Physical Activity Improves Borderline Ankle–Brachial Index Values in a Cardiovascular Risk Population

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Background: Peripheral arterial disease (PAD) is an underdiagnosed and undertreated disease because it remains asymptomatic for so long. The ankle–brachial index (ABI) is a valid method for detecting PAD in lower extremities. ABI ≤0.90 indicates incident PAD. Recent studies have found that subjects with borderline ABI values (0.91–1.00) have increased mortality rates. The objective of our 7-year follow-up study was to investigate the progression of PAD in borderline ABI subjects, who underwent a multifactorial cardiovascular intervention.

Methods: A total of 193 subjects with borderline ABI were examined in 2005–2006. None of them had previously diagnosed diabetes, cardiovascular or renal disease or intermittent claudication. They were given conventional treatment for multiple risk factors of cardiovascular diseases (hypertension, hypercholesterolemia, elevated blood glucose, smoking, and overweight). Sixty-four percent of these subjects ($n = 123$) attended a follow-up visit in 2012.

Results: Of the 123 subjects with borderline ABI (mean age 59.0 ± 6.5 years, 62% female) at baseline, 18 (15%, 95% confidence intervals [CI]: 9%–22%) developed incident PAD during the follow-up. The mean ABI was 0.97 ± 0.03 at baseline and 1.01 ± 0.12 at 7-year follow-up visit. The change in mean ABI was +0.04 (95% CI: 0.03–0.07), $P < 0.001$. ABI improved significantly in 25 (20%) subjects. In multivariate ordered logistic regression analyses high and even moderate leisure-time physical activity (LTPA; odds ratio 6.15; 95% CI: 1.99–19.1) predicted a rise in ABI in comparison to low LTPA.

Conclusions: Physical activity seems to improve significantly ABI values among men and women with borderline ABI (0.91–1.00).

INTRODUCTION

Peripheral arterial disease (PAD) is a treacherous disease. Most individuals in the general population with PAD are asymptomatic, which makes it an underdiagnosed and undertreated disease.[1] As PAD progresses, it may lead to classical intermittent claudication and critical limb ischemia. The association of PAD with more lethal manifestations of generalized atherosclerosis, coronary artery disease, and cerebrovascular ischemia, is well-recognized.[2–4]

Ankle–brachial index (ABI) has been acknowledged as a valid and simple instrument for detecting PAD in lower extremities.[4–6] A low ABI ≤0.90 has been shown to independently associate with a high incidence of cardiovascular events and mortality in numerous population cohort studies.[4,6,7]

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Traditionally, normal ABI is defined from 0.91 to 1.40. However, several recent studies have introduced a new borderline ABI definition of 0.91−1.00.[6,8] Persons with borderline ABI lack symptoms of PAD but have increased rates of major cardiovascular disease (CVD) events and mortality compared with persons with normal ABI from 1.01 to 1.40.[6,8,9] Borderline ABI has also been recognized by the American College of Cardiology and the American Heart Association (AHA).[10,11]

The aim of our 7-year follow-up study was to investigate the progression of PAD in borderline ABI subjects, who underwent a multifactorial cardiovascular intervention.

METHODS

Baseline Participants

The Harmonica project is a community-based survey designed to evaluate CVD-risk factors among the residents of the rural town of Harjavalta in Finland, in 2005 and 2006. Detailed study protocol has been described elsewhere.[12,13] A risk factor survey was mailed to all home-dwelling inhabitants (n = 2,856) aged 45−70 years, and 2,085 (73%) were willing to participate. Those who had at least one cardiovascular risk factor (n = 1,469) were invited to further investigation. Physical examination performed by a trained nurse included a measurement of height, weight, body mass index (BMI), waist circumference, and blood pressure. A generic health survey was filled by all the subjects. Medical history was obtained from medical records. ABI was measured from subjects (n = 1,076) with hypertension, metabolic syndrome, prediabetes, diabetes, BMI at least 30 kg/m^2 or a 10-year risk of CVD death of 5% or more according to the systematic coronary risk evaluation system (SCORE).[14] Participants with previously diagnosed diabetes, cardiovascular or renal disease, ABI $\geq$ 1.01 or ABI $\leq$ 0.90, and patients with intermittent claudication were excluded. Patients with borderline ABI (0.91−1.00) in the baseline examination were included to this study (n = 193).

Multifactorial Intervention

The study subjects with borderline ABI (0.91−1.00; n = 193) were assigned to receive conventional treatment for multiple risk factors of CVD. Treatment goals were set according to the 2003 European guidelines on CVD prevention in clinical practice.[15] Subjects with SCORE at least 5%, a newly diagnosed type 2 diabetes mellitus or markedly raised levels of single risk factors (total cholesterol [TC] $\geq$8.0 mmol/L, low-density lipoprotein cholesterol [LDL-C] $\geq$6.0 mmol/L, blood pressure $\geq$180/110 mm Hg) were categorized as high-risk subjects (n = 52). All the study subjects were given exercise instructions recommending physical activity for at least 30 min per day or 4 hr per week. Subjects with a smoking habit (n = 42) were given motivational counseling and prescribed an optional antismoking medication (bupropion hydrochloride). Dietary intervention was given for study subjects with BMI $\geq$25 kg/m^2. They were set a goal for at least 5% weight reduction by reducing saturated fat in their diet. The goal for blood pressure was set under 140/90 mm Hg and for newly diagnosed diabetics (n = 10) under 130/80 mm Hg. Arterial hypertension was treated primary with angiotensin-converting enzyme inhibitors or angiotensin II-receptor antagonists and secondarily with calcium-channel blockers, thiazides, or beta-blockers. Statin was prescribed for hypercholesterolemia; for the high-risk subjects the TC and LDL-C goal was set at <4.5 mmol/L and <2.5 mmol/L, respectively, and for the rest of the study cohort at <5.0 mmol/L and <3.0 mmol/L.[15]

Leisure-Time Physical Activity (LTPA)

LTPA was assessed by a questionnaire at baseline and follow-up. The questionnaire is included as a Supplemental data.

ABI Measurement

Systolic blood pressure (SBP) measurements for calculation of the ABI were obtained using appropriate-sized blood pressure cuffs and Doppler instrument (PD1v with a vascular probe of 5 MHz; UltraTec, UK). The blood pressure cuff was applied over the brachium and just above the malleoli. SBPs were measured once in all 4 limbs, the brachial and dorsalis pedis arteries with patient in supine position. If the dorsalis pedis pulse was not detected, the posterior tibial artery pulse was used. ABI was calculated by dividing the lower ankle SBP with the higher brachial SBP. At the baseline examination, ABI was measured by a single doctor and at the follow-up examination by a single trained nurse.

Blood Pressure Measurement and Laboratory Tests

Blood pressure was measured using a calibrated mercury sphygmomanometer with subjects in a sitting posture, after resting at least 5 min. In each

subject the mean of the 2 readings taken at intervals of at least 2 min was used. If study participants had no antihypertensive medication at enrollment, and the study nurse measured SBP of at least 140 mm Hg or diastolic blood pressure (DBP) of at least 90 mm Hg, participants were lent and taught to use an automatic validated blood pressure monitor (Omron M4-1; Omron, Kyoto, Japan) for home blood pressure monitoring over 1 week. Laboratory tests were determined in blood samples, which were obtained after at least 12 hr of fasting. A detailed description of the enrollment and examination methods has been published earlier.[13]

Seven-Year Follow-Up Visit

Of the 193 invited subjects, 123 (64%) attended the 7-year follow-up visit (average 6.7 years, range 6.0–7.1). A modified questionnaire, laboratory tests, and ABI measurements were repeated for them. The protocol for ABI measurement was the same than at the baseline. The reasons for not attending the follow-up were withdrawal ($n = 48$), moving to a new district ($n = 16$), and death ($n = 6$).

Definitions

Participants with an ABI between 0.91 and 1.0 were considered as borderline ABI subjects at baseline. The Trans-Atlantic Inter-Society Consensus Workgroup for the Management of PAD in 2007 (TASC II) suggests that the reporting standards for ABI require a change of 0.15 in an isolated measurement for it to be considered clinically relevant,[16] therefore we defined ABI change ≥ 0.15 to be significant. At the 7-year follow-up visit, the participants who had an ABI $\leq$0.90 were categorized as having an incident PAD. Participants with the change of ABI $<$0.15 were categorized in the stable ABI group and participants with the change of ABI $\geq$0.15 were categorized in the increased ABI group. LTPA was defined as follows; high LTPA $\geq$ 30 min exercise at a time for at least 4 times a week, moderate LTPA $\geq$ 30 min exercise at a time from 1 to 3 times a week and low LTPA $\geq$ 30 min exercise randomly or never. At the follow-up, the Edinburgh Claudication Questionnaire was used to define intermittent claudication. Incidence of foot ulcers was defined with a question ''have you had a foot ulcer caused by a diminished arterial circulation?'' Diabetes was defined according to the World Health Organization 1999 criteria; 2-hr plasma glucose concentrations of at least 12.2 mmol/L, fasting plasma glucose $\geq$ 7.0 or the use of antidiabetic medication. Hypertension was determined as the use of antihypertensive medication or the mean SBP $\geq$135 mm Hg or the mean DBP $\geq$85 mm Hg during the 1-week home monitoring period.

Informed Consent

All of the participants provided written informed consent to attend the project and subsequent medical research. The study protocol and consent forms were reviewed and approved by the ethics committee of Satakunta Hospital District.

Statistical Analysis

The data analyses were conducted in 2014 and presented as means with standard deviations or as counts with percentages. Statistical comparisons between groups were made by using analysis of variance and chi-squared test when appropriate. In the case of violation of the assumptions (non-normality), a bootstrap-type test was used. Statistical comparison of changes in ABI was performed by using bootstrap type paired *t*-test. To determine the predictors of change of ABI, multivariate ordered logistic regression analysis was applied. Correlation coefficients were calculated by the Pearson method and 95% confidence intervals (95% CI) were obtained by bias-corrected bootstrapping (5,000 replications). STATA 13.1, StataCorp LP (College Station, TX) statistical package was used for the analyses.

RESULTS

For the whole cohort, the mean ABI was 0.97 ± 0.03 at baseline and 1.01 ± 0.12 at follow-up visit, change in mean ABI was (+ 0.04 [95% CI: 0.03–0.07]), $P < 0.001$. Eighteen of 123 (15%) study patients developed PAD during the follow-up (incident PAD group). The incidence of PAD was 22 (95% CI: 13–34) per 1,000 person-years.

There were no significant changes in ABI for 80 (65%) subjects (stable ABI group). ABI improved significantly in 25 (20%) subjects (increased ABI group). Half of the cases ($n = 63$, 51%) had ABI over 1.00 at follow-up. Figure 1 displays the subjects individual ABI at the baseline and follow-up. Baseline ABI did not correlate with the change of ABI (−0.12 [95% CI −0.29 to 0.06]). None of our study subjects had an ABI above 1.40 at neither baseline nor follow-up visit.

We compared the basic demography in the 3 groups according to the change in ABI during the follow-up (incident PAD, stable ABI, and increased ABI, Table I). The incident PAD and stable ABI groups included more women than men, and

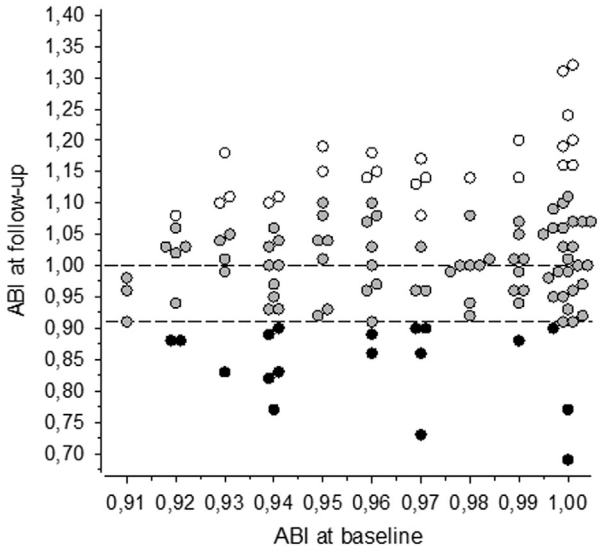

Fig. 1. ABI of the study subjects at baseline and follow-up.

high-density lipoprotein cholesterol level was especially high in the stable ABI group. There was a trend toward higher BMI in the incident PAD group. Physical inactivity was significantly more common in the incident PAD group (39%) compared with stable ABI group (10%) and increased ABI group (0%), $P = 0.003$.

In the logistic regression analysis the only independent factor, which was related to an increase in ABI during the follow-up was LTPA. High (odds ratio [OR] 7.76 [95% CI: 2.39−25.20]) or moderate LTPA ([OR] 6.15 [95% CI: 1.99−19.1]) predicted rise in ABI groups in comparison with low LTPA (Table II).

The proportion of the subjects using antihypertensive drugs increased from 48% ($n = 59$) at the baseline to 59% ($n = 73$) at the follow-up visit. For lipid lowering drugs, the usage was 22 of 123 (18%) and 56 of 123 (46%), respectively. There was no statistical difference between 3 ABI groups in the usage of antihypertensive or lipid lowering drugs at baseline or at follow-up visit (Table III).

Six subjects stopped smoking during the 7-year follow-up of 24 subjects. Surprisingly, ABI increased in 4 of 6 quitters, whereas 2 of 6 developed incident PAD. Only 5 of 123 (4%) of the subjects, all of them having no significant ABI change during the follow-up, gave positive response to the Edinburgh Claudication Questionnaire. Only 1 (1%) subject had a vascular ulcer during the 7-year follow-up, but the ulcer had healed. No amputations were done. Diabetes was diagnosed in 10 (8%) cases during the follow-up. Seven of them were in the stable ABI group, 2 in the incident PAD group and 1 in the increased ABI group. Six subjects died during the follow-up. The death rate per 1,000 person-years was 7.3 (95% CI: 2.7−15.9).

DISCUSSION

To our knowledge, this is the first longitudinal study to report the impact of multifactorial cardiovascular intervention on ABI values among subjects with borderline ABI (0.91−1.00). We found that physical activity significantly associated with improved ABI values over 7-year follow-up period. In patients with borderline ABI the incidence of PAD was 22 of 1,000 person-years.

There are only a few studies that have reported outcome of patients with borderline ABI before. Most of the studies report increased overall mortality of these patients, but none of them report the natural history of the PAD. The Edinburgh Artery Study showed that in the subjects with baseline ABI from 0.91 to 1.00, with the majority being symptom-free of PAD, the 5-year probability of survival was reduced.[9] In 2008, ABI collaboration published a large-scale meta-analysis including 16 cohort studies, with participants from the general population aged 47−78 without history of coronary heart disease. In men with borderline ABI 0.91−1.00, the hazard ratios for total mortality, cardiovascular mortality, and major coronary events were 1.61, 1.68, and 1.43, respectively, when compared with reference ABI subjects (1.11−1.20). The corresponding ratios in women were 1.52, 1.84, and 1.53.[6] In borderline ABI subjects, the increased risk was found to be significantly lower than in those with ABI $\leq$ 0.90. Surpisingly, the increased risk was substantially higher in borderline ABI patients than in those with ABI $>$ 1.40, which has been thought to indicate noncompressible arteries and associated with increased cardiovascular morbidity and mortality compared with normal ABI values.[17−19] Recent study by Natsuaki et al. showed that borderline ABI (0.91−0.99) in diabetic patients was associated with significantly higher risks for mortality and PAD compared with normal ABI.[20]

The main finding of our study was that physical activity significantly associates with improved ABI values among asymptomatic men and women with borderline ABI. High and even moderate LTPA was found to predict a rise in ABI groups compared with low LTPA. There are several prior cross-sectional studies regarding physical activity and ABI values. In the Cardiovascular Health Study, there was an inverse relation between exercise

Table I. Baseline characteristics by incident PAD, stable ABI, and increased ABI subjects

Characteristic	Incident PAD ($n = 18$)	Stable ABI ($n = 80$)	Increased ABI ($n = 25$)	*P* value
Age, years	59.2 (6.6)	58.8 (6.5)	59.3 (6.9)	0.93
Male sex, *n* (%)	7 (38.9)	25 (31.3)	15 (60.0)	0.036
Body mass index, kg/m^2	31.9 (7.8)	28.8 (5.2)	28.4 (3.6)	0.064
Current smoker, *n* (%)	4 (22.2)	17 (21.3)	3 (12)	0.57
ABI	0.96 (0.027)	0.97 (0.029)	0.97 (0.027)	0.34
Fasting glucose, mmol/L	5.77 (0.60)	5.56 (0.88)	5.60 (0.70)	0.49
2-hr glucose, mmol/L	6.19 (0.79)	5.94 (0.89)	5.73 (0.61)	0.10
SBP, mm Hg	146 (17)	155 (18)	152 (19)	0.10
DBP, mm Hg	86 (7)	90 (8)	88 (7)	0.11
Pulse pressure, mm Hg	60 (13)	66 (16)	64 (16)	0.31
TC, mmol/L	5.17 (1.14)	5.24 (0.87)	5.30 (0.69)	0.90
LDL-C, mmol/L	3.10 (0.93)	3.02 (0.88)	3.22 (0.53)	0.41
HDL cholesterol, mmol/L	1.47 (0.32)	1.64 (0.45)	1.46 (0.30)	0.035
Triglycerides, mmol/L	1.36 (0.54)	1.26 (0.62)	1.43 (0.59)	0.45
hsCRP, mmol/L	3.04 (2.31)	3.07 (4.04)	2.20 (2.38)	0.56
LTPA				0.003
Low (randomly/never), *n* (%)	7 (39)	8 (10)	0 (0)	
Moderate (1−3 times/week), *n* (%)	6 (33)	45 (58)	12 (49)	
High (≥4 times/week), *n* (%)	5 (28)	24 (31)	13 (51)	
New diabetes, *n* (%)	2 (11.1)	7 (8.6)	1 (4.0)	0.66

Data are presented as mean (standard deviation) except where indicated.
Incident PAD = ABI ≤0.90; stable ABI = ABI change <0.15; increased ABI = ABI change ≥0.15.
HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table II. Multivariate ordered[a] logistic regression analyses relating baseline cardiovascular risk factors and LTPA at follow-up

Risk factor	OR[b] (95% CI)	*P* value
Change		
SBP/SD	0.86 (0.59−1.25)	0.43
DBP/SD	1.03 (0.69−1.55)	0.87
Pulse pressure/SD	0.80 (0.55−1.16)	0.24
Body mass index/SD	0.78 (0.54−1.14)	0.20
LDL-C/SD	1.01 (0.69−1.48)	0.96
Fasting glucose/SD	0.74 (0.50−1.09)	0.13
LTPA		<0.001[c]
Low (randomly/never)	1 (reference)	
Moderate (1−3 times/week)	6.15 (1.99−19.10)	
High (≥4 times/week)	7.76 (2.39−25.20)	
Smoking	0.73 (0.26−2.05)	0.56

SD, standard deviation; LDL, low-density lipoprotein.
[a]Code: 0 = incident PAD, 1 = stable ABI, 2 = increased ABI.
[b]Adjusted by sex, age, and baseline ABI.
[c]*P* for linearity.

intensity and the prevalence of a low ABI (<0.9) in subjects aged over 65 years.[21] The Multi-Ethnic Study of Atherosclerosis (MESA) found that moderate-to-vigorous and intentional exercise associates with higher ABI value.[22] To our knowledge, only one longitudinal study has examined the association between physical activity and the progression of ABI among CVD-free individuals, similar to our study.[23] In this study by Delaney et al. participants were derived from the MESA ($n = 5,656$), their mean age was 61 years (53% female) and baseline ABI between 0.90 and 1.40. Authors suggested that participation in intentional exercise prevents incident PAD (ABI ≤ 0.90; risk ratio = 0.85 [95% CI: 0.74−0.98]), which is in agreement with our finding. Other more limited follow-up studies with more comorbid cohorts have demonstrated that physical activity associates with higher ABI values.[24,25] and may even reduce incidence of asymptomatic PAD.[26] A recent randomized trial using a 6-month supervised exercise program reported a significant improvement in ABI among subjects with uncomplicated type 2 diabetes and ABI < 1.00.[25] In our study, participants received recommendations for lifestyle modification without any further supervision, which is a manageable demand on health services in real life.

Hypertension, age, diabetes, smoking, and higher LDL-C concentration have been recognized as risk factors for declining ABI.[27,28] However, in our study, only physical activity had significant association with improved ABI. The reason why the intervention for the other traditional cardiovascular risk

Table III. Baseline and follow-up medications by incident PAD, stable ABI, and increased ABI subjects

Medication	Incident PAD ($n = 18$)	Stable ABI ($n = 80$)	Increased ABI ($n = 25$)	*P* value
Baseline				
ACE inhibitor	4 (22)	5 (6)	2 (8)	0.098
Angiotensin II-receptor antagonist	5 (28)	18 (22)	6 (24)	0.89
Diuretic	2 (11)	9 (11)	2 (8)	0.90
Calcium-channel blocker	5 (28)	10 (12)	4 (16)	0.27
Beta-blocker	2 (11)	19 (24)	4 (16)	0.48
Statin	4 (22)	12 (15)	6 (24)	0.52
Follow-up				
ACE inhibitor	5 (29)	11 (14)	3 (12)	0.29
Angiotensin II-receptor antagonist	5 (29)	22 (28)	7 (28)	0.99
Diuretic	3 (17)	20 (25)	6 (24)	0.75
Calcium-channel blocker	8 (44)	20 (25)	6 (24)	0.22
Beta-blocker	6 (33)	23 (29)	5 (20)	0.59
Statin	10 (56)	36 (45)	10 (40)	0.59

Data are presented as *n* (%).
Incident PAD = ABI $\leq$ 0.90; stable ABI = ABI change $<$ 0.15; increased ABI = ABI change $\geq$ 0.15.
ACE, angiotensin-converting enzyme.

factors did not significantly associate with improved ABI values can be diverse. First, our study cohort had a moderate overall risk factor burden at baseline. Furthermore, the participants with previously diagnosed diabetes, cardiovascular, or renal disease were excluded. New lipid lowering and antihypertension medications were used evenly between ABI groups.

The natural course of PAD includes a decline in ABI over the years. However, in our study cohort, the mean ABI values improved significantly during the 7-year follow-up time. Smith et al. investigated nonclaudicant subjects ($n = 855$) from a general population and reported an overall ABI decrease of 0.025 over 5 years.[29] We assume that our multifactorial intervention, which has never been introduced in other longitudinal ABI studies, was the main reason behind the differences in these results.

There are some limitations in the present study. We measured the ankle systolic pressure from both legs but for logistic reasons we used the dorsalis pedis pulsation and the tibialis posterior artery only if the pulsation from dorsalis pedis artery was not detected. This can reduce the validity of ABI measurements in our study. However, for the ABI calculations, we used the lower ankle systolic pressure, and thus, it is likely that we found a higher number of patients with increased risk for future cardiovascular events.[30] This method of calculation and the ABI range from 0.91 to 1.00 for defining borderline ABI we used are in line with the AHA scientific statement in 2012 for measurement and interpretation of ABI.[11] Other strengths of our prospective study include the well-defined cohort from a general population with a reasonably long follow-up time.

CONCLUSIONS

In conclusion, physical activity significantly associates with improved ABI values among nonclaudicant men and women with borderline ABI (0.91−1.00). Our results suggest that it might be beneficial to pay more attention to patients with borderline ABI and offer them cardiovascular intervention, especially emphasizing the importance of exercise.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.avsg.2015.11.004.

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