REVIEW

Use and Utility of Ankle Brachial Index in Patients with Diabetes

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Submitted 10 May 2010; accepted 16 September 2010
Available online 20 November 2010

Keywords
Ankle brachial index; Diabetes; Cardiovascular risk; Peripheral arterial disease; Screening test

Abstract
Ankle brachial index (ABI) is a simple method to screen peripheral arterial disease (PAD) and to evaluate cardiovascular (CV) prognosis in the general population. Measuring it requires a hand-held Doppler probe but it can be done also with an automatic device. ABI is an effective tool for clinical practice or clinical studies. However, in diabetic patients, it has some specific caveats. Sensitivity of the standard threshold of 0.9 appears to be lower in diabetic patients with complications. Moreover, highly frequent arterial medial calcifications in diabetes increase ABI. It has been demonstrated that measurements >1.3 are well correlated with both an increased prevalence of PAD and CV risk. Therefore, ABI thresholds of less than 0.9 and more than 1.3 are highly suspicious for PAD and high CV risk in diabetic patients. However, when there is concomitant clinical peripheral neuropathy or high risk of arterial calcification, the efficiency of ABI seems to be limited. In this case, other methods should be applied, toe pressure, in particular. Thus, the ABI could be used in patients with diabetes, but values should be interpreted with precision, according to the clinical situation.

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Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis. Its prevalence increases with age and the presence of cardiovascular (CV) risk factors.1–3

Circumstances of discovery include intermittent claudication or distal trophic lesions, but some subjects are asymptomatic, and the condition is detected during routine physical examination.4

Introduced in the late 1960s, the measurement of the ankle brachial index (ABI) is a simple test used to document PAD in clinical and scientific settings. It is the ratio of systolic pressures in the lower and upper extremities. Its current pathological value is issued from older studies.5,6 Ever since, a reduction in ABI is used as a strong indicator of PAD.7–10
Apart of being a diagnostic tool, ABI values reflect also the severity of PAD, making it a widely used marker for the presence and progression of PAD in major CV trials. Moreover, it has been reported that ABI is an independent marker for CV morbidity and mortality. These data apply to the general population. Would it also be the case for diabetic patients, who are known to have a higher incidence of vascular complications? We conducted a systematic review of use and utilities of ABI in patients with diabetes.

Methods

We searched the MEDLINE database since 1965 using a combination of the following search terms: 'ankle brachial index' and 'diabetes'. Abstracts were systematically reviewed and relevant articles obtained, based on the use of ABI for diagnostic or prognostic purposes in a population at least partially composed of patients with diabetes. Reference lists of these articles were reviewed for additional studies.

Measurements of ABI

Measurement of ABI is made in the supine position after 5 min of rest. A pneumatic cuff is placed around the ankle and the pressure is measured at both the dorsalis pedis and posterior tibial arteries using a hand-held continuous-wave Doppler probe (5–10 MHz). The same technique is also used in both arms for measuring brachial artery pressure. The higher of the two ankle pressures is divided by the brachial artery pressure. In subjects with normal lower limb arterial circulation, the systolic pressure at the ankle is usually 10–15 mmHg higher than that recorded from the arm because of pulse wave velocity, resulting in an ABI > 1.10. Major international medical societies recommend calculating the ABI by dividing the highest pressure in the leg by the highest pressure in the arm. Reproducibility of the ABI measurement seemed to be good. In the ABI study, the mean error of 8% was reported in the ABI study, the mean error of 8% within or between observers is smaller than with established screening methods.

PAD severity in each leg is assessed according to the levels of ABI:

- 0.91–1.30: normal;
- 0.70–0.90: mild occlusion;
- 0.40–0.69: moderate occlusion;
- <0.40: severe occlusion; and
- >1.30: poorly compressible vessels.

The American Diabetes Association recommends measuring ABI in all diabetic patients older than 50 years or in any patient suffering from PAD symptoms or having other CV risk factors.

Alternatives

Other options in measuring ABI are possible. The pressure recordings can be used to test the effect of exercise. Normally, the ankle systolic pressure will not decrease with moderate treadmill exercise. For patients in whom it is not clear if the exercise-induced pain is due to arterial disease or other neuromuscular causes, it is necessary to perform an exercise test.

Methods of ABI calculation could also be different. Indeed, several authors have estimated it using the lowest values of ankle pressure. Schröder et al. compared low (using the lowest value of ankle pressure) and high ABI (using the highest one) to Doppler ultrasound (DUS). They reported that the sensitivity and the specificity to diagnose PAD when having an ABI <0.9 is 0.89–0.93 with lower ABI values versus 0.68–0.99 with higher ones. In a recent study, Espinola-Klein et al. showed that the use of low ABI enhanced its use as a prognostic marker; the use of a high value could exclude patients at high CV risk. However, some authors recommend the use of the higher pressure value for improved comparability of data in epidemiological and clinical studies.

The Doppler probe could be replaced by a standard stethoscope or by an automatic device usually used for routine blood pressure measurement at the arm. The use of auscultation seems to be similar to the standard method; however, the technique has not been widely investigated. From another side, the use of an automated blood pressure recorder seems to be a reliable, fast and cost-effective method. It simply consists of measuring the pressure by placing the cuff of the device on the same anatomical sites used for Doppler. Several studies validated the efficiency of ABI measuring using this method by comparing it to standard reference techniques. Clairiotte et al. evaluated this method in diabetic subjects and showed that the results acquired with the automated recorder strongly correlated to the ones obtained using a DUS. Even though the global diagnostic performance of this technique is slightly lower than in the case of Doppler, it had the advantage of being more cost effective and easily done by the medical team.

Thresholds

Recent publications reported that the interval between 0.9 and 1.10, currently taken as normal, may not be so. Actually, the value of 0.9 is somewhat arbitrary, as the ABI is a continuous variable that indicates the severity of the arterial occlusion. McDermott et al. reported that an ABI between 0.90 and 0.99 or 1.00 and 1.09 was associated with higher coronary or carotid artery stenosis than an index between 1.10 and 1.30. In addition, a higher incidence of intermittent claudication has been reported when ABI values were within the lower normal range (0.90–0.99) than in the upper normal one (1.10–1.40). In diabetic patients, Clairiotte et al. reported that the cut-off values for the highest sensitivity and specificity for PAD screening were between 1.0 and 1.1. Therefore, a normal low ABI value could be sometimes the sign of an early or moderate atherosclerotic process of lower limbs arteries.

ABI in patients with diabetes

PAD in diabetes

PAD is a diffuse atherosclerotic vascular disease frequently present in diabetic patients. Its prevalence ranges between 9.5% and 13.6% in type 2 Diabetic (T2D) patients versus...
4% in the general population.\textsuperscript{1} It has been shown that diabetes is the main risk factor for the occurrence of PAD.\textsuperscript{3} With every 1% increase in glycosylated haemoglobin (HbA1c), there was a 28% increase in the risk of PAD in the United Kingdom Prospective Diabetes Study (UKPDS).\textsuperscript{38}

Although PAD is very common in patients with diabetes, it remains grossly under-recognised in this type of population.\textsuperscript{39} Diagnosis is often difficult when diabetes is associated with peripheral neuropathy because this last condition could mask the pain.\textsuperscript{36} Therefore, only one third of diabetic patients with PAD have intermittent claudication.\textsuperscript{38} Paradoxically, some symptoms of painful diabetic neuropathy are sometimes mistaken for intermittent claudication.\textsuperscript{40} The association of both arteriopathy and neuropathy is responsible for the high prevalence of wounds, ulcers and amputations of diabetics’ feet.\textsuperscript{41}

PAD in patients with diabetes show some specific aspects. Contrary to PAD in smokers, arteriopathy in diabetic patients is known to involve distal arteries more than proximal ones. The main vessels affected are the popliteal artery, anterior tibioperoneal trunk, posterior tibial and dorsalis pedis.\textsuperscript{22,42} Moreover, there is a strong association between diabetes and medial artery calcification (MAC).\textsuperscript{43} This last condition causes arterial wall stiffness, which results in high pressure ankle, and thus a high ABI. MAC is often associated with peripheral neuropathy and to chronic renal failure (CRF).\textsuperscript{44} In addition, an ABI $>1.3$ in CRF is frequently associated with hyperparathyroidism, suggesting a possible role of the disturbances in calcium and phosphorus metabolism in the occurrence of MAC.\textsuperscript{45}

Do these specific PAD data in diabetic patients represent an obstacle to the extrapolation of the criteria of ABI use that are valid for the general population?

**Screening and diagnosis of ABI in diabetic patients**

Using DUS as a reference method, William et al. showed in a group of diabetic patients with an intermediate vascular profile and without neuropathy that an ABI <0.9 had a sensitivity of 100% and a specificity of 88%. The results in the non-diabetic control group were almost similar (sensitivity 83% and specificity 100%).\textsuperscript{46} Alnaeb et al. reported a correlation of $-0.81$ between an ABI <0.9 and arterial DUS in the same type of diabetic patients.\textsuperscript{47} These results are in favour of the use of ABI as a screening test or a diagnostic tool in patients with diabetes (Table 1).

However, can this diagnostic efficiency of ABI be applied in all types of diabetic patients? In a recent study that evaluated patients who had undergone both ABI measurements and angiography, Chung et al. showed that the most influential factor affecting the validity of ABI was diabetes, with an odds ratio (OR) of 4.36 for the false negative results taken as a primary end point.\textsuperscript{48} Indeed, several studies showed that the decrease of the diagnostic efficiency of ABI is related to certain clinical situations related to diabetes such as neuropathy or foot wounds.\textsuperscript{49–51} For instance, the sensitivity of ABI falls to 53% (specificity 95%) in the presence of peripheral neuropathy.\textsuperscript{46} In patients with an advanced vascular profile, an ABI <0.9 had 54.4% sensitivity in diabetic versus 72.6% in non-diabetic patients when comparing it to DUS.\textsuperscript{34}

This decrease in ABI sensitivity can also be explained by arterial stiffness secondary to MAC. This results in poorly compressible vessels and a high ABI. Indeed, high index values ($>1.3–1.4$) are particularly frequent in diabetic patients,\textsuperscript{17,52} more specifically when diabetes is concomitant to kidney disease, neuropathy or foot lesions.\textsuperscript{53} In this case, high ABI values and MAC correlate with the duration and severity of diabetes.\textsuperscript{54,55} Therefore, the sensitivity of ABI seems to be limited in case of complicated or long-standing diabetes leading to more MAC. Moreover, high ABI could underestimate the prevalence of PAD in diabetes because ABI values between 0.9 and 1.3 would be falsely considered as normal and higher values could not be interpreted. Indeed, the prevalence of PAD measured with DUS was 57% in diabetic patients with high CV risk and neuropathy whereas ABI was between 0.9 and 1.3.\textsuperscript{56} Other authors also reported a high prevalence of PAD in diabetic patients with elevated ABI values, estimated between 58% and 84%.\textsuperscript{57,58} It is thought that the association between high ABI values and PAD is due to the fact that arterial stiffness is associated with a decrease in bloodstream in the lower limbs of diabetic patients.\textsuperscript{59} Furthermore, high ABI values in diabetes could be indicative of PAD. In a recent report of the National Health and Nutrition Examination Survey, the presence of a PAD is not only defined by an ABI $<0.9$ but also with values $>1.4$.\textsuperscript{60} In this case, a duplex ultrasound examination must be performed to confirm and evaluate PAD.

The diagnostic efficiency of ABI as a screening test may be limited in diabetic patients with elevated CV risk, neuropathy, nephropathy and foot lesions, because of its weak sensitivity and the high rate of biased normal values (Table 2), probably due to the high prevalence of MAC. One way to improve the diagnostic efficiency of ABI might be to use a higher threshold, around 1–1.1 or to use the lowest value of ankle systolic

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients/lower limbs</th>
<th>Characteristics of patients\textsuperscript{a}</th>
<th>Mean ABI</th>
<th>Method of reference</th>
<th>Sensibility (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameswaran GI 2005</td>
<td>57 patients/114 limbs</td>
<td>Intermediate CV risk</td>
<td>NC</td>
<td>Doppler ultrasound</td>
<td>63</td>
<td>97</td>
</tr>
<tr>
<td>Williams DT 2005</td>
<td>25 limbs</td>
<td>Intermediate CV risk, no neuropathy, no PAD</td>
<td>1.06</td>
<td>Doppler ultrasound</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>Alnaeb ME 2007</td>
<td>47 limbs</td>
<td>Intermediate CV risk</td>
<td>0.84</td>
<td>Doppler ultrasound</td>
<td>80</td>
<td>93</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Estimation of cardiovascular (CV) risk is based on prevalence of traditional risk factors, diabetes duration, and mean HbA1c when specified.
pressure for calculating it. However, in presence of MAC, Brooks et al. showed that toe-pressure measurement was more sensitive than ABI. In the same way, in the presence of clinical peripheral neuropathy (defined using International Consensus on the Diabetic Foot (ICDF) guidelines), toe pressure sensitivity was 100% but was only 53% for ABI. Hence, in some clinical situations with high risk of MAC (clinical neuropathy, nephropathy and long duration of diabetes), ABI should be interpreted carefully, and normal values are not sufficient to rule out the diagnosis of PAD. Other methods, such as toe-pressure measurements, because arteries at the level of the ankle were more frequently calcified than those at the toe level, are recommended because of their excellent sensitivity. Further studies are required to provide more specific recommendations.

**Prognostic values**

Besides its usage for diagnosing and evaluating the severity of PAD, ABI has an independent and important value in estimating global vascular prognosis. A decreased ABI is a major risk factor of CV morbidity and mortality. This prognostic value is also valid for diabetic patients. The Fremantle diabetes study showed that in T2D, an ABI < 0.9 increased the risk of cardiac death by 67%. Jue Li et al. reported that an ABI lower than 0.9 increased significantly the adjusted relative risk of CV mortality in a Chinese population of T2D; additionally, the risk was inversely correlated to the decrease in ABI. During a follow-up of 14 years in elderly Swedish diabetic patients, the rate of cardiac events was reported to be as high as 102 for 1000 patients year^{-1} with an ABI < 0.9 versus 28.4 when the ABI is within the normal range.

High ABI values (above the normal range) could also be an indicator of CV system damage. Earlier, in the 1980s, Everhart et al. showed that MAC increased the risk of mortality in T2D by a factor of 1.5. Similar data were reported in a diabetic veteran population. In a recent subanalysis of the Strong Heart Study, Resnick et al. showed that any increase of ABI above 1.4 was an independent CV risk factor. There was a U-shape association between ABI value and CV mortality.

Indeed, the adjusted risk for CV mortality was 2.52 with an ABI < 0.9 and 2.09 with an ABI > 1.4. This association was positive in diabetic patients, who represented 67.8% of patients with a high ABI > 1.4. An increased ABI reflects also coronary calcifications, suggesting that elevation of this index could reflect diffuse atheromatous disease.

In the Fremantle Diabetes study, an ABI < 0.9 is an independent risk factor for amputation with a relative risk of 2.21. In the same way, elevated ABI value increased the risk of amputation by 5.5.

Thus, not only low, but also high ABI values are prognostic of CV risk as well as the risk of occurrence of foot-related injuries and amputations. ABI provides information regarding the distribution of atherosclerotic disease.

**ABI and microangiopathy in diabetes**

**Nephropathy**

Diabetic nephropathy at the early stage of microalbuminuria may be an early sign of intrarenal vascular dysfunction and a marker of atherosclerotic disease. However, what is the relative impact of albuminuria and glomerular filtration rate (GFR) on ABI in diabetes?

Available data in the diabetic population were in favour of a low ABI in case of renal failure. In a recent analysis of the National Health and Examination Survey, Wu et al. studied the relationship between PAD, defined as an ABI < 0.9 or > 1.4, and renal failure and/or microalbuminuria in 7068 subjects of whom 1156 were diabetics. The presence of abnormal renal function, as estimated by a GFR < 60 ml^{-1} min^{-1} 1.73 m^{-2} was strongly associated with PAD in the diabetic patients (OR 2.3), whereas there was no significant association in the non-diabetic patients. Paradoxically, a urinary albumin/creatinine ratio \( \geq 30 \) mg g^{-1}, was independently associated with PAD only in non-diabetic individuals (OR 1.87). However, the Multi-Ethnic Study of Atherosclerosis showed in diabetic patients that the presence of albuminuria increases the risk of an ABI < 0.9 by 90% and by 65% after further adjustment for major CV risk factors. Moreover, in another Taiwanese study, the prevalence of an ABI < 0.9 in elderly T2D patients was 8.0, 17.1

<table>
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<th>Sensibility (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen A 2005</td>
<td>106 patients/ 140 limbs</td>
<td>Neuropathy^c</td>
<td>NC</td>
<td>Arterial angiography</td>
<td>71</td>
<td>30</td>
</tr>
<tr>
<td>Williams DT 2005</td>
<td>57 limbs</td>
<td>Neuropathy^b</td>
<td>1.21</td>
<td>Doppler ultrasound</td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td>Potier L 2009</td>
<td>83 patients/ 162 limbs</td>
<td>High CV risk</td>
<td>0.9</td>
<td>Doppler ultrasound</td>
<td>50</td>
<td>79.6</td>
</tr>
<tr>
<td>Clairotte C 2009</td>
<td>166 limbs</td>
<td>High CV risk</td>
<td>1.01</td>
<td>Doppler ultrasound</td>
<td>54.4</td>
<td>96.8</td>
</tr>
<tr>
<td>Premalatha G 2002</td>
<td>100 patients</td>
<td>Foot ulcer</td>
<td>NC</td>
<td>Doppler ultrasound</td>
<td>70.6</td>
<td>88.5</td>
</tr>
</tbody>
</table>

NC: Not communicated.

^a Estimation of cardiovascular (CV) risk is based on prevalence of traditional risk factors, diabetes duration, and mean HbA1c when communicated.

^b Neuropathy was defined using ICDF guidelines.

^c No definition of neuropathy was specified.
and 38.5%, according to the presence of normo-, micro- and macroalbuminuria, respectively.74

The decrease of GFR is strongly associated with low and high ABI in diabetic patients. Nevertheless, the impact of micro- or macroalbuminuria on the values of ABI is not so clear and requires further studies.

Neuropathy and retinopathy
Limited available data regarding the association of diabetic neuropathy and retinopathy with ABI support a higher prevalence of these microvascular complications in case of abnormal ABI values.75 High ABI is more often noticed in case of neuropathy.44,53 This observation could be explained by the role of neuropathy in the pathophysiology of MAC. In fact, sympathectomy of lower limbs causes major arterial calcification years later, through a mechanism that is not well understood.76,77 Some other studies showed a correlation between the presence of MAC and microalbuminuria or retinopathy.44,78 Thus, Everhart et al. showed that diabetic patients with MAC had a risk of 2.4 to develop proteinuria and of 1.7 to develop retinopathy.55

However, it is difficult to draw conclusions and establish a causal relationship between arteriopathy as suggested by an abnormal ABI and diabetic microangiopathy. These observations could probably be the simple reflection of the severity of diabetes: the more severe it is (long duration and poor glycaemic control), the higher is the prevalence of microvascular complications as reflected by MAC. Some data are in favour of a causal relation between high ABI secondary to MAC and microangiopathy. In this case, would these abnormally high values be an indicator for renal and neurological damage? To our knowledge, there are no data about this issue. Specific studies are required to understand clearly the link between the increase of ABI and microvascular complication of diabetes.

Conclusion
The measurement of ABI is a simple and reliable method that has proven to be efficient in diagnosing PAD and estimating CV risk in diabetes. Even when it is assessed using non-conventional methods, such as in the case of an automatic device, it remains an acceptably sensitive test in primary care or clinical studies.

ABI values <0.9 are conventionally used as a pathological threshold to define PAD and high CV risk. However, the sensitivity of this threshold appears to be lower in complicated T2D, particularly in the presence of clinical peripheral neuropathy. In this case, other tests with a higher sensitivity, such as toe blood pressure, should be performed.

Furthermore, a high ABI, which is a marker of MAC, is often associated with neuropathy and/or chronic kidney disease. These unreliable high values seem to be the marker of a particular form of PAD with more diffused atherosclerosis or even microvascular damage. Because of the high risk of amputation, special attention should be accorded to patients with such a profile.

Thus, ABI can be used in diabetic patients because of its simplicity, but values obtained should be interpreted with caution, according to the clinical situation.

Conflict of Interest
None.

Funding
None.

Ethical Approval
None.

References


