The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects

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Objective: **The presence of a high ankle-brachial index (ABI) is related to stiff ankle arteries due to medial calcification. Recently, this condition has attracted new interest after reports of a worse cardiovascular prognosis, similar to a low ABI. We sought to compare risk factors contributing to a low (≤0.90) and high (≥1.40) ABI. Additionally, we hypothesized that in instances of high ABI, occlusive PAD may coexist.**

Method: **This cross-sectional study was conducted at vascular laboratories in a university medical center. The subjects were 510 ambulatory patients (37% had diabetes) previously examined at our vascular laboratories and who responded positively to our invitation. We collected data on smoking, diabetes, hypertension, dyslipidemia, and cardiovascular disease history. The noninvasive assessment of lower limb arteries consisted of the measurement of ABI, toe-brachial index (TBI), and posterior tibial artery peak flow velocity (Pk-PT). A TBI >0.7 and a Pk-PT >10 cm/s were considered normal.**

Results: **High- and low-ABI were detected, respectively, in 2.1% and 57.8% of limbs. For a low ABI, age (odds ratio [OR], 1.29/10 y), pack-years (OR, 1.08/10 units), and hypertension (OR, 1.90) were independent significant ($P < .001$) factors. A strong association was found between diabetes and high ABI (OR, 16.0; $P < .001$). When ABI ranges were compared with TBI and Pk-PT results, those with ABI ≤0.90 and ABI ≥1.40 presented similar patterns of abnormalities. Pk-PT or TBI, or both, was abnormal in more than 80% of cases in both ABI ≤0.90 and ≥1.40 groups. The ABI vs TBI relationship appeared linear in nondiabetic patients, but had an inverted J-shape in diabetic patients, suggesting high ABI masked leg ischemia.**

Conclusions: **Diabetes is the dominant risk factor for a high (≥1.40) ABI. Occlusive PAD is highly prevalent in subjects with high ABI, and these subjects should be considered as PAD-equivalent. (J Vasc Surg 2008;48:1197-203.)**

The measurement of ankle-brachial index (ABI) is widely used for the diagnosis of peripheral arterial disease (PAD) as well as the estimation of its severity and progression. There is extensive evidence that both symptomatic and asymptomatic PAD are predictive for further cardiovascular disease (CVD) events.[1-3] Routine use of ABI in higher-risk subjects has been proposed in primary care.[1,2]

In some infrequent cases, the measurement of ankle pressures is impeded by stiff or incompressible arteries, even with pressures as high as 300 mm Hg. This leads either to the inability to obtain the ABI or to very high values. This situation has been reported to be more frequent in patients with diabetes mellitus (DM)[4-7] and in those with end-stage renal disease.[4,8] Arterial stiffening is attributed to calcifications in the arterial wall. This occurs with medial artery calcinosis (MAC), corresponding to a high accumulation of calcium in the medial layer, without any protruding lesion in the arterial lumen.[9] Because the arterial stiffness to cuff pressure precludes an accurate blood pressure measurement, several PAD epidemiologic studies have excluded patients with high or indeterminable ABI.[10,11] This has recently received new attention, because it has been reported that a high ABI is correlated with subclinical CVD[12,13] and is associated with higher rates of total and cardiovascular mortality, both in general[14,15] and coronary populations.[16]

Nevertheless, risk factors for this condition are not clearly understood. Furthermore, because ABI cannot diagnose PAD in the presence of stiff arteries, the relationship between high ABI and concomitant PAD is unknown.

Our first aim in this study was to compare the risk factors associated with a high ABI, as a marker of MAC, with those related to a low ABI, as a marker of occlusive PAD. We hypothesized that risk factors or their levels of association, or both, would differ in these two conditions. In addition, we hypothesized that a substantial fraction of limbs with a high ABI would have occlusive arterial disease when assessed by other noninvasive means. Because high rates of elevated ABI are reported among patients with DM, we also conducted analyses stratified by DM status.

METHODS

Study population. From 1990 to 1994, we studied 510 patients invited to visit our vascular laboratory for a

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Competition of interest: none.

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new, comprehensive noninvasive vascular examination of the lower limbs. They were recruited from a pool of 2265 people who visited either the San Diego Veterans Administration Center or the University of California, San Diego Medical Center vascular laboratories between 1980 and 1990. The study population consisted of survivors who were located and willing to participate. The major goal of the original study was to investigate the natural history of PAD.[17,18] Data assessment, including patient's interview, physical examination, fasting blood sample analyses, and noninvasive vascular testing has been described in detail elsewhere.[17,19]

All participants gave their informed written consent for their participation in the studies and the use of their data for future research. The study protocol and consent form were approved by the University of California, San Diego Investigational Review Board.

Data definition. Ethnicity was self-reported. The number of cigarette pack-years defined smoking history. Hypertension was defined in patients taking an antihypertensive medication or with a resting arm systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg. Participants reporting any use of lipid-lowering drugs or a total cholesterol to high-density lipoprotein cholesterol ratio ≥5 were categorized as dyslipidemic.

DM status was defined either as a self-reported DM diagnosis or taking anti-DM drugs. In additionally, those without any report of DM but with a fasting plasma glucose ≥126 mg/dL at the study visit were classified as new DM patients. DM patients aware of their condition answered questions about their use of insulin and oral medications and the date of DM onset. The length of DM diagnosis was calculated by subtracting the age of DM onset from the participant's age at the study visit. Body mass index (BMI) was calculated from values for weight and height as kg/m^2.

Noninvasive vascular tests. The ankle-brachial index (ABI) and the toe-brachial index (TBI) were obtained after blood pressure measurement at arms, ankles, and great toes by the sphygmomanometric technique. The signals were detected by photoplethysmography at the third finger for the arm and great toe for both indexes. Because of the known association between subclavian stenosis and PAD,[20] the higher brachial systolic pressure was used for the ABI and TBI denominators. Peak flow velocities of the posterior tibial artery (Pk-PT) were measured by Doppler ultrasound imaging using the maximum amplitude search technique.[21]

Normal ABI values were considered between 0.91 and 1.39, and a TBI >0.70 and Pk-PT >10 cm/s were also considered normal.[17,21,22] These criteria have been validated against angiographically documented occlusion >50%.[21,22] A significant obstructive (>50% stenosis) lesion in large vessels, from the iliac to the ankle arteries, would affect ABI results, except when the presence of MAC precluded actual ABI results. A low ABI or low Pk-PT, or both, as defined in this study, present 89% sensitivity and 99% specificity to detect PAD in those large vessels.[22] In addition, low TBI reflects the presence of any flow obstruction in leg arteries, down to the toe arteries. Because the presence of MAC at the base of the great toe is infrequent,[23] the probability of an inadequate TBI value similar to what is reported for ABI is low. Data regarding the reproducibility of these variables are reported elsewhere.[17]

Statistical methods. Except for the study population description, we performed a limb-specific analysis. The demographic and clinical characteristics were assessed, stratified by three different ABI ranges (1) low: ABI ≤0.90, (2) intermediate: ABI between 0.91 and 1.39, and (3) high: ABI ≥1.40. For the assessment of risk factors, we also classified all revascularized limbs in the low ABI group, except for those with ABI ≥1.40, which have been classified in the high ABI group. These three ABI ranges were the dependent variables used to answer the first hypothesis, all other covariates served as the independent variables.

Logistic regression analysis was used to obtain odds ratios with 95% confidence intervals (95% CI) for all variables at two ABI ranges: low ABI (≤0.90) and high ABI (≥1.40). The reference ABI range for these two models was between 0.91 and 1.39.

To assess which risk factors were predictive of a given ABI range, two sets of fully adjusted logistic regression models were used. The dependent variables were low vs intermediate ABI in the first model, and high vs intermediate ABI in the second model. All models contained CVD risk factors except gender, because we did not observe any women with stiff arteries.

The possibility of confounding was eliminated by looking at the effect on point estimates by selectively removing covariates from the model one at a time. Because of the possible correlation between observations within an individual, the same analyses were repeated with application of generalized estimated equations (GEE) methods.[24] Separate logistic regression GEE models were fit comparing ABI categories low (ABI ≤0.90) vs intermediate and high (ABI ≥1.40) vs intermediate ABI. Because the GEE models compared either high or low ABI vs intermediate ABI, five individuals with ABI ≤0.9 on one limb and ABI ≥1.4 on the other limb were excluded from the GEE analysis.

To assess the actual lower limb perfusion of legs with raised ABI, limbs in the three ABI ranges were studied for lower limb perfusion by looking at the limb's TBI and Pk-PT velocity. In this case we used actual ABI values, without considering whether the limbs were previously revascularized or not. We plotted TBI values by the corresponding ABI values and stratified limbs by DM status. We looked for different lower limb vascular patterns by fitting the data points to linear and quadratic lines. Again, due to possibly correlated values within individuals, a mixed-effects model[24] was used with outcome of the repeated TBI scores. ABI scores were the fixed-effects predictor. A random intercept term was included to account for between-subject variability. Likelihood ratio tests were used to compare the linear model with the quadratic model. Akaike information criteria values were also obtained for each model.

The study used the statistical software SAS 8.0 (SAS Inc, Cary, NC), R 2.2.1 (R Foundation for Statistical

Table I. Demographic and clinical characteristics of study participant

Variable	*No. (%) or mean (range)*
Patients, total	510
Males	448 (87.8)
Age, years	68.0 (30-100)
Ethnicity	
Non-Hispanic white	445 (87.3)
Hispanic	28 (5.5)
African American	23 (4.5)
Native American	10 (2.0)
Other	4 (0.9)
Peripheral arterial disease[a]	382 (74.9)
Previous limbs revascularization	178 (34.9)
Body mass index, kg/m^2	27.0 (17-51)
Pack-years smoked	48.6 (0-270)
DM[b]	189 (37.1)
Hypertension	404 (79.2)
Dyslipidemia	270 (52.9)
DM patients, No.[c]	158
Treatment variables	
Insulin (ever)	106 (67.1)
Oral medication (ever)	131 (82.9)
Length of diagnosis,[c] years	16.1 (0-62)

DM, Diabetes mellitus.
[a]Defined by ankle-brachial index ≤0.90 or peak tibial flow <10 cm/s.
[b]Defined as self-report, previous diagnosis, or fasting plasma glucose >126 mg/dL.
[c]Only in those with known diabetes.

Computing, Vienna, Austria), and Minitab 13.1 (Minitab Inc, State College, Pa) for data analysis.

RESULTS

Among the 2265 potential candidates, 481 had died, 1276 could not be located or declined the invitation, and 508 patients returned for a new, comprehensive, noninvasive vascular examination of the lower limbs as well as an assessment of their CVD risk factors with a standard questionnaire, and undergoing a clinical examination and providing a fasting blood sample for further analyses. Data for these 508 patients have been compared with those abstracted at baseline in 77 survivors randomly selected among those who declined the invitation or who were not located.[17] The participants had slightly less advanced PAD according to noninvasive tests, but were otherwise comparable.

The study population consisted of 448 men and 62 women. Most were non-Hispanic whites. Demographic and clinical data are reported in Table I. In addition to the 158 patients with known DM, 31 new cases were diagnosed during the study visit.

Among the 1020 limbs, six were excluded for absent ABI data due to amputations. Among the 1014 limbs available, 586 (57.8%) had an ABI ≤0.90 and 21 (2.1%) had an ABI ≥1.40. Demographic data and risk factors according to the three ABI ranges are summarized in Table II. Notably, 19 of the 21 legs (91%) with an ABI ≥1.40 belonged to DM patients. These 21 legs corresponded to 14 patients, including 12 with DM.

Table III reports the logistic regression models, looking for independent risk factors for low ABI (≤0.90) and high-ABI (≥1.40). Age, pack-years of smoking, and hypertension were the significant predictors of a low ABI, with borderline results for DM patients. For a high ABI, the odds ratio of DM was 15.97 (95% CI, 3.2-66.1). BMI presented near to significant results as a risk factor for high ABI. The model revealed dyslipidemia as a significant protective factor for stiff arteries. The results using GEE models were similar (data not presented). Notably, we redid the same analyses, keeping only patients' limbs that were both in the intermediate ABI range as the reference group; no substantial differences were found compared with the results in Table III (data not shown). Regarding the potential association of high ABI and occlusive disease, we stratified patients according to the three ABI groups and the TBI and Pk-PT results. Complete data were available for 959 limbs, including Pk-PT and TBI. Fig 1 displays the limbs distribution according to the combination of TBI and Pk-PT results in the three ABI classes. The distribution of those with a high ABI differed substantially from those with a normal ABI and was similar to the proportions obtained in limbs with PAD. In the high ABI group, 18 limbs (85.7%) presented either a TBI ≤0.7 or a Pk-PT ≤10 cm/s, or both, which is very similar to the 87.7% of cases with a low ABI, and both were much higher than the 37.6% of cases observed in the intermediate ABI group.

Table IV summarizes the same distribution according to the DM status. Because only two non-DM patients had one limb with a high ABI, we could not statistically compare their distribution with that of their low ABI counterparts. The distribution of flow abnormalities in diabetic limbs, as assessed by TBI and Pk-PT, follows the same pattern as results of limbs not stratified by DM status (Fig 1). Limbs in ABI ranges at either end of the spectrum had a low TBI. In 84.2% of cases, diabetic limbs with ABI ≥1.40 had abnormal results in at least one of the two noninvasive vascular indicators, suggestive of concomitant occlusive disease.

We plotted ABI against TBI results for the study population and found different results according to the DM status (Figs 2 and 3). In the absence of arterial stiffness, it was expected that the linear model would fit the best for presenting the relationship between ABI and TBI. In non-DM patients, the likelihood ratio test statistic comparing the linear vs the quadratic models was 14.73 (P = .0001). The Akaike information criteria for the linear and quadratic models were −522.88 and −535.62, respectively. For the DM group, the likelihood ratio test statistic was 25.67 ($P < .0001$). The Akaike information criteria were −186.27 and −209.93. Thus, in both groups, the quadratic model fit the data better than the linear model, but this was more marked in the DM group. The quadratic model in the DM group (Fig 3) suggests an inverted J-shape relationship. This nonlinear relationship, much more pronounced in the DM group, demonstrates that arterial stiffness affects the ABI-TBI relationship, slightly in non-DM subjects (Fig 2), but dramatically in the DM patients (Fig 3).

Table II. Demographic and clinical characteristics of limbs, stratified by ankle-brachial index categories

Variables	*Ankle-brachial index*		
	≤0.90	*0.91 to <1.40*	*≥1.40*
Patients, No.	586	407	21
Age, mean (range) years	68.9 (41-100)	67.0 (30-100)	63.6 (39-84)
Males, No. (%)	525 (89.6)	346 (85.0)	21 (100)
Ethnicity, No. (%)			
Non-Hispanic White	515 (87.9)	353 (86.7)	17 (81.0)
Hispanic	27 (4.6)	25 (6.1)	4 (19.0)
African American	28 (4.8)	17 (4.2)	0 (0)
Native American/Asian	15 (2.6)	5 (1.2)	0 (0)
Other	1 (0.2)	7 (1.7)	0 (0)
BMI, mean (range) kg/m^2	27.1 (18-41)	27.3 (17-52)	30.3 (21-42)
Pack-years, mean (range)	53.4 (0-270)	41.8 (0-165)	52.2 (0-225)
Diabetes mellitus[a]	227 (38.7)	129 (31.7)	19 (90.5)
Hypertension	492 (84.0)	293 (71.0)	19 (90.5)
Dyslipidemia	317 (54.1)	214 (52.6)	7 (33.3)

[a]Defined as self-report, previous diagnosis, or fasting plasma glucose ≥126 mg/dL.

Table III. Association of cardiovascular disease risk factors with low and high ankle-brachial index according to multiply adjusted logistic regression models[a]

Variables	*ABI ≤0.90*[b]		*ABI ≥1.40*[b]	
	OR[b]	P	*OR*[b]	P
Age (per 10 years)	1.29	<.001	0.79	.356
Ethnicity				
Non-Hispanic white	1.00		1.00	
Other	1.04	.810	1.35	.635
Body mass index (per kg/m^2)	1.00	.646	1.08	.102
Pack-years smoking (per 10 units)	1.08	<.001	1.04	.377
Hypertension	1.90	<.001	2.05	.372
Dyslipidemia	1.09	.550	.23	.011
History of diabetes mellitus	1.31	.067	15.97	<.001

ABI, Ankle-brachial index; *OR,* odds ratio.
[a]Reference range is 0.91 to <1.40.
[b]Vs normal ABI range (0.91 to <1.40) as the reference group.

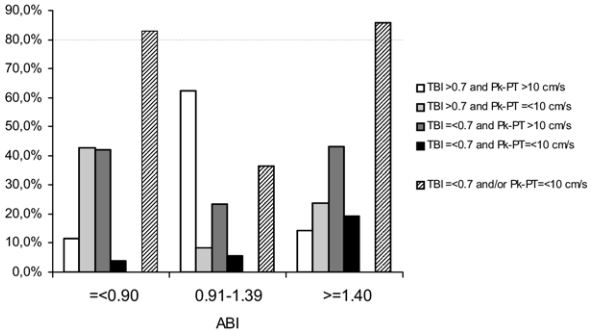

Fig 1. Proportions of limbs characterized by toe brachial index *(TBI)* and peak tibial flow velocity *(Pk-PT)*, stratified by ankle-brachial index *(ABI)* ranges.

DISCUSSION

This study confirmed our hypothesis that subjects with a high ABI are differently associated with CVD risk factors than those with a low ABI. DM appeared as the dominant risk factor for a high ABI. Our study also suggests that high ABI masks frequently occlusive PAD.

Described by Mönckeberg,[9] MAC does not affect the intima. Hence, luminal obstruction is not a consequence. After autopsy studies,[9,25] these lesions were well documented in the living using soft-tissue radiographs, with an aspect likened to railroad tracks.[26] This condition can also be revealed by an excessive resistance to the cuff pressure.

Data on MAC epidemiology are sporadic. In a German survey conducted on 4814 subjects aged 45 to 75 years, the prevalence of ABI >1.30 and ABI >1.50 was reported at 13.3% and 1.1% in men and 6.9% and 0.5% in women, respectively.[27] In the Epidemiology of Diabetes Complication study in young patients with type 1 DM, DM duration, hypertension, and the triglycerides/apolipoprotein A1 ratio were independent risk factors of MAC.[6] The Cardiovascular Health Study[14] and the National Health and Nutrition Examination Survey[7] showed DM prevalence as high as twice in those with an ABI >1.40 compared with normal groups. Several pathways are proposed to explain arterial stiffening in DM patients. Insulin triggers cultured smooth muscle cell proliferation.[28] Hyperglycemia is responsible of nonenzymatic glycosylation of several proteins, including collagen and elastin.[29] It has also been suggested that MAC is related to diabetic neuropathy.[30-33]

We found an inverse association between dyslipidemia and high ABI. This has also been reported in the Cardiovascular Health Study (CHS).[14] One explanation is that the combination of high low-density lipoprotein and DM is highly atherogenic.[34] This would favor the development of occlusive rather than stiffening disease, shifting some patients with mild MAC and occlusive disease to the intermediate ABI range.

Forty years ago, Ferrier[26] revealed a positive association between MAC and the narrowing and occlusion in amputated foot arteries. In Native Americans with DM, radio-

Table IV. Proportions of limbs characterized by toe-brachial index and peak tibial flow velocity ranges, stratified by ankle-brachial index levels and diabetes status[a]

	ABI low, no. (%)		*ABI intermediate, no. (%)*			
	Diabetes		*Diabetes*		*ABI high, no. (%)*	
TBI and Pk-PT	*Yes (n = 200)*	*No (n = 279)*	*Yes (n = 150)*	*No (n = 353)*	*Yes (n = 19)*	*No (n = 2)*
TBI >0.70 and Pk-PT >10 cm/s (n = 362)	20 (10.9)	32 (12.0)	92 (64.8)	215 (62.0)	3 (15.8)	0 (0)
TBI >0.70 and Pk-PT ≤10 cm/s (n = 49)	1 (0.6)	16 (6.0)	4 (2.8)	24 (6.9)	3 (15.8)	1 (50)
TBI ≤0.70 and Pk-PT >10 cm/s (n = 311)	78 (42.6)	110 (41.4)	31 (21.8)	83 (23.9)	8 (42.1)	1 (50)
TBI ≤0.70 and Pk-PT ≤10 cm/s (n = 237)	84 (45.9)	108 (40.6)	15 (10.6)	25 (7.2)	5 (26.3)	0 (0)
TBI ≤0.70 or Pk-PT ≤10 cm/s (n = 627)	174 (89.7)	246 (88.5)	51 (35.7)	138 (39.1)	16 (84)	2 (100)

Pk-PT, Peak tibial flow velocity; *TBI,* toe-brachial index.
[a]In each cell, only limbs with the corresponding data available were included.

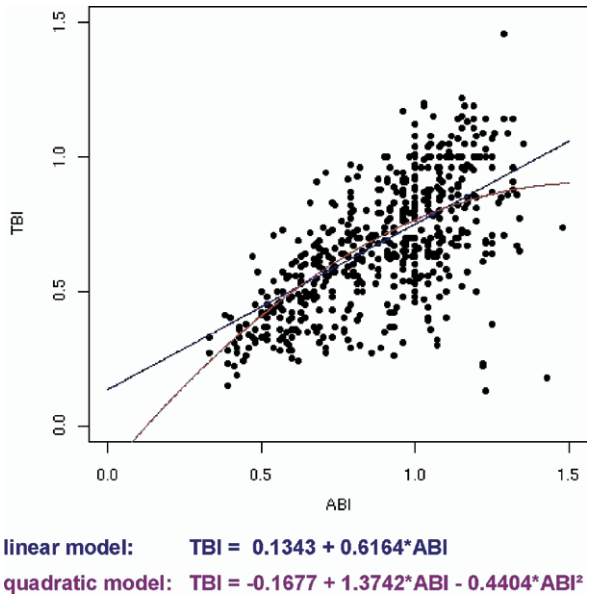

Fig 2. Distribution of toe brachial indices *(TBI)* by ankle-brachial indices *(ABI)* in nondiabetic patients as well as the linear *(blue slope)* and quadratic relationships *(purple curve)* between both indexes.

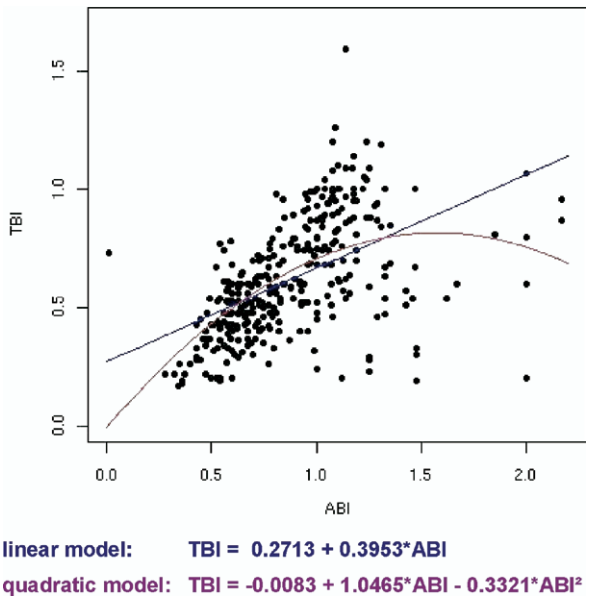

Fig 3. Distribution of toe brachial indexes *(TBI)* by ankle brachial indexes (ABI) in diabetic patients as well as the linear *(blue slope)* and quadratic relationships *(purple curve)* between both indexes.

graphic MAC was associated with a 5.5 times increased risk for an ipsilateral amputation, suggestive of concomitant occlusive disease.[31] Using ^{133}xenon, Christensen[35] reported a decreased muscular blood flow in DM patients with MAC. Among 42 DM patients, angiographic occlusive lesions were significantly more frequent in vessels with radiographic MAC than those without MAC.[32] Quigley et al[36] found that the relationship between ankle Doppler pressure and skin perfusion pressure differed in patients with and without DM. The authors concluded that even in normal ABI ranges, the actual foot perfusion pressure might be overestimated at some level in DM patients.

In a series of DM patients with foot ulcers,[37] angiography revealed ≥50% stenosis in 16 of 17 cases, with an ABI ≥1. In another series of patients with chronic limb ischemia, those with incompressible arteries had higher rates of amputation.[38] This underlines the pitfall of a normal ABI reading in DM patients. In addition, the profunda femoral artery is mostly affected in DM patients,[39] but abnormalities cannot be detected by ABI because it does not contribute to ankle perfusion, except when it supplies a pathologic superficial femoral artery.

In a study combining a community-dwelling cohort with two cohorts from vascular laboratories,[40] the prevalence of any kind of leg pain decreased progressively from the lowest ABI range up to the 1.20 to 1.29 range, and rose again beyond this range. The rates of atypical pain and classic claudication in the ≥1.40 group were similar to those observed in the 0.90 to 0.99 group, suggesting that a similar level of occlusive disease exists in these two ABI ranges.

The parallel between radiologic MAC and high ABI should be made with caution. It is probable that x-rays

might detect MAC in an earlier stage, and high ABI might reflect a more progressed disease.[23,33] Therefore, the principal contribution of our study here should be interpreted in the light of recent findings on the prognostic value of a high ABI.[14-16] Without reconsidering the prognostic information provided by a high ABI, our findings suggest that many—but not all—patients with high ABI actually have associated PAD, and this might at least partially explain the prognostic value of a high ABI.

Recently, Suominen et al[41] published similar findings in a population referred to a vascular surgery unit for PAD diagnosis. Using a more liberal high ABI criterion (>1.30), they found a DM prevalence of 49%. According to their criterion, 62.5% of the patients in our study with an ABI >1.30 in at least one limb had DM. In patients with an ABI >1.30, they report a PAD prevalence of 62.2%, defined only by a TBI of <0.60.[41] Using the same 1.30 ABI threshold, we found 54.2% of our patients with a TBI of <0.70. Thus, the findings in our study are concordant with their report.

Our study presents some limitations. We studied neither the presence of peripheral neuropathy[42] nor heredity, both considered as independent risk factors of MAC.[24,43] In addition, we did not assess the osteogenic process, which is involved in median calcinosis formation in vascular smooth muscle cells.[4,44] Finally, subjects were usually referred to the vascular laboratory for evaluation for PAD, and we cannot expand our findings to the general population.

CONCLUSION

In this cross-sectional study, a low ABI was associated with standard CVD risk factors, whereas a high ABI was only associated with DM. Nonetheless, associations between low and high ABI levels and other measures of distal perfusion were similar, indicating that a high ABI is frequently associated with occlusive PAD. This confirms the necessity for requiring other noninvasive tests in patients with an ABI ≥1.40. Because these additive methods will frequently diagnose underlying PAD, these patients should be considered as PAD equivalents, not only from a general prognostic point of view but also for the potential trophic and functional consequences of lower limb malperfusion.

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AUTHOR CONTRIBUTIONS

Conception and design: VA, EH, MC
Analysis and interpretation: VA, EH, JD, LH, LN, MC
Data collection: JO, MC
Writing the article: VA, EH, JD, LH, LN, MC
Critical revision of the article: VA, MC
Final approval of the article: VA, EH, JD, LH, LN, MC
Statistical analysis: LH, LN
Obtained funding: MC
Overall responsibility: MC

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