex								
Men	1.22 (0.08)	0.99 (0.02)	1.24 (0.08)	1.00 (0.02)	1.19 (0.15)	0.97 (0.03)	1.07 (0.05)	0.99 (0.02)
Women	1.01 (0.06)	0.80 (0.02)	1.02 (0.08)	0.81 (0.02)	0.98 (0.08)	0.75 (0.03)	0.98 (0.13)	0.74 (0.01)
Race/ethnicity								
Non-Hispanic white	1.13 (0.06)	0.90 (0.01)	1.14 (0.08)	0.90 (0.02)	1.11 (0.12)	0.90 (0.03)	1.05 (0.11)	0.87 (0.01)
Non-Hispanic black	1.19 (0.06)	1.06 (0.07)	1.22 (0.08)	1.09 (0.09)	1.06 (0.05)	0.99 (0.11)	0.85 (0.05)	0.92 (0.02)
All Hispanic	1.08 (0.15)	0.79 (0.03)	0.94 (0.10)	0.81 (0.03)	1.31 (0.24)	0.74 (0.04)	0.82 (0.07)	0.75 (0.02)
Mexican American	0.89 (0.13)	0.79 (0.02)	0.92 (0.16)	0.80 (0.03)	0.79 (0.04)	0.77 (0.04)	0.93 (0.09)	0.76 (0.02)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.11. Mean Urinary Albumin-to-Creatinine Ratio (mg/g) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	244.9 (83.90)[1]	87.7 (11.97)	340.6 (128.07)[1]	102.5 (15.05)	54.8 (23.12)[2]	56.4 (13.80)	[3]	16.3 (1.45)
Age (years)								
40–64	[3]	83.4 (16.26)	[3]	91.5 (18.69)	21.5 (9.69)[2]	66.0 (21.72)[1]	17.7 (5.37)[1]	14.4 (1.75)
65–74	[3]	95.2 (20.72)	[3]	128.6 (31.32)	[3]	30.4 (6.93)	[3]	18.7 (3.52)
≥75	127.2 (46.13)[1]	95.1 (31.94)[1]	172.3 (74.99)[2]	109.6 (46.14)[2]	40.9 (20.37)[2]	62.9 (16.21)	54.8 (17.74)[1]	31.9 (4.39)
Sex								
Men	360.5 (143.53)[1]	106.4 (20.08)	549.1 (226.78)[2]	126.1 (25.29)	[3]	70.5 (22.49)[1]	59.6 (18.81)[1]	18.2 (2.80)
Women	86.3 (25.56)	65.0 (9.49)	88.5 (28.24)[1]	76.8 (13.39)	[3]	34.6 (6.99)	[3]	14.6 (1.47)
Race/ethnicity								
Non-Hispanic white	212.1 (98.79)[2]	62.1 (11.01)	[3]	75.5 (15.94)	51.3 (25.50)[2]	36.6 (4.97)	[3]	14.6 (1.53)
Non-Hispanic black	[3]	164.7 (43.61)	[3]	179.3 (50.43)	16.0 (2.09)	[3]	36.0 (15.19)[2]	33.8 (8.10)
All Hispanic	265.6 (98.57)[1]	167.0 (42.99)	330.2 (105.47)[1]	176.6 (48.31)	[3]	[3]	31.7 (10.10)[1]	14.7 (1.94)
Mexican American	234.3 (71.54)[1]	201.3 (55.66)	[3]	203.7 (49.19)	417.4 (151.71)[1]	[3]	51.0 (15.69)[1]	18.5 (3.15)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

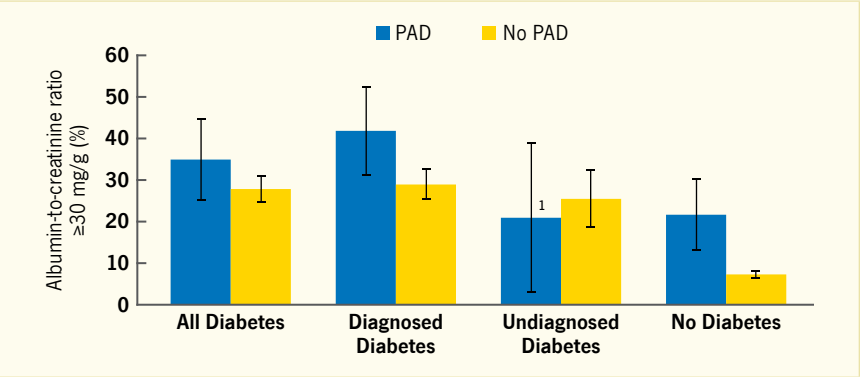
SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Diabetes Treatment and PAD Risk

In the EDIC study, intensive insulin therapy compared to conventional therapy during the DCCT resulted in decreased progression of carotid artery intima-media thickness 6 years after the end of the trial (57). Progression of carotid intima-media thickness was associated with the traditional risk factors mentioned above for PAD, including age, systolic blood pressure, smoking, the ratio of low-density lipoprotein to HDL cholesterol, urinary albumin excretion rate, and mean A1c value during the DCCT. The A1c value explained 96% of the differences between treatment groups in intima-media thickness of the common carotid artery at year 6 of follow-up. These findings argue that progression of atherosclerosis can be impeded with intensive glycemic control. Whether these results would apply as well to the peripheral arteries of the lower extremities is not known.

Persons with diagnosed diabetes and PAD included in the NHANES 1999–2004 more frequently reported insulin use (Table 20.13) for all examined age, sex, and race/ethnicity categories in analyses conducted for *Diabetes in America*. This finding should not be interpreted to imply that insulin is associated with a higher prevalence of PAD, as insulin is often used for intensive control. In standard medical practice, insulin use may be a marker for more severe diabetes, and the association between insulin use and higher PAD prevalence may be another example of confounding by indication. The use of oral medications for diabetes treatment was slightly less common in persons with PAD and diagnosed diabetes (Table 20.14). This is not a surprising finding given that the same persons were more likely to be treated with insulin, which often replaces oral diabetes treatments.

FIGURE 20.12. Prevalence of Urinary Albumin-to-Creatinine Ratio ≥30 mg/g Among Adults Age ≥40 Years, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. Error bars represent 95% confidence intervals. See Table 20.12 for further details. A1c, glycosylated hemoglobin.

[1] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Outcomes of PAD

PAD is a progressive condition that exacts a substantial toll in terms of morbidity and need for medical interventions. Estimates derived from population data show that approximately 27% of patients with PAD experience progression of symptoms over a 5-year period (1). In a study of 257 patients with intermittent claudication referred to a Copenhagen hospital-based physiology clinic for initial evaluation, the rate of clinical progression to rest pain or gangrene was 7.5% in the first year after initial referral and 2.2% per year after that

TABLE 20.12. Prevalence of Urinary Albumin-to-Creatinine Ratio ≥30 mg/g Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	34.9 (4.9)	27.8 (1.6)	41.8 (5.3)	29.0 (1.9)	21.0 (9.0)[2]	25.5 (3.5)	21.7 (4.3)	7.3 (0.5)
Age (years)								
40–64	45.2 (7.9)	26.0 (2.3)	64.3 (9.8)	26.6 (2.5)	[3]	24.7 (5.0)	8.9 (4.2)[2]	5.7 (0.6)
65–74	29.8 (8.3)	32.1 (3.1)	32.0 (7.6)	33.6 (3.8)	[3]	29.3 (6.4)	31.5 (7.9)	10.6 (1.7)
≥75	30.6 (5.5)	28.7 (3.1)	33.8 (8.4)	32.3 (4.2)	24.5 (10.5)[2]	20.9 (5.7)	31.0 (6.4)	18.1 (1.9)
Sex								
Men	40.5 (7.3)	31.0 (2.5)	57.5 (7.9)	32.9 (2.6)	[3]	27.5 (5.0)	25.4 (5.1)	6.2 (0.6)
Women	27.1 (7.6)	24.0 (2.5)	22.9 (5.8)	24.7 (2.8)	[3]	22.3 (4.9)	19.5 (5.5)	8.3 (0.8)
Race/ethnicity								
Non-Hispanic white	32.0 (6.5)	24.9 (1.9)	36.1 (7.1)	24.9 (2.0)	25.0 (11.6)[2]	25.1 (4.5)	22.0 (5.2)	6.4 (0.6)
Non-Hispanic black	44.4 (8.3)	31.3 (3.6)	55.8 (7.6)	35.8 (4.1)	[3]	19.3 (5.3)	24.6 (9.6)[1]	12.5 (1.4)
All Hispanic	44.6 (15.6)[1]	37.4 (4.3)	65.6 (9.7)	37.3 (4.7)	[3]	37.9 (8.4)	[3]	7.3 (1.5)
Mexican American	44.9 (9.1)	32.2 (3.1)	52.2 (7.4)	34.2 (3.5)	[3]	27.5 (5.8)	18.5 (5.9)[1]	9.2 (1.3)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

(58). In this study, the cumulative rate of reconstructive lower extremity surgery at 5 years was 9.5%, and the cumulative amputation rate was 6.8%. In a new analysis of cross-sectional data from the NHANES 1999–2004 population, a greater proportion of persons with PAD reported fair or poor health regardless of diabetes status (Table 20.15). There were too few persons with undiagnosed diabetes and PAD to produce stable estimates by age, sex, and race/ethnicity strata; although in the strata in which such estimates were available, the same trend was seen with poorer health reported by persons with PAD (Table 20.15).

TABLE 20.13. Prevalence of Insulin Use Among Adults Age ≥40 Years With Diagnosed Diabetes, Overall and by Age, Sex, Race/Ethnicity, and Peripheral Arterial Disease, U.S., 1999–2004

	PERCENT (STANDARD ERROR)	
CHARACTERISTICS	PAD	No PAD
Overall	38.6 (6.2)	20.0 (2.1)
Age (years)		
40–64	32.5 (10.8)[1]	18.2 (2.7)
65–74	40.9 (7.3)	26.2 (3.9)
≥75	41.1 (9.6)	17.0 (3.6)
Sex		
Men	33.8 (6.4)	18.3 (2.7)
Women	44.3 (9.6)	21.8 (2.9)
Race/ethnicity		
Non-Hispanic white	36.7 (7.9)	19.2 (3.3)
Non-Hispanic black	49.3 (7.6)	26.7 (3.2)
All Hispanic	16.7 (5.9)[1]	16.7 (2.1)
Mexican American	25.9 (7.8)[1]	20.0 (2.6)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Among those with diagnosed diabetes, 64% of participants with PAD and 71% of participants without PAD used oral diabetes medications.

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Cardiovascular Outcomes

Patients with symptomatic PAD have four to seven times the risk of mortality from all causes and a fifteenfold higher risk of mortality from CVD than persons who do not have PAD (59). Mortality rates appear to be related to the severity of the obstructive process as measured by the ABI. In prospective studies, PAD mortality outcome by diabetes status is not available, although a 6-year study showed that low ABI was strongly associated with increased mortality, independent of age or presence or absence of diabetes (60). Although the presence of arterial obstructive disease of the legs is a hallmark of generalized atherosclerosis and, therefore, would be expected to confer an increased risk of cardiovascular or cerebrovascular death, severe PAD appears to carry a particularly ominous prognosis. Patients with an ABI ≤0.30 had a very high 6-year cumulative mortality rate (64%) (60). Among the NHANES 1999–2004 population, a new data analysis showed that presence of PAD was associated with a substantially higher overall frequency of past history of coronary heart disease, angina, or myocardial infarction regardless of diabetes status and in all strata defined by age, sex, or race/ethnicity with enough subjects to permit stable estimates (Figure 20.13, Table 20.16). These data support the coexistence of vascular arterial disease in the lower extremities with the same disease process in the coronary circulation.

Those with PAD severe enough to warrant revascularization have particularly poor outcomes. One study of outcomes in

revascularization found the cumulative 6-year mortality rate was 62% in patients with symptoms sufficiently severe to require femoropopliteal bypass (61), while another showed that 48% of patients with claudication, 80% of those with ischemic rest pain, and 95% of those with gangrene died within 10 years of undergoing femoropopliteal bypass grafting (62). A university-based vascular surgery clinic in the Netherlands prospectively studied 3,209 patients for an average of 8 years and found that resting and post-exercise ABI values were strong and independent predictors of mortality (53). Mortality increased by 8% for every 0.1 decrease in resting ABI and by 9% for every 0.1 decrease in post-exercise ABI. Among those who began the study with a normal ABI, a reduction in the post-exercise ABI by 6%–24% was associated with a 1.6-fold increased risk of mortality; those with a reduction of 25%–55% had a 3.5-fold increase in mortality; and those with a >55% reduction in ABI had a 4.8-fold increase in mortality.

The risk of stroke is approximately doubled among those with an ABI <0.9, indicating that the presence of PAD is associated with disease elsewhere in the arterial system. The Honolulu Heart Program enrolled 8,006 men of Japanese ancestry age 45–68 years without known atherosclerosis, living on Oahu, Hawaii, and followed them for 3–6 years. The risk of stroke associated with an ABI <0.9, adjusted for cardiovascular risk factors, was 2.0 (37). The Atherosclerosis Risk in Communities (ARIC) Study enrolled 15,792 people age 45–64 years and followed them for 7 years. Those with the lowest ABI also had approximately double the risk of stroke (39). As with the association between PAD and coronary heart disease in the

TABLE 20.14. Prevalence of Oral Diabetes Medication Use Among Adults Age ≥40 Years With Diagnosed Diabetes, Overall and by Age, Sex, Race/Ethnicity, and Peripheral Arterial Disease, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	PAD	No PAD
Overall	64.3 (6.4)	70.7 (2.2)
Age (years)		
40–64	62.9 (11.4)	72.7 (2.8)
65–74	63.5 (9.3)	68.2 (4.4)
≥75	67.1 (10.4)	64.8 (4.8)
Sex		
Men	64.5 (8.9)	71.5 (3.0)
Women	64.1 (6.7)	69.8 (3.0)
Race/ethnicity		
Non-Hispanic white	66.4 (8.1)	69.8 (3.4)
Non-Hispanic black	64.8 (6.1)	69.9 (3.0)
All Hispanic	48.1 (11.5)	70.6 (4.9)
Mexican American	69.0 (7.7)	79.0 (2.8)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Among those with diagnosed diabetes, 39% of participants with PAD and 20% of participants without PAD used insulin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.15. Prevalence of Fair or Poor Self-Reported Health Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	48.5 (5.6)	35.4 (2.4)	57.1 (5.8)	40.7 (2.6)	31.3 (11.7)[1]	24.1 (3.2)	33.4 (5.3)	17.1 (1.0)
Age (years)								
40–64	49.3 (12.4)	36.6 (3.2)	60.6 (11.6)	41.8 (3.5)	[3]	25.4 (4.7)	34.3 (8.8)	16.2 (1.1)
65–74	57.9 (8.1)	31.4 (3.3)	68.4 (6.5)	35.9 (3.7)	[3]	22.5 (6.1)	35.7 (7.9)	18.7 (2.1)
≥75	34.5 (8.5)	36.9 (4.6)	36.1 (9.6)	44.3 (4.8)	31.7 (12.6)[1]	20.3 (7.9)[1]	29.5 (6.6)	22.8 (2.3)
Sex								
Men	40.6 (7.4)	29.9 (2.8)	50.0 (7.6)	34.9 (3.3)	[3]	20.9 (3.8)	40.1 (7.4)	16.1 (1.2)
Women	59.1 (9.5)	42.0 (2.6)	65.4 (9.6)	47.0 (3.2)	43.1 (18.9)[2]	28.9 (5.6)	29.3 (6.7)	18.0 (1.4)
Race/ethnicity								
Non-Hispanic white	42.2 (6.4)	31.0 (3.4)	51.5 (7.2)	36.5 (4.0)	25.8 (12.6)[2]	20.7 (3.9)	31.0 (5.9)	14.8 (1.3)
Non-Hispanic black	69.4 (6.6)	44.3 (3.3)	68.1 (7.8)	49.2 (3.6)	73.9 (16.0)	31.0 (8.2)	31.9 (8.9)	21.7 (2.8)
All Hispanic	57.0 (17.0)	52.6 (4.4)	75.2 (7.7)	55.5 (6.0)	[3]	44.5 (7.8)	62.0 (9.1)	31.7 (2.9)
Mexican American	63.6 (13.7)	57.3 (2.7)	61.6 (11.8)	60.5 (3.0)	69.8 (27.2)[1]	49.8 (5.9)	46.8 (10.5)	30.8 (2.5)

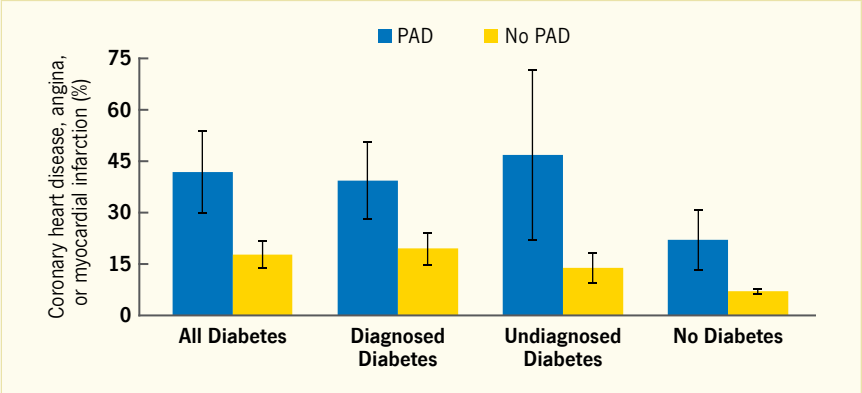
Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

NHANES 1999–2004, the same positive association is seen between PAD and a previous diagnosis of stroke among persons with and without diabetes in cells with sufficient sample size to permit a stable estimate, further affirming the coexistence of arterial vascular disease in other beds in those with disease affecting the lower extremities (Table 20.17).

FIGURE 20.13. Percent of Adults Age ≥40 Years Previously Diagnosed With Coronary Heart Disease, Angina, or Myocardial Infarction, by Peripheral Arterial Disease and Diabetes Status, U.S., 1999–2004



Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Previous diagnosis of coronary heart disease, angina, or myocardial infarction is based on self-report. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* Error bars represent 95% confidence intervals. See Table 20.16 for further details. A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.16. Percent of Adults Age ≥40 Years Previously Diagnosed With Coronary Heart Disease, Angina, or Myocardial Infarction, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	41.8 (6.1)	17.7 (2.0)	39.3 (5.6)	19.5 (2.4)	46.8 (12.4)	13.8 (2.3)	22.0 (4.4)	7.0 (0.5)
Age (years)								
40–64	42.0 (14.8)[1]	11.9 (1.8)	30.0 (10.4)[1]	12.6 (2.2)	60.9 (20.9)[1]	10.5 (2.9)	16.7 (8.2)[2]	4.4 (0.6)
65–74	41.0 (8.5)	26.1 (4.6)	37.9 (7.9)	28.3 (5.3)	49.0 (23.0)[2]	21.9 (5.7)	24.0 (6.9)	14.9 (1.7)
≥75	42.8 (9.5)	31.3 (3.6)	51.7 (9.0)	39.4 (4.2)	[3]	13.6 (4.0)	27.9 (6.9)	20.8 (2.1)
Sex								
Men	52.2 (9.2)	20.1 (2.7)	44.8 (8.1)	22.2 (3.5)	64.6 (13.9)	16.3 (3.4)	37.5 (8.4)	9.3 (0.8)
Women	27.6 (7.5)	14.7 (1.8)	32.5 (8.4)	16.6 (2.1)	[3]	9.8 (3.4)[1]	12.5 (4.0)[1]	5.1 (0.7)
Race/ethnicity								
Non-Hispanic white	47.7 (7.6)	20.2 (2.4)	45.3 (6.6)	23.0 (3.1)	51.8 (15.1)	15.0 (2.7)	22.5 (5.1)	7.6 (0.6)
Non-Hispanic black	28.1 (5.4)	16.0 (2.2)	26.1 (6.6)	14.0 (2.8)	35.6 (16.9)[2]	21.4 (6.1)	[3]	4.5 (1.0)
All Hispanic	[3]	8.0 (1.7)	[3]	9.1 (2.1)	[3]	4.9 (2.4)[2]	34.8 (15.2)[2]	4.6 (1.5)[1]
Mexican American	[3]	10.9 (2.3)	12.4 (6.2)[2]	12.2 (2.3)	[3]	8.0 (3.9)[2]	27.8 (11.2)[2]	3.5 (0.7)

Previous diagnoses of coronary heart disease, angina, and myocardial infarction are based on self-report. Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.17. Percent of Adults Age ≥40 Years Previously Diagnosed With Stroke, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
CHARACTERISTICS	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	17.2 (4.2)	5.8 (1.0)	19.9 (5.6)	6.2 (1.0)	[3]	5.0 (1.8)[1]	8.3 (2.8)[1]	2.8 (0.4)
Age (years)								
40–64	16.4 (4.3)	4.0 (1.1)	[3]	3.8 (1.2)[1]	[3]	[3]	[3]	1.7 (0.4)
65–74	21.1 (7.5)[1]	8.4 (1.7)	20.2 (6.8)[1]	10.5 (2.1)	[3]	[3]	17.6 (7.3)[2]	4.8 (1.2)
≥75	12.5 (4.6)[1]	10.4 (3.0)	17.3 (7.2)[2]	10.7 (3.2)	[3]	9.5 (4.4)[2]	9.1 (3.7)[2]	10.7 (1.4)
Sex								
Men	16.5 (3.9)	5.6 (1.0)	23.7 (7.0)	4.9 (0.9)	[3]	6.8 (2.8)[2]	12.2 (4.5)[1]	2.1 (0.4)
Women	18.2 (8.0)[2]	6.2 (1.5)	15.5 (6.4)[2]	7.7 (1.8)	[3]	[3]	6.0 (2.9)[2]	3.5 (0.5)
Race/ethnicity								
Non-Hispanic white	15.1 (5.4)[1]	6.5 (1.6)	18.0 (7.2)[1]	6.8 (1.5)	[3]	6.0 (2.5)[2]	7.0 (3.0)[2]	2.9 (0.4)
Non-Hispanic black	30.6 (6.3)	3.3 (1.0)[1]	30.1 (10.2)[1]	3.0 (1.1)[1]	[3]	4.0 (2.0)[2]	[3]	2.9 (0.9)[1]
All Hispanic	[3]	3.1 (1.2)[1]	[3]	3.3 (1.6)[2]	[3]	[3]	[3]	1.7 (0.7)[1]
Mexican American	[3]	3.5 (1.2)[1]	[3]	3.3 (1.5)[2]	[3]	[3]	[3]	1.7 (0.5)

Previous diagnosis of stroke is based on self-report. Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FOOT ULCERS

INTRODUCTION

Diabetic foot ulcer (DFU) is defined as a chronic full thickness skin defect distal to the malleoli. It occurs frequently as a complication of diabetes, with an estimated lifetime risk of 12%–25% (63,64,65,66). Reported DFU annual incidence ranges from 1.6% (67) to 7.2% (68) for first DFU development and from 7.8% (69) to 48.0% (70) for DFU recurrence. The reported prevalence of current or past history of DFU ranges between 10.4% (71) and 57.9% (72). DFU annual incidence from 2006 to 2008 in Medicare beneficiaries with diabetes was between 6% and approximately 13% in those with diabetes and PAD (73). According to a new analysis of NHANES 1999–2004 data, 0.77% of all patients with diabetes (including those undiagnosed) presented with active foot lesions on physical examination. For this survey, foot lesions were defined as presence of any of the following: bandages, blisters, ulcers, abrasions, lacerations, and sutures. Moreover, those without diabetes compared to those with diabetes had a higher frequency of foot lesions on exam (Table 20.18). As the NHANES examiners used a very broad definition of foot lesions that was not specific for

TABLE 20.18. Percent of Adults Age ≥40 Years With Foot Lesions, Overall and by Diabetes Status, U.S., 1999–2004

PERCENT (STANDARD ERROR)				
Overall	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	No Diabetes
0.81 (0.20)	0.77 (0.33)[2]	0.73 (0.28)[1]	[3]	0.81 (0.23)

Foot lesions are defined by the presence of bandages, blisters, ulcers, abrasions, lacerations, and sutures. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.

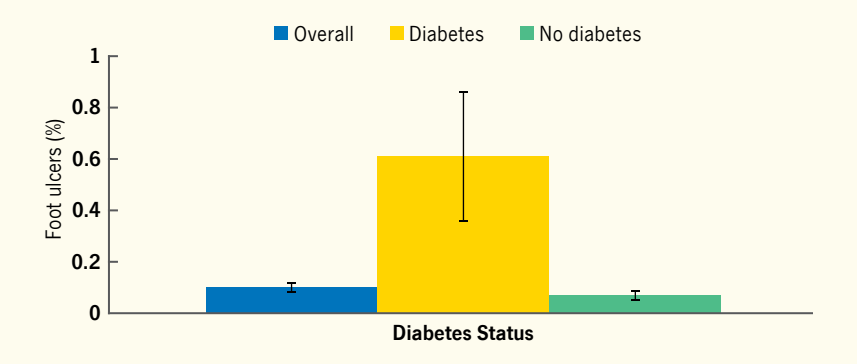
[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

FIGURE 20.14. Percent of Outpatient Visits to a Physician Pertaining to Foot Ulcers Disease, by Diabetes Status, U.S., 2002–2009



Foot ulcers are defined based on ICD-9 codes 040.0, 440.24, 785.4, 440.23, and 707.1. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Error bars represent 95% confidence intervals. ICD-9, International Classification of Diseases, Ninth Revision.
All relative standard errors ≤30%

SOURCE: National Ambulatory Medical Care Surveys 2002–2009

foot ulcer, the meaning of this finding is uncertain, but most likely the lesions detected were mainly not those that would be typically classified as a foot ulcer related to diabetes. Conversely, based on International Classification of Diseases, Ninth Revision (ICD-9) codes, new analysis of the National Ambulatory Medical Care Surveys 2002–2009 that captured outpatient visits to a physician pertaining to foot ulcers found a nearly ninefold greater frequency of such visits among persons with compared to those without diabetes (Figure 20.14). A similar higher frequency of hospital discharges listing foot ulcer in those with diabetes was seen in the National Hospital Discharge Surveys from 2002–2009 (Figure 20.15, Table 20.19). Persons with diabetes age 45–64 years compared to other age categories, women, and American Indian/Alaska Native ethnic groups had the highest frequencies of hospital discharges listing foot ulcer.

PATHOPHYSIOLOGY AND RISK FACTORS

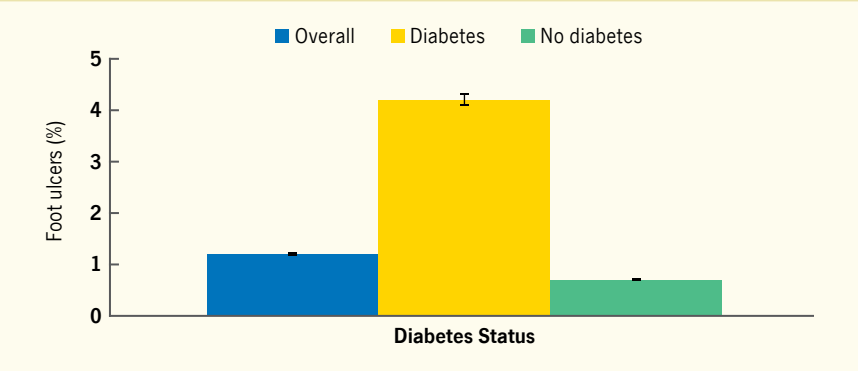
DFU scarcely occurs due to a single cause (74,75). Instead, a number of factors contribute to its development and maintenance. Chronic hyperglycemia progresses to diabetic peripheral neuropathy (DPN) and/or arteriosclerosis, which in the presence of trauma may result in DFU and, in advanced cases, lower extremity amputations (LEA) (64,66,74,76,77,78,79,80).

Neuropathy

Chronic hyperglycemia causes changes in cell membrane function, mainly through ischemia of the endoneural microvascular circulation (79), damaging the nerves (especially those with smaller diameter and less myelination) (65), thus affecting somatic and autonomic fibers (63,65,79,81,82). The majority of DFUs have as a primary cause the presence of DPN (66,79,83,84), which is considered a major factor for their occurrence (74,80). Thus, a slower motor nerve conduction velocity has been associated with the presence of DFU (67,85,86,87).

Motor Neuropathy. Motor neuropathy may lead to paresis, ataxic gait, weakness and atrophy of the small intrinsic foot muscles, foot deformities, and metatarsal verticalization, which create areas on the foot with elevated pressure peaks (63,65,82). At the same time, the metatarsal fat pad is dislocated, reducing its natural function (66,79,81,82) of dissipating the weight-bearing forces in all directions (82). This process leads to a triangular forefoot that is difficult to adapt to regular shoes (79). These changes increase the risk of dorsal and plantar DFU (81). Less commonly, motor neuropathy can also affect a single major peripheral motor nerve and cause anterior crural muscle atrophy, producing ankle equinus. This biomechanical alteration causes an increase in the forefoot pressure and shearing forces (65,66,81,82) and was identified as a precipitant factor for the development, recurrence, and recalcitrance of DFU (66). Changes in lower extremity reflexes have been associated with DFU in several studies (88,89,90,91,92,93); however, no studies have assessed the association of changes in these reflexes with muscle wasting.

FIGURE 20.15. Percent of Hospital Discharges Listing Foot Ulcers Disease, by Diabetes Status, U.S., 2002–2009



Foot ulcers are defined based on ICD-9 codes 040.0, 440.24, 785.4, 440.23, and 707.1. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Error bars represent 95% confidence intervals. Confidence intervals were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. See Table 20.19 for further details. ICD-9, International Classification of Diseases, Ninth Revision.
All relative standard errors ≤30%

SOURCE: National Hospital Discharge Surveys 2002–2009

TABLE 20.19. Percent of Hospital Discharges Listing Foot Ulcers, Overall and by Age, Sex, Race, and Diabetes Status, U.S., 2002–2009

	PERCENT (STANDARD ERROR)		
Characteristics	Overall	Diabetes	No Diabetes
Overall	1.2 (0.01)	4.2 (0.06)	0.7 (0.01)
Age (years)			
<45	0.2 (0.01)	3.1 (0.14)	0.1 (0.01)
45–64	1.7 (0.03)	4.9 (0.10)	0.9 (0.02)
65–74	2.0 (0.04)	4.3 (0.12)	1.2 (0.04)
≥75	2.1 (0.03)	3.8 (0.10)	1.7 (0.03)
Sex			
Men	0.9 (0.01)	3.2 (0.07)	0.6 (0.01)
Women	1.5 (0.02)	5.4 (0.10)	0.9 (0.02)
Race			
White	1.1 (0.02)	4.1 (0.08)	0.7 (0.01)
Black	1.5 (0.03)	4.5 (0.14)	0.9 (0.03)
AIAN	1.3 (0.19)	4.9 (0.81)	0.6 (0.16)
Asian	0.5 (0.06)	2.2 (0.35)	0.3 (0.05)

Foot ulcers are defined based on ICD-9 codes 040.0, 440.24, 785.4, 440.23, and 707.1. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AIAN, American Indian/Alaska Native; ICD-9, International Classification of Diseases, Ninth Revision.

SOURCE: National Hospital Discharge Surveys 2002–2009

Autonomic Neuropathy. Autonomic neuropathy leads to decreased sweating, dry skin, and callus formation in areas of higher pressure, since the autonomic nervous system regulates perspiration, skin temperature, and arteriovenous shunting. Measurement of autonomic function is generally performed by assessment of cardiovascular reflexes that may not reflect function in the extremities. An indicator test for sudomotor function has been associated with clinical severity of DPN (94) and active or recently healed DFU (95), as well as excellent reproducibility (94) and high accuracy for small-fiber impairment detection. Autonomic neuropathy also leads to vasodilatation of the dorsal foot veins (63,65,66,74,76,79,81,82,83), and arteriovenous shunts increase pressure and arterial flow and may thereby lead to peripheral edema and impaired microvascular response to damage (66). Baseline edema was associated with DFU development in two studies (89,96) conducted by the same group, but not in another (97). Furthermore, according to the neurovascular theory, such blood flow alteration can lead to bone reabsorption and weakening and consequent Charcot neuroarthropathy. This foot deformity occurs in up to 13% of persons with diabetes and DPN (98) and was described as being associated with DFU occurrence (89,99), but not with its recurrence (70,100). With the denervation of dermal structures, skin loses its integrity, mainly through cracks and fissures that facilitate microbial invasion and infection (63,66,80,81,82). Conversely, *tinea pedis* presence may be a clinical marker for intact autonomic function due to the need for a moist medium for fungal growth. *Tinea pedis* was associated with a reduced risk for DFU development in two studies (96,97).

Sensory Neuropathy. Motor and autonomic neuropathy would have a smaller impact if it were not for the simultaneous presence of sensory neuropathy (66,75,81,82,101), which is responsible for loss of protective sensation in the diabetic foot (79). Sensory neuropathy progresses from distal to proximal, in a stocking pattern (81), and diminishes pain and temperature perception (63,81), affecting the protective response to potential causes of foot trauma. Neuropathy symptoms, such as numbness, pain, and/or tingling, are associated with DFU (89,102,103,104). In fact, all patients with an active or recently healed DFU have at least one of these symptoms (102).

Several instruments have been developed to detect loss of protective sensation. The most widely used are the Semmes-Weinstein monofilament (SWM) and the biothesiometer, which were associated with DFU in 21 (69,86,88,89,90,91,92, 93,96,97,102,105,106,107,108,109,110, 111,112,113,114) and 19 (67,68,72,84,85, 91,93,102,104,105,107,111,114,115,116, 117,118,119,120) studies, respectively. For the SWM, no collection procedure (sites and number of applications) has been widely implemented, and therefore, several studies have been conducted to identify the best cutoff (102,107,112,119). The tuning fork is a cheaper alternative to the biothesiometer, since it was consistently associated with DFU in five studies (88,89,90,92,119). Several methods for thermal sensitivity evaluation have been studied (warm and cool rods, thermaesthesiometer, Sensortek™, and other thermal testers), and all have been reported to be associated with DFU (84,85,88,109). Several scores have been created for DPN screening. The Neuropathy Symptom Score (88,103,114,117,121) and the Neuropathy Disability Score (88,106,111,114,117,119,122) have been associated with DFU. The Michigan Neuropathy Screening Instrument has high accuracy for DPN detection (123,124) and reproducibility (123); however, only one study has reported its association with DFU development (68).

Peripheral Arterial Disease

PAD rarely leads directly to DFU but is believed to be a protagonist in the pathway to DFU (66,79). PAD diminishes oxygen levels in tissues, decreasing their resilience (82), which together with trauma and/or sensory and motor nerve alterations leads to tissue anoxia, cell death (125), and DFU (65,75). Noninvasive testing is crucial, because usual signs are less frequent in persons with diabetes due to DPN and more distal arterial stenosis localization (107,125,126). In persons with diabetes, complications in the small and large vessels frequently do not advance at an equal pace, so one may easily observe toes with ischemic signs caused by small vessel alterations, while foot pulses may remain intact (125). An association between the foot palpable pulse number and DFU was reported in several studies (88,90,91,104,111). One of two studies reported an association of ABI value with the development of DFU (89,91), whereas an association of ABI value with DFU recurrence has not been observed (100,127). Only one study has assessed the hallux-brachial index, observing that values ≤0.7 were associated with higher rates of active or recently healed DFU (93). Transcutaneous oxygen pressure is widely used for DFU prognostic assessment. However, research is scarce regarding DFU prediction by this measure (89,100,127).

Elevated Pressure Mechanisms and Measurement

Weight, Height, Waist Circumference, and BMI. Weight, height, waist circumference, and BMI are related to high foot pressure and macrovascular complications. In addition, obesity may result in poor ability to see the feet, which impairs foot self-care (126). However, insufficient evidence is available to support the idea that higher weight (67,89,96), waist circumference (71,93), or BMI (85,92,114,128) is related to an increased risk of DFU. On the other hand, height was associated with DFU in four studies (71,89,93,99), which may be due to the observation that longer nerve axons are more prone to DPN (71).

Foot Deformity and Callus. Several foot deformities, such as abnormal foot (89,96,97,108), rigid toe deformity (88,89,108), hallux limitus or rigidus (89,108), hallux abductus valgus (108), subtarsal (108,111) and first metatarso-phalangeal joints (89,111) mobility

limitation, have been consistently associated with DFU development. Evidence regarding DFU recurrence and foot deformities is scarce. Hyperkeratotic areas (callus) are a natural reaction to pressure or friction, but they create even more pressure to the subcutaneous tissues, and hemorrhaging into the callosity is a common clinical finding (125,129), especially in patients with DPN (125). Presence of callus at baseline was associated with DFU in two studies (99,129), but not in another (96); yet, the number of areas with callus does not seem to influence the DFU risk (129).

Pressure Measurements. Subjects with greater peak plantar pressure values consistently have a higher risk of DFU occurrence (67,104,105,111,116,129,130, 131). Surprisingly, greater peak plantar pressure had no impact in the prediction of recurrent DFU (100). Caselli *et al.* (116) found that patients with high forefoot peak pressure and a forefoot/rearfoot ratio >2 were more likely to have advanced DPN and a higher risk of DFU development. Sauseng *et al.* (87) showed that maximum plantar pressure, plantar loading over time, and relative contact time in the first metatarsal head were higher in subjects with a neuropathic plantar DFU. Almost no evidence is available on the effect of daily weight-bearing physical activity on DFU risk. Three studies concluded that less than average daily activity was associated with a higher risk for DFU (69,118,132). These results are in agreement with the "physical stress theory" proposed by Maluf and Mueller, which states that a gradual increase in physical stimulation leads to plantar protective tissue hypertrophy, preventing skin breakdown (69,118). Conversely, one study (132) reported that higher activity variability represented an increased risk.

Diabetes Characteristics and Glycemic Control

Poorer glycemic control is associated with the development of several diabetic foot complications (104,115), but no clinical trial data are available on intensive glycemic control and DFU risk. Type of treatment has been examined, with insulin treatment associated with an increased risk for DFU (89,90,96,99,103). This association may reflect greater diabetes severity in persons treated with insulin compared to lifestyle or oral medication. There is no evidence for an association between type of diabetes and the risk of DFU development. Longer diabetes duration is associated with a higher risk of DPN (133) and/or PAD, and greater diabetes duration also increases the risk of DFU (71,87,88,89,90,91,95,96,99, 103,104,105,110,111,118,120,128,130, 134,135,136,137). Poor glucose control as reflected by higher A1c has been associated with DFU risk. A majority of studies showed a statistically significant association between A1c value and DFU development (85,89,96,97,110,134), but not with DFU recurrence (110,138).

Physical Impairments

Good visual acuity and physical ability are essential for correct foot self-care (123). Studies analyzing the impact of poor vision (88,89,96,97), retinopathy (97,134), and laser photocoagulation history (89,96) reported positive associations between these variables and risk for DFU. Only one study reported physical impairment to be associated with DFU development (97).

Other Risk Factors

In the great majority of studies, an association between sex and DFU occurred, and men were consistently at higher risk for DFU (84,88,95,97,104,105,111,130, 138,139). Regarding race/ethnicity, several studies concluded that whites had higher rates of DFU compared with blacks and/or Asians (105,128,135,140,141). No study detected an association between smoking habits (96,97,100,110,113), any of the items of the lipid profile (100,113,127,134), or low educational attainment (71,86,92,97,100,104,128,142) with risk of initial or recurrent DFU. Insufficient evidence is available regarding the impact of depression, physical inactivity, alcohol consumption habits, or cardiovascular complications on DFU risk. Several authors (143) affirm that nephropathy should be included in diabetic foot classification, because it has been associated with DFU occurrence in several studies (88,104,110,135). Conversely, one study presents results indicating that nephropathy can be a potential confounding variable (144). No studies have shown nephropathy to be related to DFU recurrence (100,117,127,138,145). Onychomycosis was linked to higher risk of DFU development in two studies (96,97); however, the use of therapeutic nail lacquer did not reduce the risk in a randomized controlled trial (RCT) (146). Previous foot complications (DFU or LEA) were consistently related with a new DFU occurrence (85,88,89,91,96,97,99,104, 107,110,111,117,129,134,135,138,141). The association between previous DFU and new DFU development was observed in a retrospective study even after adjustment for age, sex, visual acuity, physical impairments, diabetes type and duration, PAD complication history, diabetes complication count, and previous LEA (147).

NATIONAL SURVEY RESULTS

Self-reported telephone survey data from the Behavioral Risk Factor Surveillance System (BRFSS) were used in new analyses for *Diabetes in America* to assess the frequency of "ever having foot lesions that took more than 4 weeks to heal" among persons with diabetes. Such lesions have a good likelihood of representing DFU, although no assessment has been done to confirm this. One must keep in mind that other chronic lower limb wounds often occur in persons with diabetes, such as venous leg ulcers, pressure wounds, and infectious and malignant dermatologic pathologies. The overall frequency of self-reported skin lesions did not vary much over the BRFSS 2000–2007 cycles (Table 20.20). A number of characteristics were associated with higher frequency of self-reported foot lesions, including age <65 years, Hispanic or American Indian ethnicity, insulin treatment, diabetes onset before age 30 years, current smoker, not having exercised in the past month, higher BMI, and using special equipment for disability (Table 20.20).

TABLE 20.20. Percent With Foot Lesions Among Adults Age ≥18 Years With Diagnosed Diabetes, Overall and by Age, Sex, Race/Ethnicity, Insulin Use, Age of Diabetes Onset, Smoking, Alcohol Use, Exercise, BMI, and Disability, U.S., 2000–2007

CHARACTERISTICS	PERCENT (STANDARD ERROR)							
	2000	2001	2002	2003	2004	2005	2006	2007
Overall	12.7 (0.7)	11.5 (0.5)	11.6 (0.7)	13.0 (0.6)	11.9 (0.5)	11.0 (0.4)	11.8 (0.4)	11.3 (0.4)
Age (years)								
18–39	16.1 (1.9)	11.9 (1.5)	13.0 (2.6)	19.0 (2.8)	12.8 (1.5)	11.6 (1.4)	13.5 (1.6)	13.2 (2.2)
40–64	14.4 (1.1)	12.9 (0.8)	12.9 (0.9)	14.5 (0.8)	13.9 (0.8)	12.6 (0.6)	13.8 (0.7)	13.1 (0.6)
65–74	10.5 (1.1)	9.9 (1.1)	9.1 (1.0)	10.5 (0.9)	9.2 (0.8)	9.3 (0.8)	9.2 (0.7)	8.6 (0.6)
≥75	8.4 (1.0)	8.8 (1.0)	10.0 (2.2)	7.5 (0.7)	8.7 (1.0)	7.6 (0.7)	8.1 (0.8)	8.3 (0.7)
Sex								
Men	12.8 (1.0)	11.6 (0.8)	11.5 (0.9)	14.1 (0.8)	12.7 (0.8)	11.1 (0.6)	11.7 (0.7)	12.0 (0.7)
Women	12.6 (0.8)	11.4 (0.7)	11.7 (1.0)	11.9 (0.8)	11.0 (0.6)	10.8 (0.5)	11.8 (0.6)	10.6 (0.5)
Race/ethnicity								
Non-Hispanic white	12.7 (0.6)	10.8 (0.6)	11.1 (0.5)	12.0 (0.5)	11.6 (0.5)	11.1 (0.4)	11.3 (0.5)	10.9 (0.4)
Non-Hispanic black	9.1 (1.0)	10.0 (1.4)	8.5 (1.2)	12.4 (1.6)	10.4 (1.1)	10.3 (0.9)	10.3 (0.9)	10.1 (1.0)
All Hispanic	15.5 (2.7)	14.7 (1.9)	17.9 (3.3)	15.1 (2.0)	13.1 (1.7)	11.0 (1.6)	13.7 (1.6)	13.8 (1.6)
American Indian	15.0 (4.6)[1]	25.1 (6.4)	10.3 (2.5)	21.9 (6.8)[1]	14.1 (3.0)	8.6 (2.7)[1]	17.2 (3.8)	12.8 (2.2)
Insulin use								
Yes	18.7 (1.4)	17.1 (1.3)	17.6 (1.7)	20.7 (1.2)	17.4 (0.9)	17.4 (0.9)	18.8 (1.0)	18.4 (0.9)
No	10.4 (0.7)	9.5 (0.6)	9.4 (0.6)	10.3 (0.6)	10.1 (0.6)	8.8 (0.4)	9.4 (0.5)	8.7 (0.4)
Age of diabetes onset								
<30 years	21.1 (2.0)	17.6 (2.0)	17.4 (2.2)	21.9 (2.5)	19.5 (1.6)	19.8 (1.7)	19.7 (1.9)	19.5 (2.2)
≥30 years	11.7 (0.7)	10.6 (0.6)	10.8 (0.7)	11.9 (0.6)	11.0 (0.5)	10.0 (0.4)	10.9 (0.5)	10.4 (0.4)
Smoking status								
Never smokers	10.6 (0.7)	9.9 (0.8)	11.1 (1.1)	11.5 (0.8)	11.4 (0.7)	10.4 (0.6)	11.1 (0.7)	10.8 (0.7)
Former smokers	12.7 (1.0)	12.0 (0.9)	11.2 (1.1)	12.1 (0.8)	10.6 (0.7)	10.1 (0.6)	11.3 (0.7)	10.2 (0.5)
Current smokers	18.4 (2.4)	14.9 (1.4)	13.5 (1.2)	18.6 (1.7)	16.1 (1.4)	14.5 (1.0)	15.1 (1.0)	15.5 (1.0)
Alcohol use								
<1 drink/day	12.7 (1.2)	11.4 (0.6)	11.8 (0.7)	13.0 (0.6)	11.8 (0.5)	10.9 (0.4)	11.9 (0.5)	11.4 (0.4)
≥1 drink/day	8.4 (3.0)[1]	9.7 (1.8)	7.6 (1.6)	11.1 (2.5)	14.2 (3.5)	12.5 (2.7)	12.6 (1.9)	10.0 (1.5)
Exercise in past month								
Yes	10.6 (0.8)	9.3 (0.7)	9.7 (0.9)	10.7 (0.6)	10.4 (0.6)	8.7 (0.4)	9.4 (0.5)	9.1 (0.5)
No	16.2 (1.2)	14.7 (0.9)	14.6 (1.0)	16.9 (1.1)	14.2 (0.8)	14.1 (0.7)	15.5 (0.9)	14.8 (0.7)
BMI (kg/m²)								
<25	12.7 (1.6)	12.8 (1.5)	10.4 (1.0)	13.8 (1.9)	10.6 (1.0)	11.2 (0.9)	10.6 (1.2)	12.1 (1.4)
25–29.9	10.3 (0.9)	9.9 (0.8)	9.6 (0.9)	12.8 (0.9)	10.5 (0.9)	9.5 (0.6)	11.9 (0.9)	9.9 (0.7)
30–39.9	13.9 (1.3)	11.2 (0.9)	12.0 (1.1)	12.1 (0.8)	12.8 (0.8)	11.1 (0.6)	11.5 (0.6)	11.2 (0.6)
≥40	21.2 (2.8)	15.3 (2.1)	15.7 (2.7)	17.0 (1.7)	15.4 (1.7)	14.4 (1.3)	15.3 (1.3)	14.7 (1.2)
Use special equipment for disability*								
Yes	-	-	-	23.6 (1.5)	22.4 (1.3)	20.7 (1.0)	21.7 (1.3)	20.7 (1.0)
No	-	-	-	10.5 (0.6)	9.5 (0.5)	8.5 (0.4)	8.9 (0.4)	8.7 (0.5)

Foot lesions were determined based on self-report of ever having lesions that took more than 4 weeks to heal. BMI is based on self-reported height and weight. Diagnosed diabetes is based on self-report. BMI, body mass index.

* Use of special equipment for disability was only asked in 2003–2007.

[1] Relative standard error >30%–40%

SOURCE: Behavioral Risk Factor Surveillance System 2000–2007

A NHANES 1999–2004 survey question on global assessment of health status was analyzed for *Diabetes in America*. Participants with diagnosed diabetes and foot lesions had a higher frequency of fair/poor self-reported health (Table 20.21) than those without foot lesions. Data were too sparse to permit stratification by age, sex, and race/ethnicity. Similar findings were seen from this survey for all persons with diabetes with regard to number of days in the past 30 days that physical health was not good (Table 20.22).

PREVENTION STRATEGIES

Guidelines from 2004 advocate that education should be provided to all diabetic patients on foot care and that they should have their risk status assessed at least annually (76,148). This recommendation is frequently neglected (104,125,142). In a U.K. study, <20% of diabetic patients had their feet examined by a health care professional, and the foot exam annual rate ranged from 30% to 50% in the physician's office (125). A complete assessment was performed in only about 10% of the diabetic population in outpatient clinics and in 14% of those admitted to hospital due to DFU (80). This low assessment rate may be partly explained by the lack of knowledge of the most important items to assess during the screening evaluation (104). In addition, evidence regarding the impact of podiatric care (91,135,149) and diabetic foot educational programs on DFU risk is insufficient (88,150,151,152). Additional data on the utilization of podiatry care in outpatient settings in the United States are provided in Chapter 39 *Medication Use and Self-Care Practices in Persons With Diabetes*, Chapter 40 *Health Care Utilization and Costs of Diabetes*, and Chapter 41 *Quality of Care in People With Diabetes*.

Diabetic Foot Risk Classifications

Several classification systems have been proposed for stratifying patients with diabetes by risk of DFU development (143). The most widely known (145) are the (1) American Diabetes Association, (2) International Working Group on Diabetic Foot (IWGDF), (3) Scottish Intercollegiate Guidelines Network (SIGN), and (4) University of Texas systems, and (5) the Seattle risk score. Despite differences in the number of risk strata and number and types of variables included in each system, the majority of the systems had identical core variables: DPN, PAD, foot deformity, and previous diabetic foot complications (DFU and LEA). A systematic review concluded that the overall evidence quality around these systems is low, because little validation has been conducted (145). A retrospective cohort study of 270 participants with a 1-year follow-up, designed to validate all of the systems simultaneously, found no differences in accuracy (153). Further prospective research to assess the described systems' predictive accuracy and evaluate new pertinent variables is needed.

Foot Self-Care Behaviors and Inspection

Evidence of foot self-care impact on DFU risk is scarce. One study (97) reported that poor nail care at baseline was not associated with DFU development. Irregular or insufficient moisturizing represented a higher risk for DFU development in one study (113), but not in another (97). No association was found between foot self-care habits, such as washing, sock use, or soaking, and the risk of DFU development in one study (113). However, patients with higher foot care scores had a lower risk of DFU recurrence in another study (93). Foot care practices, including self-care and exams by a health care provider, are also described in Chapter 39.

Footwear

In several studies, footwear was the most frequent precipitating factor for foot ulceration (97,154,155) and half of all diabetic amputations (156). The use of high-risk footwear, according to a classification proposed by Abbott *et al*. (68), increased the risk of DFU development in two studies (88,97). The use of therapeutic footwear was related to a decrease in DFU development (89,157) and recurrence (136,154) in some studies, but not in all (70,158). All studies assessing the impact of therapeutic shoes compliance verified that greater compliance with wearing the recommended footwear was associated with a lower rate of DFU occurrence (141,157,159).

TABLE 20.21. Percent of Adults Age ≥40 Years With Diagnosed Diabetes With Fair or Poor Self-Reported Health, by Foot Lesion Status, U.S., 1999–2004

PERCENT (STANDARD ERROR)	
Foot Lesions	No Foot Lesions
53.5 (20.6)[1]	42.4 (2.3)

Foot lesions are defined as bandages, blisters, ulcers, abrasions, lacerations, and sutures. Diagnosed diabetes is based on self-report.

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.22. Mean Days Physical Health Was Not Good in the Past 30 Days Among Adults Age ≥40 Years With Diabetes, by Foot Lesion Status, U.S., 1999–2004

MEAN (STANDARD ERROR)	
Foot Lesions	No Foot Lesions
16.1 (6.9)[1]	5.4 (0.5)

Mean days physical health was not good is based on self-report. Foot lesions are defined as bandages, blisters, ulcers, abrasions, lacerations, and sutures. Diabetes includes both diagnosed and undiagnosed diabetes. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

[1] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Home Temperature Monitoring

DFU is accompanied by an inflammatory response, one manifestation of which is a cutaneous temperature increase. Foot temperature assessment has been examined as a potential tool for predicting complications and leading patients to seek medical care (139,160,161,162,163). The use of self-administered infrared temperature sensors was related to a significant reduction in the risk of DFU development (161,162) and recurrence (163). However, this tool as a baseline one-time measurement failed to accurately predict DFU development in a 2-year prospective cohort study (160). Nevertheless, a 2013 systematic review and meta-analysis concluded that this instrument is effective in predicting DFU occurrence and may therefore be of use in identifying persons at risk for this outcome who might benefit from preventive measures (164).

RESEARCH ON CLINICAL COURSE

Foot Ulcer Healing

DFU is the most frequent cause of LEA in persons with diabetes (101,165). Each DFU requires 15–20 weeks on average to heal, and until re-epithelialization has occurred, the risk for infection is substantially increased (165). The time range for healing, though, is skewed. The Eurodiale study reported that after 1 year, 12% of DFUs were still under treatment (166).

Classification, Staging, and Treatment

Location, Depth, Area, and Duration. The most frequent location of DFU is the pulp of the hallux and beneath the first metatarsal (167). DFU located on the toes present a better prognosis in comparison with those located on other areas of the foot (168,169,170). A greater depth (166,168,171,172,173,174,175), cross-sectional area (166,171,173,175,176,177,178), duration at first assessment (166,169,173,176,177), and multiple DFU (169,173,176) are associated with longer time to heal and poorer prognosis. Initial healing progress with a reduction in area at 1–2 weeks has been associated with greater chance of complete healing (179).

Neuropathic, Neuro-Ischemic, and Ischemic DFU. Most DFUs can be classified as neuropathic, neuro-ischemic, or ischemic (101), which depends upon the diagnosis of DPN and/or PAD. Therefore, both DPN (170,171,172,174,180) and PAD (66,101,166,168,170,171,172,175,178, 180,181,182), diagnosed by absent pulses, ABI <0.7, and/or a transcutaneous partial pressure of oxygen (TcPO2) <40 mmHg, are associated with a poorer prognosis. While about 55%–60% of DFU are purely neuropathic, 35%–45% are caused by neuropathic and ischemic factors (66,74). In one study, the healing rate of patients with PAD, diagnosed through absence of pulses, was comparable to the rate in patients with DPN and significantly superior to those with both complications (172).

Prognostic Systems. A systematic review identifying the available DFU scoring systems concluded that there are a great variety of prognostic stratification systems, but only a few were validated (183,184). The systems considered were: (1) Curative Health Services (CHS); (2) Depth of the Ulcer, Extent of bacterial colonization, Phase of ulcer and Association aetiology (DEPA); (3) Diabetic Ulcer Severity Score (DUSS); (4) Infectious Diseases Society of America–International Working Group on Diabetic Foot (IDSA-IWGDF); (5) Levine and O'Neal; (6) Lipsky *et al.*; (7) Meggit-Wagner; (8) Margolis *et al.*; (9) Perfusion, Extent, Depth/tissue loss, Infection, Sensation (PEDIS); (10) Size (Area, Depth), Sepsis, Arteriopathy, Denervation [S(AD) SAD] system; (11) Saint Elian Wound Score System (SEWSS); (12) Scottish Intercollegiate Guidelines Network (SIGN); (13) Site, Ischemia, Neuropathy, Bacterial infection, and Depth (SINBAD); (14) Texas University Classification (TUC); and (15) Van-Acker/Peter. The SIGN classification is the only one that was validated, in 2006, for DFU development and, in 2007, also for LEA occurrence prediction (172,185). The most frequently validated systems for DFU healing were the Meggit-Wagner (n=9), S(AD)SAD (n=5), and TUC (n=5), showing lower rates of DFU healing as the systems' grade and/or stage increased (183). Accuracy measures varied greatly, and further studies validating, refining, and comparing the existing systems are still needed. The most frequently included and validated variables were PAD, DFU depth, and infection (183).

Other Methods to Predict Outcome. Several other factors have a significant impact on DFU healing. In the Eurodiale study, end-stage renal disease was associated with a higher rate of DFU nonhealing (166). Older (110,166,169,172,177) and male patients presented lower healing rates in several studies (166,173,177). Subjects with previous DFU or LEA history have lower healing rates (168,180). Chronic hyperglycemia is linked to compromised cellular matrix reorganization (186) and white blood cell function (79), phenomena that would be expected to impede wound healing delay and increase the risk of LEA (66). However, no RCT has been conducted to determine whether intensive glycemic control improves healing of DFU (79,187).

Treatment Strategies. Several therapeutic technologies have been created to improve DFU treatment and its prognosis. Results have been discouraging, with little benefit shown over and above standard wound care with appropriate debridement and pressure offloading (188). Debridement should be adequately conducted before any healing technology application (63). In fact, an RCT of becaplermin reported that those patients with more frequent debridement presented higher healing rates (189). A systematic review investigating the effect of surgical debridement on DFU healing identified five RCTs (190) of debridement that demonstrated better outcomes with more frequent application of this intervention. Due to the low number of included studies and methodological disparities, the authors concluded that further research is needed.

Pressure offloading is the other cornerstone of appropriate wound care. Unless repetitive pressure and shear forces are diminished, wound healing will be impaired (189). Multiple offloading strategies are available, with published data favoring the total contact cast (TCC), which can reduce pressure at the DFU site by 84%–92%. This technique has consistently proved to be the most effective regarding healing rates and time to heal (both in observational studies and RCTs) in comparison to other offloading modalities (191,192) and with other therapeutic procedures, such as becaplermin, bioengineered tissue, or electrical stimulation (186). A Cochrane review provided further support for the use of nonremovable, pressure relieving casts in the treatment of DFU, finding benefit in healing from this intervention (193). Due to time and a high level of expertise required, TCC is not widely adopted by the medical community (191). On the other hand, the use of therapeutic shoes to promote healing still lacks sufficient evidence to prove its effectiveness (191).

A meta-analysis of four RCTs concluded that the group treated with becaplermin showed higher healing rates compared with placebo gel. However, becaplermin is expensive, and therefore, its widespread use is limited (194,195). Concerning skin equivalents, two studies, one using Dermagraft and another Apligraf, demonstrated that they are safe and effective in the treatment of DFU. Hyperbaric oxygen therapy, which is available in few centers, is potentially effective but very expensive (196). This intervention has shown some promise in the treatment of DFU, as a meta-analysis only including RCTs, concluded that subjects undergoing this therapy were at a reduced risk of major but not minor LEA (197,198,199).

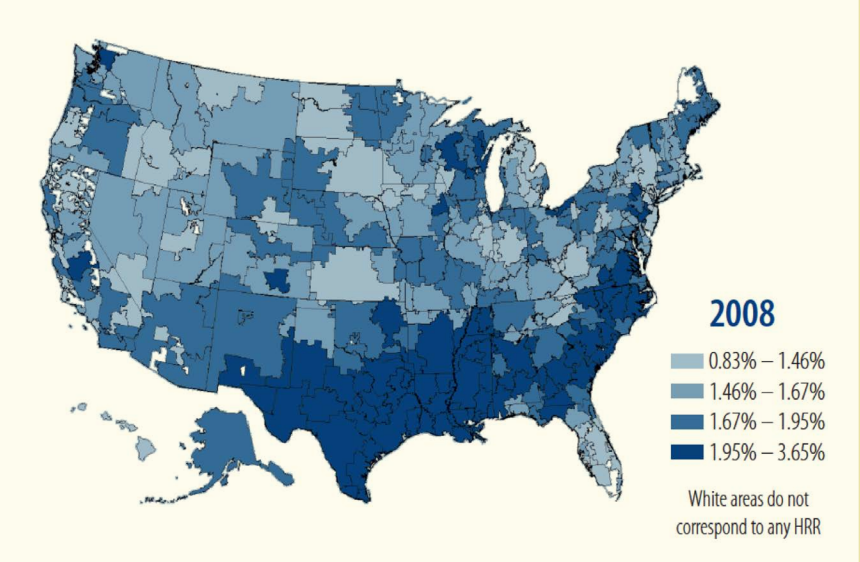
LOWER EXTREMITY AMPUTATION

INTRODUCTION

LEA frequently complicates the clinical course of diabetes and is often associated with other diabetes complications. In 1997, diabetes accounted for more than half of all nontraumatic LEAs in the United States (200). The magnitude of increase in risk of LEA associated with diabetes was estimated at 7.19 (95% CI 4.61–11.22) among 14,407 subjects in the NHANES Epidemiologic Follow-up Study who were observed prospectively between 1971 and 1992 (201). A similar magnitude eightfold increase in risk of LEA was reported from a population-based cohort study in Sweden (202). Depending on the reason for amputation and the vascular status of the patient, the level may involve toe, partial foot, ankle, below the knee, above the knee, hip dysarticulation, or hemipelvectomy. A national study of U.S. veterans with diabetes from 1998 found that toe amputation was performed most frequently, followed by below the knee amputation (203).

The frequency of LEA among persons with diabetes in the United States declined from the 1990s to the 2000s. The Centers for Disease Control and Prevention noted a fall in hospitalizations for LEA per 1,000 persons with diabetes age ≥40 years from 11.2 in 1996 to 3.9 in 2008 based on data from the National Hospital Discharge Survey to capture amputation hospitalizations and National Health Interview Survey data to estimate diabetes prevalence (204). LEA rates were found to fall in all demographic groups considered. Rates were not reported by amputation level, so all levels from toe to hemipelvectomy were included in this analysis. A very similar LEA rate of 4 per 1,000 persons with diabetes in 2008 was estimated from U.S. national Medicare Parts A and B data using the same ICD-9 codes to capture amputation, with the exception that the sample did not include amputations higher than above the knee (73). Persons age ≥65 years were predominant in this sample, but others eligible for Medicare were represented as well, including persons with end-stage renal disease, amyotrophic lateral sclerosis, or who have a severe and permanent disability as determined by the Social Security Administration. In the same Medicare population in 2008, the prevalence of LEA among persons with diabetes was 18 per 1,000 persons (205). Prevalence of LEA varied nationally, with higher rates seen mainly in the South and Southwest (Figure 20.16), consistent with the higher prevalence of diabetes in the Medicare population in the same general regions (Figure 20.17) (205,206). National variation in amputation incidence between 2007 and 2010 was also noted across the United Kingdom (207). Incidence also varied by race/ethnicity, with lower incidence noted in both Asians

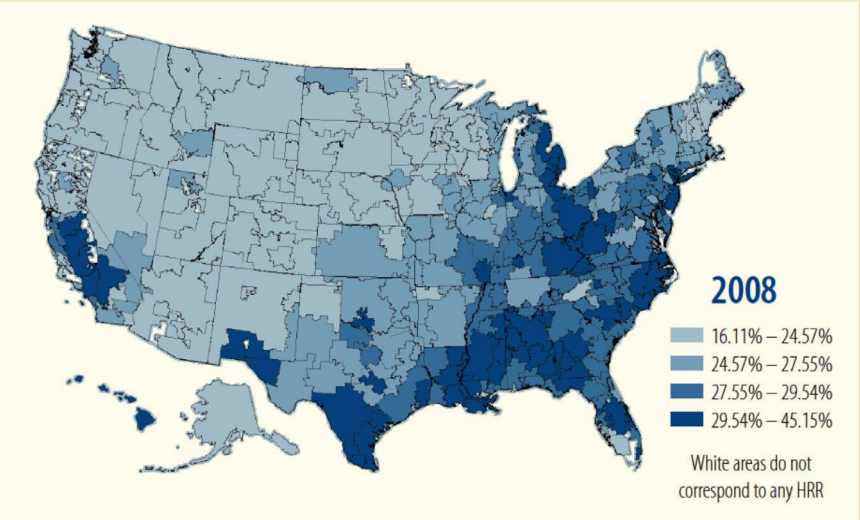
FIGURE 20.16. Prevalence of a Primary or Secondary Diagnostic Code for Lower Extremity Amputation, Medicare Beneficiaries, U.S., 2008



Prevalence of a primary or secondary diagnostic code for lower extremity amputation among Medicare beneficiaries with diabetes continuously enrolled in Parts A and B Fee-for-Service plans for at least 12 months by Dartmouth Atlas of Health Care Hospital Referral Regions (HRR) (*www.dartmouthatlas.org*).

SOURCE: Reference 73

FIGURE 20.17. Prevalence of Diabetes Based on Claims Data in a 12-Month Continuous Medicare Enrollment Period, U.S., 2008



Prevalence of two or more claims with ICD-9 codes consistent with diabetes or at least one inpatient claim with ICD-9 codes consistent with diabetes in the 12-month period of continuous enrollment in Parts A and B Fee-for-Service plans among Medicare beneficiaries by Dartmouth Atlas of Health Care Hospital Referral Regions (HRR) (*www.dartmouthatlas.org*). ICD-9, International Classification of Diseases, Ninth Revision.

SOURCE: Reference 205

and blacks (207). Amputation rates based on the Medicare Diabetes Analytics File in the United States and a Department of Veterans Affairs study, though, found the opposite results with regard to blacks who had a higher LEA frequency (203,208).

Type of diabetes and amputation level are typically not reported in national surveys of LEA incidence and prevalence. Data from the NHANES 1999–2004 were examined for *Diabetes in America* to estimate prevalence of amputation by level as assessed by physical examination (Table 20.23). Overall prevalence of amputation was 0.18%, but this estimate is imprecise due to the small number of participants noted to have had an LEA. The majority of amputations involved at least the entire foot. The exact level at the foot or a more proximal location was not specified. A higher prevalence was seen among persons with diagnosed and undiagnosed diabetes, but statistical inference is not possible in these data due to the large standard errors. According to a new analysis of survey data, the percentage of outpatient physician visits related to amputation were infrequent overall in the National Ambulatory Medical Care Surveys 2002–2009 but five times more likely to occur in persons with compared to those without diabetes (Table 20.24).

PATHOPHYSIOLOGY

The main indication for LEA is tissue nonviability due to ischemia, infection, or injury (209). The effect of diabetes is one step removed but acts through pathways that increase risk of ischemia due to PAD and infection following the development of a foot ulcer (210). LEA in diabetes is frequently preceded by a nonhealing foot ulcer that may lead to extensive infection involving soft tissue and bone for which the only effective treatment is amputation (210). Severe PAD associated with diabetes may require amputation as treatment for a nonhealing ulcer, gangrene, or refractory pain (209). History of DFU and PAD appear to have independent roles in predicting amputation risk, as a positive DFU history was linked to a higher risk of LEA even when adjusted for PAD and number of diabetic complications (147).

TABLE 20.23. Prevalence of Lower Extremity Amputations Determined by Physical Examination Among Adults Age ≥40 Years, Overall and by Diabetes Status, U.S., 1999–2004

	PERCENT (STANDARD ERROR)		
AMPUTATIONS	Overall	All Diabetes	No Diabetes
Overall	0.18 (0.07)[1]	0.28 (0.11)[1]	0.17 (0.07)[2]
n	13	9	4
n toe	4	3	1
n partial foot	0	0	0
n entire foot	9	6	3

Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.
[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 20.24. Percent of Outpatient Visits to a Physician Pertaining to Nontraumatic Amputations, by Diabetes Status, U.S., 2002–2009

PERCENT (STANDARD ERROR)		
Overall	Diabetes	No Diabetes
0.02 (0.004)	0.10 (0.044)[1]	0.02 (0.003)

Amputation is defined based on ICD-9 codes V49.7 and V52.1. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9, International Classification of Diseases, Ninth Revision.
[1] Relative standard error >40%–50%
SOURCE: National Ambulatory Medical Care Surveys 2002–2009

TABLE 20.25. Percent of Hospital Discharges Listing Nontraumatic Amputations, Overall and by Age, Sex, Race, and Diabetes Status, U.S., 2002–2009

	PERCENT (STANDARD ERROR)		
CHARACTERISTICS	Overall	Diabetes	No Diabetes
Overall	0.19 (0.01)	0.72 (0.03)	0.11 (0.004)
Age (years)			
<45	0.05 (0.003)	0.43 (0.05)	0.04 (0.003)
45–64	0.34 (0.01)	0.93 (0.05)	0.18 (0.01)
65–75	0.33 (0.02)	0.79 (0.06)	0.18 (0.02)
≥75	0.25 (0.01)	0.55 (0.04)	0.18 (0.01)
Sex			
Men	0.12 (0.01)	0.49 (0.03)	0.07 (0.004)
Women	0.29 (0.01)	1.00 (0.05)	0.17 (0.01)
Race			
White	0.18 (0.01)	0.65 (0.04)	0.11 (0.01)
Black	0.32 (0.02)	0.98 (0.07)	0.18 (0.01)
AIAN	0.53 (0.12)	1.90 (0.46)	0.25 (0.11)[1]
Asian	0.06 (0.03)[1]	[2]	[2]

Amputations are defined based on ICD-9 codes V49.7 and V52.1. Diabetes is defined based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AIAN, American Indian/Alaska Native; ICD-9, International Classification of Diseases, Ninth Revision.
[1] Relative standard error >40%–50%
[2] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.
SOURCE: National Hospital Discharge Surveys 2002–2009

Risk Factors

LEA risk is similar in persons with type 1 or type 2 diabetes (211,212). The major reported risk factors for amputation include diabetes severity and duration, neuropathy, PAD, advanced age, and presence of other diabetic complications (73,180,211,212). These risk factors closely parallel those of DFU, as described elsewhere in this chapter. Some racial/ethnic differences have been demonstrated in risk of LEA. Compared to European/Caucasians, American Indians are at higher risk and South and East Asian

men and women and Afro-Caribbean men at lower risk (213,214,215). The incidence of LEA per 1,000 persons in 2008 assessed in the U.S. Medicare population differed by race/ethnicity as follows: white, 4; black, 7; Asian, 2; Hispanic, 5; and American Indian/Alaska Native, 8 (73). Smoking was not related to amputation risk among persons with diabetes in several cohort studies (180,201,216), despite the strong association between this habit and PAD (217).

Regarding the association of LEA with glycemia, a meta-analysis based on 94,640 subjects from 14 prospective studies estimated a 1.26-fold increase in LEA risk in relation to each 1% increase in A1c (211). A study based at a large Northern California health plan confirmed an increase in amputation risk not only with elevated A1c but also with higher serum triglyceride concentration (216). The DCCT and the UKPDS assessed outcomes in relation to an intensive compared to a standard glucose control strategy. Neither study to date has reported whether this intervention resulted in fewer amputations or foot ulcers.

National Hospital Discharge Survey data from 2002–2009 were assessed for *Diabetes in America* to identify characteristics associated with amputation (Table 20.25). The proportion of discharges for amputation among persons with diabetes was approximately sevenfold higher compared to persons without diabetes. The highest proportion of discharges for amputation among persons with diabetes occurred in the 45–64-years age range. This pattern was not seen among persons without diabetes. Similar patterns of sex (higher in women) and race (higher in black and American Indian/Alaska Native) differences were seen between persons with and without diabetes.

Outcomes of LEA

Reamputation. An initial LEA increases the risk of subsequent amputation to the ipsilateral (same) or contralateral (other) limb. Estimates of the degree of this risk vary depending on the extent of the initial surgical procedure. For example, a toe amputation will carry a higher risk of reamputation of the ipsilateral limb than a more proximal (nearer the hip) amputation, such as trans-tibial, because the more distal (nearer the toe) procedure may not be adequate to resect the diseased area to permit healing. Since more limb remains, the potential for additional amputation is higher. Prior amputation was associated with an approximately threefold increase in risk of subsequent amputation in a model that controlled for PAD, neuropathy, diabetes duration, and treatment with insulin, but risk in relation to level of initial amputation was not examined (180). A systematic review of the reamputation rate following a limb-salvaging ray resection (toe and metatarsal) yielded only five studies that included a total of 435 patients undergoing this procedure, among whom 86 (19.8%) required reamputation (218). A higher risk of ipsilateral reamputation among patients who had undergone more distal amputation was generally seen in other investigations (219,220). A high risk of amputation to the contralateral limb at 5-year follow-up varied by level of the initial amputation, with risk ranging from 18.8% for an initial toe to 53.3% for an initial below the knee amputation.

Functional Status. Little information is available to assess the effects of LEA on functional status and quality of life among persons with diabetes specifically. In general, diabetes is associated with functional impairment, as assessed by the Medical Outcomes Study Short Form 20 (221). Mexican Americans with diabetes had an approximately twofold increase in the risk of having a significant impairment in a lower body activity of daily living compared to persons without diabetes. Perhaps not surprisingly, the presence of an LEA increased the risk of any significant lower body impairment 2.3-fold among those with diabetes in this population (222). Diabetic LEA was associated with a significantly higher Sickness Impact Profile score among persons with diabetes, but this difference was primarily due to poorer physical dimension scores, as psychosocial dimension scores did not significantly differ by amputation status (223).

Mortality. Both prevalent and incident LEA were associated with a high annual risk of death in the Medicare population in 2008 of 170 and 206 per 1,000, respectively, compared to the Medicare population without LEA (73). A retrospective study conducted in the United Kingdom found a similar 1-year mortality of 170 per 1,000 among persons with diabetes who had undergone LEA (224). However, the association between higher mortality and having experienced a LEA is inconsistent, as a study in Fremantle, Australia, found no difference in the risk of cardiac death between diabetic persons with and without LEA followed longitudinally after adjustment for other risk factors for CVD and diabetes-related complications (225).

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ABI. . . . . ankle-brachial index
BMI . . . . . body mass index
BRFSS . . . . . Behavioral Risk Factor Surveillance System
CI . . . . . confidence interval
CVD . . . . . cardiovascular disease
DCCT. . . . . Diabetes Control and Complications Trial
DFU . . . . . diabetic foot ulcer
DPN. . . . . diabetic peripheral neuropathy
EDIC . . . . . Epidemiology of Diabetes Interventions and Complications study
eGFR . . . . . estimated glomerular filtration rate
HDL. . . . . high-density lipoprotein
ICD-9 . . . . . International Classification of Diseases, Ninth Revision
IL . . . . . interleukin
IWGDF . . . . . International Working Group on Diabetic Foot
LEA . . . . . lower extremity amputation
NHANES . . . . National Health and Nutrition Examination Survey
NO . . . . . nitric oxide
PAD . . . . . peripheral arterial disease
RCT . . . . . randomized controlled trial
S(AD)SAD . . . Size (Area, Depth), Sepsis, Arteriopathy, Denervation
SIGN . . . . . Scottish Intercollegiate Guidelines Network
SWM . . . . . Semmes-Weinstein monofilament
TCC . . . . . total contact casting
TUC . . . . . Texas University Classification
UKPDS. . . . . United Kingdom Prospective Diabetes Study

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DUALITY OF INTEREST

Drs. Boyko, Monteiro-Soares, and Wheeler reported no conflicts of interest.

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APPENDICES

APPENDIX 20.1. Mean Body Mass Index (kg/m^2) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

CHARACTERISTICS	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	30.0 (0.5)	31.4 (0.3)	30.5 (0.5)	31.3 (0.4)	28.9 (0.8)	31.4 (0.5)	27.9 (0.8)	27.9 (0.2)
Age (years)								
40–64	31.0 (1.2)	32.2 (0.4)	31.9 (0.9)	32.1 (0.5)	29.4 (1.7)	32.5 (0.7)	30.3 (1.7)	28.0 (0.2)
65–74	30.9 (0.9)	30.5 (0.4)	31.5 (1.1)	30.7 (0.4)	29.3 (1.0)	29.9 (0.7)	26.1 (0.8)	28.1 (0.3)
≥75	27.5 (0.5)	28.4 (0.4)	27.2 (0.7)	28.5 (0.5)	28.0 (0.6)	28.0 (0.9)	26.4 (0.9)	26.1 (0.3)
Sex								
Men	29.4 (0.5)	30.7 (0.4)	30.0 (0.6)	30.8 (0.5)	28.3 (0.7)	30.5 (0.5)	26.2 (0.6)	28.1 (0.2)
Women	30.9 (0.7)	32.2 (0.5)	31.2 (0.8)	31.9 (0.5)	30.1 (1.2)	32.8 (1.2)	29.1 (1.3)	27.7 (0.3)
Race/ethnicity								
Non-Hispanic white	30.2 (0.6)	31.6 (0.5)	31.1 (0.7)	31.9 (0.5)	28.7 (0.8)	31.1 (0.6)	27.9 (1.0)	27.8 (0.2)
Non-Hispanic black	30.3 (0.8)	32.2 (0.4)	30.5 (0.9)	31.7 (0.5)	29.4 (1.7)	33.5 (0.8)	29.3 (1.1)	29.4 (0.3)
All Hispanic	27.9 (1.9)	30.3 (0.4)	26.5 (2.2)	29.8 (0.5)	30.3 (2.2)	31.8 (0.8)	28.3 (0.9)	28.2 (0.3)
Mexican American	31.0 (0.9)	30.9 (0.3)	29.9 (0.9)	30.3 (0.4)	34.6 (1.6)	32.6 (0.6)	28.3 (1.4)	28.7 (0.2)

Body mass index is based on measured height and weight. Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

APPENDIX 20.2. Mean Waist Circumference (cm) Among Adults Age ≥40 Years, Overall and by Age, Sex, Race/Ethnicity, Peripheral Arterial Disease, and Diabetes Status, U.S., 1999–2004

CHARACTERISTICS	MEAN (STANDARD ERROR)							
	All Diabetes		Diagnosed Diabetes		Undiagnosed Diabetes		No Diabetes	
	PAD	No PAD	PAD	No PAD	PAD	No PAD	PAD	No PAD
Overall	106.7 (1.2)	107.4 (0.8)	107.9 (1.5)	107.3 (0.9)	104.4 (2.0)	107.6 (1.1)	98.6 (1.4)	97.0 (0.5)
Age (years)								
40–64	109.0 (3.0)	108.3 (1.1)	112.6 (2.2)	108.1 (1.3)	103.3 (4.0)	108.8 (1.5)	101.2 (3.0)	96.8 (0.6)
65–74	108.4 (2.1)	107.4 (0.9)	109.5 (2.7)	107.5 (1.1)	105.9 (2.6)	107.1 (1.7)	96.8 (2.2)	99.1 (0.9)
≥75	101.9 (1.4)	102.2 (0.9)	100.9 (1.9)	102.3 (1.0)	103.9 (1.3)	102.0 (2.1)	96.4 (1.7)	95.6 (0.8)
Sex								
Men	108.2 (1.8)	108.5 (1.1)	110.6 (1.9)	108.7 (1.4)	104.2 (2.5)	108.0 (1.5)	99.8 (1.4)	101.8 (0.5)
Women	104.7 (1.5)	106.0 (1.1)	104.7 (2.0)	105.7 (1.2)	104.8 (2.3)	106.9 (2.4)	97.8 (2.4)	92.7 (0.7)
Race/ethnicity								
Non-Hispanic white	107.6 (1.5)	109.1 (1.2)	109.9 (1.8)	109.6 (1.3)	103.9 (2.3)	108.2 (1.4)	98.9 (1.7)	97.4 (0.6)
Non-Hispanic black	106.9 (1.4)	106.7 (0.9)	106.7 (1.7)	106.2 (1.1)	107.7 (2.7)	108.2 (1.6)	98.8 (2.6)	97.3 (0.7)
All Hispanic	99.1 (4.6)	102.8 (1.0)	95.3 (5.4)	101.7 (1.1)	105.7 (3.3)	105.8 (2.3)	99.4 (2.4)	95.9 (0.8)
Mexican American	105.7 (2.0)	104.5 (0.7)	103.9 (2.8)	103.4 (1.0)	111.5 (3.8)	107.0 (1.5)	98.7 (3.1)	97.2 (0.6)

Peripheral arterial disease (PAD) is defined as ankle-brachial index <0.9 on either leg. Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin.
All relative standard errors ≤30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004