Peripheral arterial disease - epidemiological aspects

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Abstract: As many as 10 million people in the USA have peripheral arterial disease (PAD) with a prevalence over 10% in people aged more than 60 years old. Generally, men have a higher prevalence of PAD than women. The risk factors for PAD are similar to those for coronary artery disease (CAD) and cerebrovascular disease (CBVD), but diabetes and cigarette smoking have a particularly strong association with PAD. Patients with PAD also have CAD and CBVD as co-morbidities, although the extent of co-morbidity depends on the sensitivity of assessment. The risk of mortality is proportional to the severity of PAD, and the relative risk of all-cause mortality due to PAD is unaltered by the presence of CAD or CBVD. PAD is under-recognized and under-treated, even though it should be regarded as a severe disease leading to significant death and disability from stroke and myocardial infarction (MI). Thus, accurate diagnosis of PAD could provide an early indication of the need for intervention and help prevent future morbidity and mortality.

Key words: cerebrovascular disease; coronary artery disease; epidemiology; peripheral arterial disease

Prevalence and diagnosis of peripheral arterial disease

Major clinical manifestations of atherosclerosis and atherothrombosis include transient ischemic attack (TIA), ischemic stroke (IS), angina pectoris, myocardial infarction (MI) and intermittent claudication (IC).[1] It is estimated that as many as 10 million people in the USA have peripheral arterial disease (PAD) and 4 million have IC.[2] The diagnosis of PAD has been based on vascular history, physical examination, ankle–brachial index (ABI) measurement, non-invasive vascular laboratory assessments and arteriography, although it is likely that estimates of the prevalence of the disease depend on the standards of definition and the sensitivity of the assessment methods.[3] PAD patients may be asymptomatic or have atypical symptoms, and the true incidence and prevalence of PAD may be greatly underestimated. The ABI has proved to be a sensitive index for the detection of symptomatic or asymptomatic PAD.[4–8] The normal ABI value is 0.95–1.5, whereas a value of $\leq$0.9 is indicative of PAD. A ratio of $<$0.4 indicates advanced ischemic disease.

Prevalence of PAD versus IC

The prevalence of IC in people aged $>$50 years has been reported to be 2–7% in men and 1–2% in women.[9–11] However, the prevalence of IC underestimates the presence of PAD, the latter being two to five times more common than is suggested by a history of IC.[11]

The prevalence of PAD is highly age-dependent. In a survey conducted in San Diego, in an older defined population, the prevalence was 2.5% in people aged $<$60 years old; this rose to 8.3% at 60–69 years, and reached 18.8% in people $>$70 years of age, as illustrated in Figure 1.[11] In all, 4.7% of men (12/256) and 1.9% of women (6/309) had severe PAD (ABI: $\leq$0.6); the respective percentages for moderate PAD (ABI: 0.6–0.9) were 3.5% (9/256) and 2.9% (9/309) for men and women, respectively (Table 1).[12] However, in a study of 7715 subjects aged $\geq$55 years, the prevalence of PAD was higher in women (20.5%) than in men (16.9%), although the prevalence of IC was 2.2% in men and 1.2% in women.[13]

PAD, CAD and CBVD

There is considerable overlap between PAD, CAD (coronary artery disease) and CBVD (cerebrovascular disease), although the extent of the overlap depends on the sensitivity of the assessment methods. In a number of stud-

Table 1 PAD severity (San Diego: 1985). (Adapted from ref. 12 with permission.)

PAD category	Men			Women		
	n	%		*n*	%	
Normal	183	71.5		225	72.8	
Isolated small vessel	39	15.2		51	16.5	
Isolated post-tibial	13	5.1		18	5.8	
Moderate	9	3.5	13.3%	9	2.9	10.6%
Severe	12	4.7		6	1.9	
Total	256	100		309	100	

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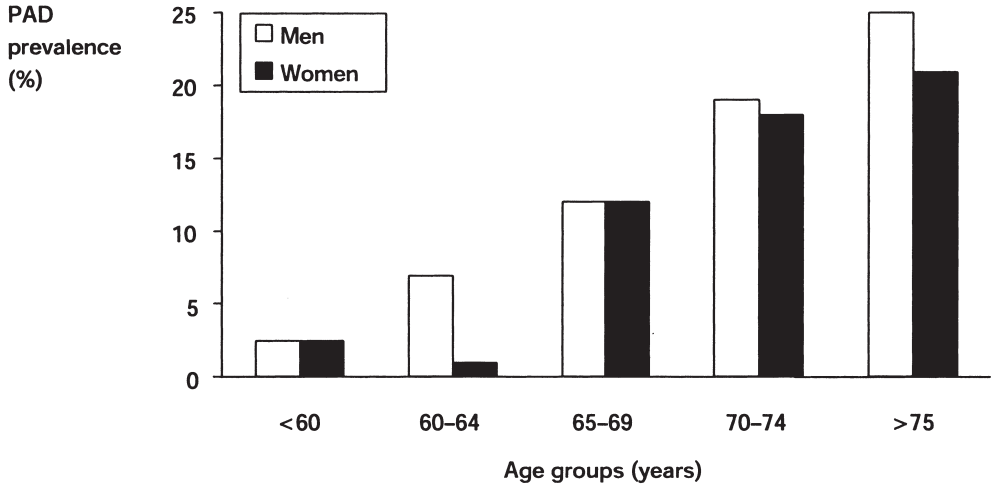

Figure 1 Age-dependent prevalence of PAD. (Reproduced from ref. 11 with permission.)

ies, the prevalence of CBVD in patients with PAD varied from 0.5% to 15% based on clinical history.[14] The prevalence of CBVD in PAD patients would be ≥50% if more sensitive measurements were made. A study in the USA showed that in patients with PAD, 29.4% of men and 21.2% of women also had CAD or CBVD. The corresponding percentages for those without PAD CBVD were 11.5% of men and 9.3% of women.[3]

The prevalence of CAD in patients presenting with ischemia of the leg varies from 19% to 90%, the variation reflecting the differences in sensitivity of the assessment methods.[14] Clinical history and ECG results suggested that <50% of PAD patients had CAD. The prevalence of CAD in patients with PAD was ~60% when a stress test was used, and this percentage rose to 90% when angiography was performed.[14]

Thus, PAD is part of the atherosclerotic disease process, co-existing with CAD and CBVD.

Risk factors for PAD

The two most prominent risk factors for PAD are smoking and diabetes. Both of these risk factors are related to heart disease and stroke, but are even more specifically linked to PAD.[15] Based on a PAD diagnosis of an ABI <0.9, the relative risk (RR) for PAD was 4.05 for diabetes and 2.55 for current smoking in the Cardiovascular Health Study (CHS) (Table 2).[16]

Table 2 Independent risk factors for PAD.

Variable	Relative risk	95% CI
Reported diabetes[16]	4.05[a]	2.8–5.9
Current smoker[16]	2.55[a]	1.76–3.68
Age (5-year increments)[16]	1.54[a]	1.50–1.92
Reported hypertension[16]	1.51[a]	1.15–1.99
Hyperhomocysteinemia[28]	1.44[b]	1.10–1.87
Total cholesterol (per 10 mg/dl increment)[16]	1.10[a]	1.06–1.14

[a]PAD diagnosis based on ABI <0.9.
[b]PAD diagnosis based on history of peripheral arterial reconstruction or limb amputation, or an ABI <0.5.

The association between glycemic level and PAD has been shown in a number of studies. In an elderly Caucasian population,[17] 20.9% of patients with diabetes mellitus and 15.1% of patients with a diabetic glucose tolerance test result had an ABI <0.9. The respective prevalence rates for any PAD (ABI: <0.9, vascular surgery, or ≥one monophasic or absent Doppler flow curve) were 41.8% and 29.2%. A survey in a Swedish healthcare district found that 21% of diabetic patients had signs of PAD, the majority of whom (87%) had non-insulin-dependent diabetes mellitus (NIDDM).[18] In another study, the duration of diabetes correlated significantly ($p = 0.002$) with the presence of PAD in 193 patients with NIDDM, and a significant correlation ($p = 0.020$) was also noted between triglyceride concentrations and PAD.[19]

In a case–control study, the RR of PAD was sevenfold higher in ex-smokers than in those who had never smoked, and the risk increased to 16-fold in current smokers compared with those who had never smoked.[20] The authors noted that the fraction of PAD attributable to smoking was 76%. Based on blood measurements taken after two cigarettes had been smoked within a 10-min period, cigarette smoking was shown to acutely lower the ABI in chronic smokers from 0.64 ± 0.14 to 0.55 ± 0.11 ($p = 0.008$), indicating an acute as well as chronic deleterious effect of cigarette smoking on the peripheral circulation.[21]

The typical dyslipidemia found in PAD patients is similar to that found in subjects with insulin resistance, which is concordant with the strong association of diabetes with PAD. PAD patients have low levels of high-density lipoprotein (HDL) cholesterol levels compared with normal subjects,[15,22,23] as well as high plasma triglyceride concentrations.[15,24,25] Although the RR of total cholesterol for PAD was only 1.1 for each 10 mg/dl increase in the CHS[16] (Table 2), in another study 66% of patients undergoing revascularization for PAD and carotid arterial disease were hypercholesterolemic.[26] In a study of risk factors in patients with PAD, a significantly higher ($p < 0.01$) percentage of patients with PAD were hypercholesterolemic (48.2%) and hypertriglyceridemic (53.7%) compared with control subjects (21.6% and 26.1%).[24] The prevalence of PAD in patients with familial hypercholesterolemia was also high,

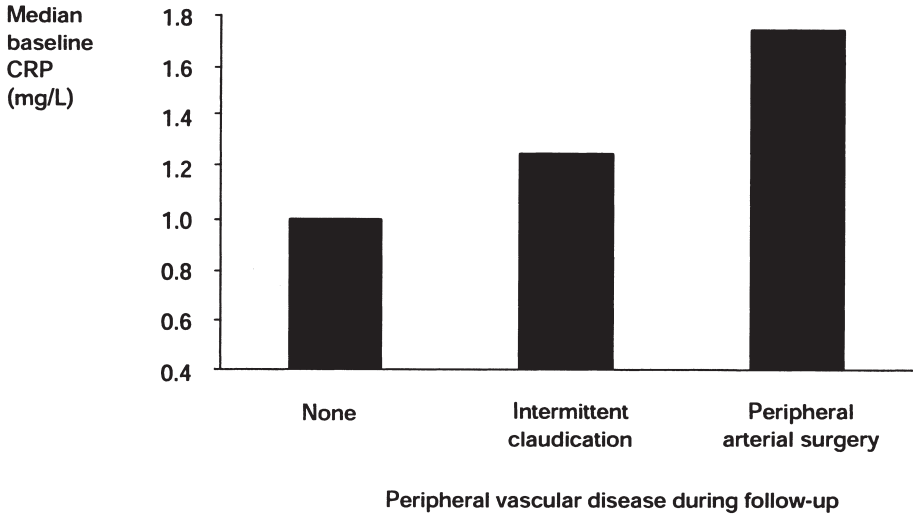

Figure 2 C-reactive protein levels: prospective case and control subjects. (Reproduced from ref. 31 with permission.)

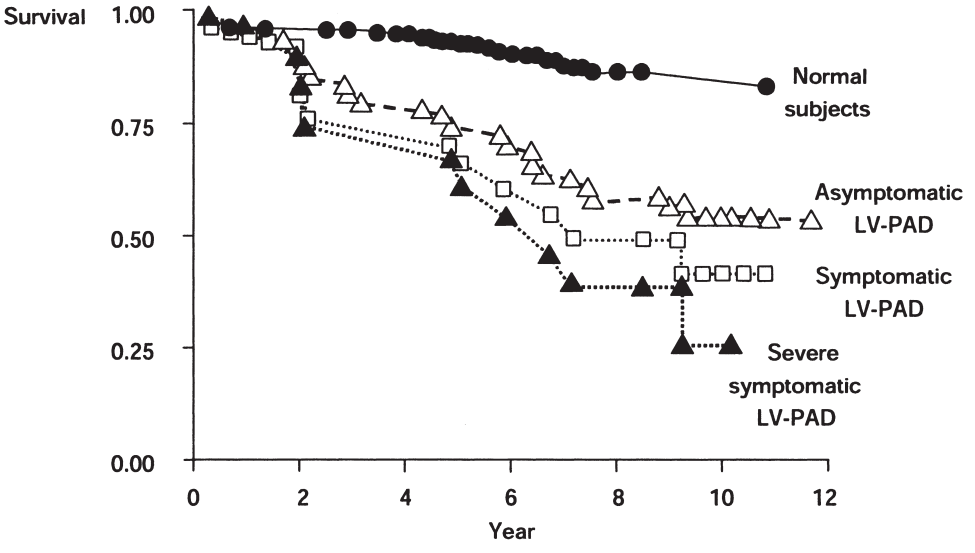

Figure 3 Kaplan-Meier survival curves based on mortality from all causes. PAD and subsequent mortality. (LV-PAD, large-vessel PAD.) (Reproduced from ref. 5 with permission.)

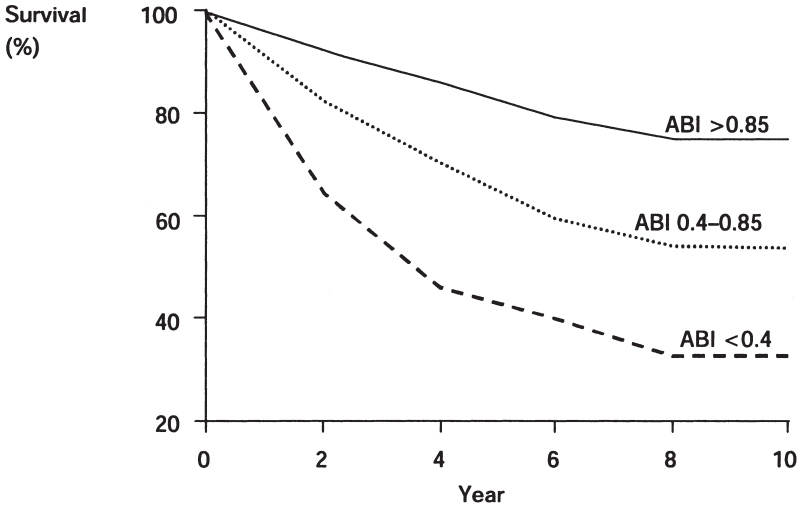

Figure 4 Survival curves for three levels of ABI. (Reproduced from ref. 4 with permission from Elsevier Science.)

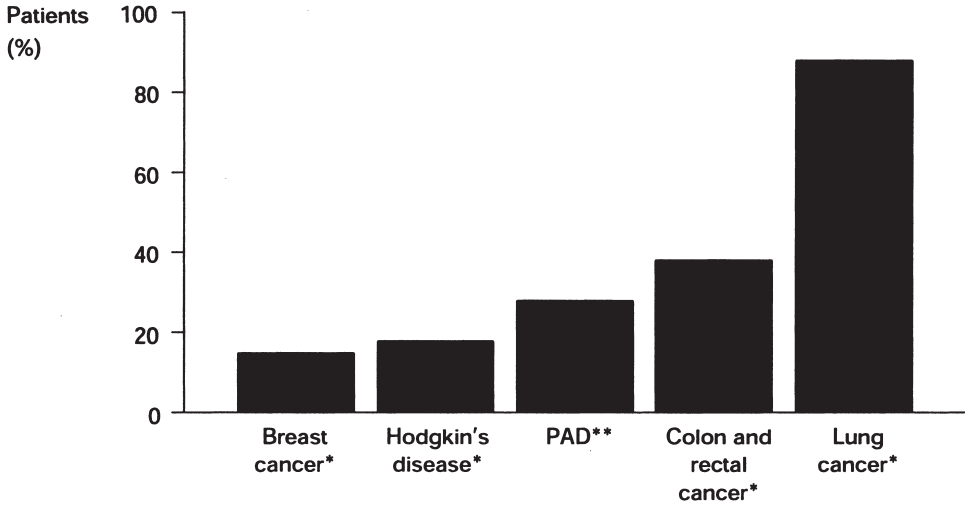

Figure 5 Five-year mortality rates. (*American Cancer Society. *Cancer facts and figures 1997*; **Kampozinski RP, Bernard VM. In: Rutherford RB (ed). *Vascular surgery*. Philadelphia: WB Saunders, 1989: chapter 53.)

with 31% of patients versus only 3.7% of controls having hemodynamically significant PAD.[27]

Hyperhomocysteinemia has been reported to have a somewhat stronger association with PAD, RR = 1.44 per 5 μmol/l (Table 2), than with CAD (RR = 1.25) or CBVD (RR = 1.24).[28]

An interesting marker of risk for PAD and CAD is C-reactive protein (CRP); CRP levels were higher in patients with CAD (7.1 ± 11.2 mg/l) compared with patients undergoing coronary angiography but who had normal angiograms (4.8 ± 4.0 mg/l), and in control subjects (2.3 ± 3.6 mg/l).[29] CRP concentrations were shown to be a risk factor for development of CAD in healthy subjects (RR = 1.5 per standard deviation of log CRP).[30] CRP is considered to be a marker for an ongoing inflammatory process in atherosclerosis, rather than being a risk factor like high blood pressure or cigarette smoking. Indeed, there seems to be a linear relationship between CRP concentrations and the severity of incident PAD (Figure 2).[31]

Morbidity and mortality associated with PAD

PAD patients have widespread arterial disease, and develop much more CAD and CBVD than healthy controls.[32] In a follow-up study investigating the relationship between PAD and mortality from all causes, mortality rates of 61.8% after 10 years were reported for men with PAD, compared with 16.9% in normal men.[5] The corresponding mortality rates for women were 33.3% and 11.6%, respectively. Less than a quarter of patients with severe symptomatic PAD survived 10 years (Figure 3). The increase in total mortality was due to a sharp increase in the risk of cardiovascular mortality, and the risk was proportional to the severity of PAD. The mortality risk of PAD was present even after adjustment for cardiovascular risk factors and pre-existing CAD and CBVD at baseline.

In a study from a vascular laboratory, the RR of mortality from all causes for an ABI of ≤0.85 was similarly elevated, 2.36 (95% CI: 1.6, 3.48), which increased to a RR of 4.49 (95% CI: 3.52, 5.64) for an ABI of <0.4. A strong trend ($p < 0.0001$) for increasing risk of mortality was noted for decreasing ABI[4] (Figure 4).

In terms of 5-year mortality, patients with PAD have a lower survival rate than patients with breast cancer or Hodgkin's disease (Figure 5).

Therapy for patients with PAD or CAD

PAD is often asymptomatic and sometimes remains undiagnosed until it is at an advanced stage, with severe symptoms or limb-threatening gangrene. Even if there is early diagnosis of PAD, it is often untreated since the risks associated with the disease are unrecognized or underestimated – PAD is perceived as a less significant problem than CAD. However, aggressive treatment of atherosclerosis may prevent disease progression both in the affected limb and in other beds of the vascular system.[33] Treatment should include patient education about the disease, the role of exercise, dietary modifications, cessation of smoking, control of dyslipidemia, hypertension, and diabetes, and antiplatelet medication.[34,35]

Conclusions

There is a strong predictive value of PAD for subsequent all-cause mortality, due to a sharply increased risk of CAD and CBVD mortality. Measurement of ABI is easy to perform, is inexpensive and has high sensitivity and specificity for PAD. This is important because early identification of PAD and aggressive modification of risk factors, including antiplatelet therapy, show great promise for improving the prognosis of patients with PAD.

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