Association Between Ankle–Brachial Index and Risk Factor Profile in Patients Newly Diagnosed With Intermittent Claudication

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Background The primary objective of the present study was to determine whether there is an association between the ankle–brachial index (ABI) and the risk factor profile in patients with newly diagnosed peripheral arterial disease (PAD). A secondary objective was to identify the risk factor profile of these patients, and evaluate how well these factors are controlled in the primary care setting.

Methods and Results In this cross-sectional study, all new consecutive patients referred by primary care to a vascular surgery outpatient clinic, after diagnosis of PAD was confirmed, were subsequently referred to the Risk Factor Modification Clinic for assessment and management of their risk factors. Patients with intermittent claudication (n=170) (age 68.7±10.6 years; 118 men; ABI 0.65±0.13) were included. In patients not on lipid-lowering drugs, low-density lipoprotein-cholesterol (LDL-C) was inversely correlated with the ABI (r=–0.42, p<0.0001). Also ABI was significantly correlated with serum creatinine (r=–0.38, p<0.0001) (and estimated glomerular filtration rate), high-sensitivity C-reactive protein (hsCRP) (r=–0.20, p=0.009) and plasma fibrinogen (r=–0.18, p=0.018). In stepwise multiple linear regression analysis, hsCRP and creatinine levels and diabetes were independent predictors of ABI (p<0.0001). Only 32.4% of the patients had normal blood pressure and 25.9% had an optimal LDL-C level <2.6 mmol/L (100 mg/dl); 85.3% were ever smokers; 44.1% had diabetes/impaired fasting glucose; 84.7% had hsCRP >3.0 mg/L; 78.8% fibrinogen >3.0 g/L (300 mg/dl); and 68.8% homocysteine >12.0 μmol/L (44.7% >15.0 μmol/L).

Conclusions For the first time, a significant inverse correlation between ABI and LDL-C was shown in patients not on lipid-lowering drugs, and also between ABI and creatinine, hsCRP and fibrinogen in all patients, supporting a link between the severity of PAD and atherogenic and inflammatory risk factors. HsCRP, creatinine and diabetes were independently associated with the ABI. Despite the increased vascular risk, PAD remains undertreated in the primary care setting. Increased awareness will overcome this barrier to effective secondary prevention of vascular events. (Circ J 2008; 72: 441–448)

Key Words: Ankle–brachial index; Intermittent claudication; Peripheral arterial disease; Primary care; Risk factors

Peripheral arterial disease (PAD) affects up to 20% of adults older than 55 years and is associated with silent or symptomatic arterial disease in other vascular beds1–3 Although the majority of PAD patients are asymptomatic with a low rate of local symptoms and complications, both symptomatic and asymptomatic PAD patients carry a higher risk for vascular events.1–4 PAD is considered as a coronary heart disease (CHD) equivalent and is characterized by high mortality rates (approximately 25–30% within 5 years for patients with symptomatic PAD), mainly from stroke and myocardial infarction.5,6 It follows that PAD patients should have their modifiable vascular risk factors aggressively controlled: these include diabetes mellitus (DM) and smoking as major factors.1–4,7,8 Advanced age, male sex, hypertension, hyperlipidemia, and the presence of the metabolic syndrome (a cluster of metabolic abnormalities) are also important risk factors for PAD.1–4,8 Furthermore, emerging risk factors, such as high circulating levels of homocysteine, C-reactive protein (CRP), fibrinogen, interleukin (IL)-1 and IL-6, creatinine and cystatin C are also associated with PAD.5,9–16 However, to our knowledge there has not been a study estimating the association between traditional and emerging risk factors and the ankle–brachial index (ABI), a marker of the hemodynamic disease severity of PAD.

The primary objective of our study was to determine whether there is a correlation between vascular risk factors and the ABI in patients newly diagnosed with PAD. A
The medical (including vascular) history, and the medications of each patient were recorded. The systolic and diastolic blood pressures (BP) were measured in both arms after a 10-min rest while supine. The ABI, defined as the ratio of the ankle systolic BP (measured by Doppler ultrasound) and the higher of the 2 (right and left arm) brachial systolic pressures, was also recorded!

A venous blood sample was collected from each patient after a 12-h fast (water only allowed). Laboratory measurements (using established methods) included: (1) total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides; the low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald equation when triglyceride levels were <4.5 mmol/L (410 mg/dl), (2) glucose and creatine kinase levels, and renal, thyroid and liver functions, and (3) high-sensitivity CRP (hsCRP) (measured by Olympus Latex CRP assay, Olympus GmbH, Hamburg, Germany), fibrinogen [measured by the Clauss method (clotting activity) using an autoanalyzer (ACL 300 Research, IL Labs, Warrington, UK)], and homocysteine [measured by the AxSYM Homocysteine immunoassay (Abbott, IL, USA), based on microparticle enzyme immunoassay technology]. All measurements were performed in the Departments of Haematology and Chemical Pathology at Ealing Hospital. The methods used are subject to national and international quality control schemes.

The estimated glomerular filtration rate (e-GFR) was calculated for all patients using the Modification of Diet in Renal Disease (MDRD) study equation.7

The medical notes were reviewed to assess previously reported diseases, investigations, interventions and laboratory results.

Patients were considered hypertensive if they had BP ≥140/85 mmHg, or ≥130/80 mmHg in those with DM or chronic kidney disease, or if they were being treated with antihypertensive medication according to the Joint British Societies’ guidelines.8 BP control was evaluated.

Patients were hyperlipidemic if they had serum LDL-C levels >2.6 mmol/L (100 mg/dl) [National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines], or were being treated with lipid-lowering drugs and had a baseline serum LDL-C level >2.6 mmol/L (100 mg/dl).5,6

DM was diagnosed according to the American Diabetes Association’s criteria.6 A fasting glucose level ≤5.6 mmol/L (100 mg/dl) was considered normal, 6.1–6.9 mmol/L (110–125 mg/dl) indicated impaired fasting glucose (IFG) and ≥7.0 mmol/L (126 mg/dl) or antidiabetic treatment was categorized as DM. Patients with unknown DM and IFG status had a second fasting glucose measurement to confirm the diagnosis. In diabetic patients, glycemic control was also assessed by measuring glycosylated hemoglobin A1c (HbA1c).

Patients with fasting glucose levels between 6.1 and 7.0 mmol/L (110–126 mg/dl) and/or HbA1c between 6.2 and 7.5% were considered as adequately controlled, whereas for those with fasting glucose levels >7.0 mmol/L (126 mg/dl) and/or HbA1c ≥7.5% control was considered to be inadequate.18

Regarding smoking, the patients were classified as current smokers, lifelong non-smokers, and ex-smokers if they had quit smoking more than 6 months before entry to the study (to reduce the risk of relapse).

The weight and the height of each patient were measured, and the body mass index (BMI) was calculated using the following formula: BMI (kg/m²) = weight (kg)/height² (m).

### Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 13.0; SPSS Inc, Chicago, IL, USA). A

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**Table 1 Patients’ Profiles at Presentation**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>M/F, n (%)</th>
<th>Age, years (mean, SD)</th>
<th>ABI</th>
<th>BMI, kg/m²</th>
<th>CHD/CVD, n (%)</th>
<th>Smoking (never/ex/current), n (%)</th>
<th>Total cholesterol/LDL-C, mmol/L</th>
<th>HDL-C, mmol/L</th>
<th>Triglycerides, mmol/L</th>
<th>Total cholesterol/HDL-C</th>
<th>LDL-C/HDL-C</th>
<th>hsCRP, mg/L</th>
<th>Creatinine, µmol/L</th>
<th>Homocysteine, µmol/L</th>
<th>TSH, IU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>118/52 (69.4/30.6)</td>
<td>68.7±10.6</td>
<td>0.65±0.13</td>
<td>26.3±2.3</td>
<td>74 (43.5%)</td>
<td>25/76/69 (14.7/44.7/40.6)</td>
<td>5.35±1.08</td>
<td>3.26±0.98</td>
<td>1.50 (1.20–2.13)</td>
<td>4.31±1.0</td>
<td>2.62±0.87</td>
<td>94 (82–111)</td>
<td>14.7 (11.5–17.8)</td>
<td>1.40 (0.99–2.41)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; ABI, ankle-brachial index; BMI, body mass index; CHD, coronary heart disease; CVD, cerebrovascular disease; BP, blood pressure; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein; TSH, thyroid stimulating hormone.

Results are shown as number and percentage for categorical variables, and for continuous variables as mean ± SD (for parametric variables) or median (interquartile range) (for non-parametric variables).

To convert: mmol/L of glucose to mg/dl, multiply by 18; mmol/L of total cholesterol to mg/dl, multiply by 88.5; µmol/L of creatine to mg/dl, multiply by 0.0113; g/L of fibrinogen to mg/dl, multiply by 100.
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2-tailed $p \leq 0.05$ was considered significant. The tests used are shown in the Results section. Corrections for multiple comparisons were performed. A risk score was created and is also explained in the Results section.

Results

Patient Characteristics

A total of 170 patients with PAD were referred to the RFMC from February 2002 to July 2005 [mean age (standard deviation, SD): 68.7 (10.6) years; 118 (69.4%) men]. The women were significantly older than men (71.6±9.1 vs 67.4±11.0 years; $p=0.015$). The ABI of the worst affected leg was 0.65±0.13. The patients’ characteristics at presentation are shown in Table 1.

Hypertension

The systolic BP of the patient population was 142±19 mmHg with a median of 140 [interquartile range (IQR) 130–150] and a range of 90–210 mmHg. The diastolic BP was 78±10 mmHg (median 80, IQR 70–85, range 60–100 mmHg). Overall, only 32.4% of the whole population (55/170) had normal BP and it is interesting that only 5.9% (10/170) had optimal BP (<120/80 mmHg). Fig 1A illustrates the distribution of hypertensive patients and their treatment. Table 2 shows the distribution of antihypertensive drugs among the patients, and Table 3 shows the number of patients taking 1, 2 or ≥3 antihypertensive drugs, and the number and percentage of patients adequately controlled in each of these categories. The higher the number of drugs used the higher the percentage of subjects with

![Fig 1.](image)

![Table 2](table)

![Table 3](table)
well-controlled hypertension.

Dyslipidemia

Of the total group, 164 patients (96.5%) were hyperlipidemic; that is, they had LDL-C >2.6 mmol/L (100 mg/dl), or were on a lipid-lowering medication and had a baseline serum LDL-C levels >2.6 mmol/L (100 mg/dl). Overall, 44 of the 170 (25.9%) patients had optimal LDL-C <2.6 mmol/L (100 mg/dl). More specifically, only 53.6% were on lipid-lowering medication, and of those, only 43.2% had LDL-C <2.6 mmol/L (100 mg/dl) (Fig 1B). Furthermore, 33 patients (19.4%) had HDL-C <1.0 mmol/L (40 mg/dl) (NCEP ATP III recommended value), and 72 patients (42.4%) had triglyceride levels >1.7 mmol/L (150 mg/dl) (borderline raised level).

DM

In total, 95 patients (55.9%) had no history of DM, 55 (32.3%) had DM, and 20 (11.8%) had IFG (Fig 1C). Six patients with DM and 5 with IFG were unaware of their glycomic status. Of the 49 diabetic patients with known DM, only 5 (10.2%) had adequately controlled DM, the rest had a fasting glucose test >7.0 mmol/L (126 mg/dl) and/or HbA1c ≥7.5%.

Smoking

Never smokers numbered only 25 (14.7%) patients, 85.3% were ever-smokers, 76 (44.7%) were ex-smokers, and 69 (40.6%) were current smokers.

Antithrombotic Medication

Most of the patients (141/170) were on antithrombotic treatment (82.9%); 6 were on warfarin, 112 on aspirin alone, 3 on aspirin plus dipyridamole, 9 on aspirin plus clopidogrel, and 11 on clopidogrel alone. The remaining 29 patients were not on any antithrombotic treatment; 3 had a history of asthma (currently controlled), and 2 had a history of gastrointestinal ulcer, and 8 of these 29 patients were not being treated although they had a history of CHD and no contraindications.

Previously undiagnosed biochemical hypothyroidism was identified in 3 patients.

Emerging Risk Factors

Of the patients, 84.7% (144/170) had hsCRP levels >3.0 mg/L (associated with a higher risk of vascular events); 21 78.8% (134/170) had fibrinogen levels >3.0 g/L (300 mg/dl); 22 68.8% (117/170) had homocysteine levels >12.0 μmol/L (suggested treatment threshold for high-risk patients), and 44.7% (76/170) >15.0 μmol/L. Serum creatinine levels were at the upper limit of the normal range [median (IQR): 94 (82–111) μmol/L; 1.06 (0.93–1.25 mg/dl)] (Table 1). The median (IQR) e-GFR (as calculated by the MDRD equation17) was 66 (54–78) ml·min−1·1.73 m−2.

Correlations and Multivariate Analysis

After correcting for multiple comparisons19 ABI was significantly correlated (Spearman correlations, rs) with: creatinine: rs=−0.38, p<0.0001, hsCRP: rs=−0.20, p=0.009, and, fibrinogen: rs=−0.18, p=0.018.

The correlation between creatinine and e-GFR was rs=−0.83, p<0.0001, and as expected the correlation between ABI and e-GFR was similar to that between ABI and creatinine (rs=0.32, p<0.0001).

Furthermore, although there was no significant correlation between ABI and LDL-C (rs=−0.14, p=0.068), when patients untreated with lipid-lowering drugs were considered separately, a significant correlation was noted (rs=−0.42, p<0.0001).

A risk score was created using the 3 variables identified as highly correlated with ABI (ie, creatinine, hsCRP and fibrinogen) and the median values of these variables were calculated. Values below the median were recoded as value 1, and values above the median as value 2. The risk score was the summation of the recoded values for the 3 variables. The score could range from 3 (all values below the median) to 6 (all above the median); therefore, 4 groups were formed, 1 for each score (3–6). The 1-way ANOVA showed that there was a significant difference between groups in the distribution of the ABI (p<0.0001). Tukey’s
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Table 4 Stepwise Multiple Linear Regression Model

<table>
<thead>
<tr>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>t statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.750</td>
<td>0.033</td>
<td>23.013</td>
</tr>
<tr>
<td>HsCRP</td>
<td>-0.004</td>
<td>0.001</td>
<td>-0.294</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.001</td>
<td>0.000</td>
<td>-0.202</td>
</tr>
<tr>
<td>DM</td>
<td>0.039</td>
<td>0.019</td>
<td>1.453</td>
</tr>
</tbody>
</table>

Dependent variable = ABI. Total $R^2=0.157$, $R=0.397$, F statistic with 3 degrees of freedom =10.21, $p<0.0001$.

Discussion

Several processes are known to play a role in atherosclerosis, including inflammation, endothelial dysfunction, oxidative stress, dyslipidemia, platelet activation, thrombosis, vascular smooth cell activation, altered matrix metabolism, remodeling and genetic factors.24–27

In the present study, most of the patients had levels of emerging risk factors higher than those associated with increased risk of vascular events.21–23

Probably the most interesting finding is that the ABI was inversely correlated with LDL-C levels in patients not treated with lipid-lowering drugs. Hyperlipidemia is a well-established risk factor for PAD and vascular events;1–6 however, to our knowledge this is the first time that a graded relationship (inverse) between LDL-C and the severity of PAD (as expressed with ABI) has been noted. The Cardiovascular Health Study (n=8,888; men and women ≥65 years) showed that in subjects with an ABI between 0.9 and 1.4 (in 1992–1993), higher LDL-C levels [odds ratio (OR) = 1.60, 95% confidence intervals (CI) = 1.03–2.51] and lipid-lowering drug use (OR = 1.74, 95% CI = 1.05–2.89) were independent predictors of ABI decline in 1998–1999.8 That correlation is important as it can shed some light on the pathogenesis of PAD and merits further research. Previous studies have found lipid abnormalities in PAD patients. For example, in a recent study the atheregenic lipoprotein phenotype of patients with intermittent claudication was compared with age–BMI-matched controls. In PAD patients the low-density lipoprotein (LDL) size was significantly smaller, with decreased larger subclasses (LDL-I, LDL-IIa) and increased smaller particles (LDL-IIIa, LDL-IIIb, LDL-IVa, LDL-IVb). The presence of PAD was independently associated, among other factors, with elevated small, dense LDL (OR = 6.7, 95% CI = 1.1–45.1). In another study the titer of autoantibodies against oxidized LDL was higher in patients with PAD than in patients with CHD.29 Oxidative modification of LDL alters its structure, allowing the LDL to be taken up by scavenger receptors on macrophages, endothelial and smooth muscle cells, leading to the formation and progression of atherosclerotic plaques.29 In this context, it is possible that statins exert their beneficial effect in vascular disease (and PAD) through various mechanisms targeting different lipid abnormalities.30–32

Our study also showed that the ABI was significantly inversely correlated with creatinine (and e-GFR), hsCRP and fibrinogen levels. Many studies have reported both cross-sectional and longitudinal associations between baseline renal insufficiency and PAD.15,16,33 It was also noted that the prevalence of PAD appears to be much higher among end-stage renal disease patients than in the general population.34 The graded association between ABI and creatinine found in our study is interesting, because it suggests that renal and vascular disease may progress in parallel. Although this association may reflect a shared risk factor profile between renal disease and atherosclerosis, we were not able to explain this association by controlling for many of the known risk factors. It has been suggested that because the kidney is a highly vascular organ whose function depends on an intact circulatory system, systemic atherosclerotic disease could be causaly associated with declining renal function; in this context, systemic atherosclerosis may also be a risk factor for renal insufficiency as it is for myocardial infarction, stroke and PAD.33

Previous studies support that PAD is not only associated with higher creatinine levels and chronic kidney disease but that it also predicts an increase in creatinine levels over time.35 Furthermore, renal impairment is associated with an increased risk for mortality in patients with advanced PAD, irrespective of the presence of hypertension and DM.35 We found a strong correlation between creatinine and e-GFR (a more accurate method of estimating renal function than serum creatinine) and, hence, between ABI and e-GFR; furthermore, the fact that e-GFR emerged as an independent determinant of ABI in the stepwise multiple linear regression model confirmed that renal function is independently associated with the ABI. The strong association of ABI with a rise in serum creatinine level (and a decline in e-GFR) highlights the possible importance of ABI measurement as a means of identifying patients at greatest risk for deterioration of renal function over time.33

HsCRP is a marker of inflammation and increased levels are associated with a higher cardiovascular risk.11 CRP can provide additive prognostic information over standard lipid measures, and can predict the development of PAD in apparently healthy men, independently of elevated blood lipid levels.10,11 It is relevant that inflammation may play a role in functional decline, not only in patients with PAD, but also in subjects without PAD.16 Higher levels of inflammatory markers can also predict future vascular events.2,12
Vainas et al also showed that the serum hsCRP level was related to the severity of PAD.44

Likewise, previous studies have shown an association between higher fibrinogen levels and PAD.33,14 In a study by Lane et al, multivariate analysis determined that a history of CHD and elevated serum fibrinogen level were the stronger predictors of premature PAD (<60 years).28 Furthermore, increased circulating levels of homocysteine, CRP and fibrinogen have been noted in PAD patients, and can predict the occurrence of vascular events.12 However, to our knowledge our present study is the first to record a direct inverse correlation between ABI and fibrinogen. Furthermore, we created a risk score from the variables that were highly correlated with ABI (ie, creatinine, hsCRP, fibrinogen) and found that the higher the score the lower the ABI value (p<0.0001).

In our stepwise multiple linear regression analysis, after correcting for all other confounders (including treatment), circulating hsCRP and creatinine levels and a history of DM (including IFG) were independent predictors of the ABI. DM is a major risk factor for PAD;1,2,26,39–41 however, hsCRP and creatinine were better determinants of the ABI, suggesting that emerging risk factors might be more relevant than the traditional risk factors for PAD (Table 4).

We found that the risk factors of patients referred from primary care with suspected PAD were poorly controlled and undertreated. Also, 43.5% of the patients had known CHD or cerebrovascular disease/events as confirmed by their histories. However, the percentage of patients with angiographically detected disease might be much higher.42,43 Interestingly, it has been shown that ABI is an effective tool in detecting CHD in outpatients in clinical practice.44 In our study, all patients had intermittent claudication with a low mean ABI, at 0.65±0.13, probably because they had been referred and, therefore, more advanced cases were included. Most of the patients (69.4%) were men, and women were significantly (p=0.015) older than men, which accords with the literature.1,2,42,45 It is relevant that high-risk patients with PAD, who need vigorous control of modifiable vascular factors, were actually undertreated, and were referred by primary care at an advanced stage of intermittent claudication (as defined by the low ABI). The fact that this was identified in an urban hospital (London, UK) underlines the severity of the situation. Our findings support the belief that there is room for improvement, and indicate the need for increased physician and patient awareness for the early detection of PAD so that prevention and treatment can be more effective and beneficial.56–49 These findings also stress the need for RFMCs to provide aggressive, titrated medical treatment, tailored to individual patients, in order to prevent vascular events, and improve symptomatology in PAD patients. We are currently investigating whether referral to the RFMC made a difference in the overall management of this high-risk population.

Study Limitations

Our findings may not be generalizable to all patients with PAD, because this cohort probably had more advanced PAD, being consecutive patients referred by primary care to a vascular surgery outpatient clinic. It is not possible to establish a cause-and-effect relation of the associations observed in a cross-sectional study. Therefore, whether increases in circulatory levels of blood markers represent a contributing factor and/or a consequence of increased ABI remains unclear. However, previous evidence supports our findings, suggesting an important role for inflammation and lipid disturbances in the pathophysiology of PAD.6,10–16,24–38

We measured ABI in all patients, but angiography was not routinely performed. Angiography is an invasive technique with a complication rate of 1–2%.50 and was only performed if a decision was made for intervention (angioplasty or surgery). The ABI is highly sensitive and specific for diagnosing PAD; an ABI <0.90 is up to 95% sensitive in detecting angiography-positive disease and it can also be an independent predictor of vascular events.4–36

We measured serum creatinine levels as an estimate of renal function; however, good correlation between serum creatinine and GFR has been established.31 Furthermore, we calculated the e-GFR, the validity and accuracy of which has been previously reported.33

The lack of control subjects to test the correlations found herein is a possible limitation; however, our endpoint was to determine independent predictors of low ABI. In the absence of low ABI (ie, in the control group) the associations found in our study cannot be tested.

Conclusion

A significant inverse correlation between ABI and LDL-C was found for the first time in patients not on lipid-lowering drugs, and also between the ABI and creatinine, hsCRP and fibrinogen levels in all patients. After adjusting for relevant confounders, hsCRP and creatinine levels and a history of DM were independent predictors of ABI, supporting a link between the severity of PAD and atherogenic and inflammatory risk factors. Whether aggressive treatment with evidence-based medication can improve the risk factor profile and symptomatology with the aim of preventing progression to more severe disease or even improve the ABI, remains to be determined and is a topic for future research. The future looks promising; new treatments for PAD may be added to the clinicians’ armory.52,53

As most PAD patients are asymptomatic, screening should be routine practice at the primary care level.32–46,48 Given the overwhelming evidence on the known benefits of cardioprotective medications, their underuse is puzzling in a population at high risk.2,54 Increased awareness will overcome this barrier to effective secondary prevention of vascular disease. Current evidence stresses the need for vascular specialists, and indicates the importance of specialist clinics aimed at risk factor modification, as well as close follow-up, in order to achieve optimal management of these high-risk patients. It is time to translate the evidence into practice.

References

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