This Weeks Question:

Which of the following statements is False:

1. PAD is a major risk factor for lower-extremity amputation.
2. Hypertension and hyperlipidemia are the strongest risk factors for PAD.
3. Data from the Framingham Heart Study revealed that 20% of symptomatic patients with PAD had diabetes.
4. Of those with PAD, over one-half are asymptomatic or have atypical symptoms.
5. The most common symptom of PAD is intermittent claudication,

PAD is a manifestation of atherosclerosis characterized by atherosclerotic occlusive disease of the lower extremities and is a marker for atherothrombotic disease in other vascular beds. PAD affects ~12 million people in the U.S.; it is uncertain how many of those have diabetes. Data from the Framingham Heart Study[1] revealed that 20% of symptomatic patients with PAD had diabetes, but this probably greatly underestimates the prevalence, given that many more people with PAD are asymptomatic rather than symptomatic. As well, it has been reported that of those with PAD, over one-half are asymptomatic or have atypical symptoms, about one-third have claudication, and the remainder have more severe forms of the disease.[2]

The most common symptom of PAD is intermittent claudication, defined as pain, cramping, or aching in the calves, thighs, or buttocks that appears reproducibly with walking exercise and is relieved by rest. More extreme presentations of PAD include rest pain, tissue loss, or gangrene; these limb-threatening manifestations of PAD are collectively termed critical limb ischemia (CLI).

PAD is also a major risk factor for lower-extremity amputation, especially in patients with diabetes. Moreover, even for the asymptomatic patient, PAD is a marker for systemic vascular disease involving coronary, cerebral, and renal vessels, leading to an elevated risk of events, such as myocardial infarction (MI), stroke, and death.

Diabetes and smoking are the strongest risk factors for PAD. Other well-known risk factors are advanced age, hypertension, and hyperlipidemia.[3]

Potential risk factors for PAD include elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B, lipoprotein(a), and plasma viscosity. An inverse relationship has been suggested between PAD and alcohol consumption.

In people with diabetes, the risk of PAD is increased by age, duration of diabetes, and presence of peripheral neuropathy. African Americans and Hispanics with diabetes have a higher prevalence of PAD than non-Hispanic whites, even after adjustment for other known risk factors and the excess prevalence of diabetes. It is important to note that diabetes is most strongly associated with femoral-popliteal and tibial (below the knee) PAD, whereas other risk factors (e.g., smoking and hypertension) are associated with more proximal disease in the aorto-ilio-femoral vessels.

The true prevalence of PAD in people with diabetes has been difficult to determine, as most patients are asymptomatic, many do not report their symptoms, screening modalities have not been uniformly agreed upon, and pain perception may be blunted by the presence of peripheral neuropathy. For these reasons, a patient with diabetes and PAD may be more likely to present with an ischemic ulcer or gangrene than a patient without diabetes. While amputation has been used by some as a measure for PAD prevalence, medical care and local indications for amputation versus revascularization of the patient with critical limb ischemia widely vary. The nationwide age-adjusted amputation rate in diabetes is ~8/1,000 patient years with a prevalence of ~3%. However, regional patterns differ—there is nearly a ninefold variation of major amputations in people with diabetes across the U.S. Therefore, the incidence and prevalence of amputation may be an imprecise measure of PAD.

The reported prevalence of PAD is also affected by the methods by which the diagnosis is sought. Two commonly used tests are the absence of peripheral pulses and the presence of claudication. Both, however, suffer from insensitivity. A more accurate estimation of the prevalence of PAD in diabetes should rely upon a validated and reproducible test. Such a test is the ankle-brachial index (ABI), which involves measuring the systolic blood pressures in the ankles (dorsalis pedis and posterior tibial arteries) and arms (brachial artery) using a hand-held Doppler and then calculating a ratio. Simple to perform, it is a noninvasive, quantitative measurement of the patency of the lower extremity arterial system. Compared with an assessment of pulses or a medical history, the ABI has been found to be more accurate. It has been validated against angiographically confirmed disease and found to be 95% sensitive and almost 100% specific.[4] There are some limitations, however, in using the ABI. Calcified, poorly compressible vessels in the elderly and some patients with diabetes may artificially elevate values. The ABI may also be falsely negative in symptomatic patients with moderate aortoiliac stenoses. These issues complicate the evaluation of an individual patient but are not prevalent enough to detract from the usefulness of the ABI as an effective test to screen for and to diagnose PAD in patients with diabetes. Using the ABI, one recent survey[5] found a prevalence of PAD in people with diabetes >40 years of age to be 20%, a prevalence greater than anticipated using less reliable measures, such as symptoms or absent pulses. Moreover, another survey of patients with diabetes >50 years of age showed a prevalence of PAD of 29%.[6] Thus, the prevalence of PAD in diabetes appears higher than previously estimated.

Impact of PAD

The impact of PAD can be assessed by its progression, the presence of symptoms, and the excess cardiovascular events associated with systemic atherosclerosis. Approximately 27% of patients with PAD demonstrate progression of symptoms over a 5-year period, with limb loss occurring in ~4%. While the majority of patients remain stable in their lower-limb symptomatology, there is a striking excess cardiovascular event rate over the same 5-year time period, with 20% sustaining nonfatal events (MI and stroke) and a 30% mortality rate.[7] For those with CLI, the outcomes are worse: 30% will have amputations and 20% will die within 6 months.[8] The natural history of PAD in patients with diabetes has not specifically been studied longitudinally, but it is known from prospective clinical trials of risk interventions that the cardiovascular event rates in patients with PAD and diabetes are higher than those of their nondiabetic counterparts.

Diagnosis of PAD

Diagnosing PAD is of clinical importance for two reasons. The first is to identify a patient who has a high risk of subsequent MI or stroke regardless of whether symptoms of PAD are present. The second is to elicit and treat symptoms of PAD, which may be associated with functional disability and limb loss. PAD is often more subtle in its presentation in patients with diabetes than in those without diabetes. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in diabetic patients the lesions are more likely to be more diffuse and distal. Importantly, PAD in individuals with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback. Thus, a classic history of claudication may be less common. However, a patient may elicit more subtle symptoms, such as leg fatigue and slow walking velocity, and simply attribute it to getting older. It has been reported that

patients with PAD and diabetes experience worse lower-extremity function than those with PAD alone.[9] Also, diabetic patients who have been identified with PAD are more prone to the sudden ischemia of arterial thrombosis[10] or may have a pivotal event leading to neuroischemic ulceration or infection that rapidly results in an acute presentation with critical limb ischemia and risk of amputation. By identifying a patient with subclinical disease and instituting preventative measures, it may be possible to avoid acute, limb-threatening ischemia.

PAD in diabetes also adversely affects quality of life, contributing to long-term disability and functional impairment that is often severe. Patients with claudication have a slower walking speed (generally <2 mph) and a limited walking distance. This may result in a "cycle of disability" with progressive deconditioning and loss of function. Finally, there are significant economic costs of health care, reduced productivity, and personal expenses associated with a chronic manifestation of atherosclerotic disease such as PAD.

References for:

1. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF: Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation* 96:44 -49, 1997

2. Hiatt WR: Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 344:1608-1621, 2001

3. Criqui MH: Peripheral arterial disease: epidemiological aspects. *Vascular Medicine* 6 (Suppl. 1):3-7, 2001

4. Bernstein EF, Fronek A: Current status of non-invasive tests in the diagnosis of peripheral arterial disease. *Surg Clin North Am* 62:473- 487, 1982

5. Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JJF: Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Practical Diabetes Int* 16:163-166, 1999

6. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286:1317-1324, 2001

7. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM: Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 94:3026-3049, 1996

8. Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD): TASC Working Group: TransAtlantic Inter-Society Concensus (TASC). *J Vasc Surg* 31:S1-S296, 2000

9. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, Schneider JR, Mandapat AL, Martin G, McDermott MM: Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care* 25:113-120, 2002

10. McDaniel MD, Cronenwett JL: Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 3:273- 277, 1989

Diabetes Care 26(12):3333-3341, 2003