Summary

Peripheral arterial disease (PAD) is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is much higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in nondiabetic individuals. Moreover, the presence of PAD is a potent marker of increased cardiovascular risk. Because the major threat to patients with diabetes and PAD is from cardiovascular events, the primary therapeutic goal is to modify atherosclerotic risk factors. Risk factor management includes lifestyle modifications, treating associated conditions (diabetes, dyslipidemia, and hypertension), and preventing ischemic events with aggressive antiplatelet therapy such as clopidogrel. Revascularization has an important role in both extra-cranial carotid artery stenosis and symptomatic lower extremity atherosclerosis in the management of patients for whom risk factor modification and pharmacological treatment prove inadequate. The American Diabetes Association consensus statement strongly recommends that cardiologists act cooperatively and effectively with other clinical specialists to reduce the death and disability in patients with diabetes and PAD.

Key Words: Peripheral arterial disease (PAD); carotid stenosis; dyslipidemia; critical limb ischemia (CLI); ipsilateral stroke; antiplatelets; revascularization; intermittent claudication; type 2 diabetes.

INTRODUCTION

Morbidity and mortality in patients with type 2 diabetes mellitus is most often owing to vascular disease (1). Atherosclerosis and the associated arterial obstructive diseases account for 80% of mortality and over 70% of hospitalizations in patients with type 2 DM (1). Although the 2 to 4-fold risk of coronary disease in diabetic patients is well recognized, the prevalence of cerebrovascular disease and peripheral arterial disease is vastly underappreciated. PAD affects 12 million individuals in the United States and is as common as coronary artery disease (CAD) (2). Cerebrovascular disease is rapidly growing and affects 5 million Americans (3). In both PAD and cerebrovascular disease, a disproportionate number of patients have type 2 DM (4). Among patients with type 2 DM, 20–25% over the age of 45 have either cerebrovascular disease or PAD (5).

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Atherosclerosis is a progressive disorder, which, if unchecked, leads to narrowing of arteries and ischemia to end organ tissues. The major vascular beds affected are the coronary circulation, the cerebrovascular bed, and the lower extremity arterial circulation. The major causes of vascular death directly parallel these focal vascular beds: myocardial infarction and heart failure, stroke, and critical limb ischemia. Type 2 diabetes is an independent risk factor for atherosclerosis (6). Numerous epidemiological studies have confirmed a strong association between type 2 DM and CVD/PAD, implying a relationship between insulin resistance and associated metabolic abnormalities and much of the pro-atherosclerotic tendencies of the arteries, leading to increased cardiovascular disease (4).

Cardiovascular care in the US has vastly improved over the last 3 decades, mostly owing to improved technologies and evidence based medicines designed to treat risk factors for vascular disease, leading to a marked decline in cardiovascular mortality over that past 2 decades (7). Unfortunately, outcomes for diabetic patients have not improved and seem unlikely to do so in the near future (8). The frequency of the metabolic syndrome continues to increase. Conservative estimates project 22 million cases of type 2 DM by 2025 (8). This will cause an unprecedented drain on medical resources owing to poor cardiovascular outcomes.

This chapter will primarily focus on the prevalence, pathophysiology, diagnosis and treatment of cerebrovascular disease and peripheral arterial disease in patients with type 2 diabetes mellitus. A special emphasis will be given to evidenced based treatment decisions and how they can be implemented into everyday clinical practice.

**EPIDEMIOLOGY AND NATURAL HISTORY OF PERIPHERAL VASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES**

**Peripheral Arterial Disease**

Peripheral arterial disease (PAD) results from atherosclerosis that decreases perfusion to the lower extremities (9). PAD is now recognized as a major health problem, currently affecting 8 to 12 million Americans (2). As the incidence of diabetes continues to increase, prevalence of PAD will likely follow suit. The prevalence of PAD in nondiabetic patients is 6–9% by the age of 50 yrs and 20–25% after the age of 70. In diabetic patients, 21% over the age of 50 have abnormal ankle brachial indices and PAD, and 45–61% over the age of 70 have PAD (2). The duration of and severity of diabetes correlates with the extent of PAD. In the United Kingdom Prospective Diabetes Study (UKPDS), the data showed a higher prevalence of PAD in those with a longer duration of diabetes (10). In addition every 1% increase in glycosylated hemoglobin confers a 28% increase in the risk of PAD (10).

PAD is defined as infra-aortic arterial obstructive disease that leads to abnormal measures in lower extremity blood pressure and pulses. PAD is present as a spectrum of disease ranging from asymptomatic silent ischemia to critical limb ischemia leading to gangrene and amputation. The 2 major clinical manifestations of peripheral arterial disease of the lower extremity are intermittent claudication (IC) and critical limb ischemia (CLI) (11). Patients with critical limb ischemia have a 25–40% risk of suffering either major amputation or death within 6 mo (12). These events in patients with intermittent claudication occur at an annual rate of only 1–2% per year (8). Although intermittent claudication is also a major health problem, patients with CLI experience substantially greater morbidity and mortality (11), and there are no medical treatment options (12).

Patients with type 2 DM more commonly present with symptomatic PAD manifested as intermittent claudication (13). Nondiabetic patients with PAD only have classic claudication 30% of the time, as compared to diabetic patients with PAD who present with classic claudication 40–51% of the time. (8). Of those with IC, 20% will develop CLI, compared to only 4% in subjects without diabetes (14). However, patients with type 2 diabetes may also present with CLI without warning and progress to limb amputation and death more quickly (14). Faglia et al observed a positive correlation between PAD severity and amputation rates in patients with type 2 DM (15). Patients with DM and CLI have 15 times the risk of amputation as nondiabetics without DM (1).

**Cerebrovascular Disease**

Among patients presenting with stroke the prevalence of DM is 3 times that of matched controls (1). Similarly, patients with diabetes have a 3–4-fold increased risk of stroke (1,16) Diabetes increases the risk of stroke in younger patients (less than 55 yr of age ). Additionally, among patients with type 2 diabetes, African Americans and Hispanics have a 2-fold increase in stroke mortality compared to whites (1). Finally, asymptomatic cerebrovascular