

# Ankle brachial pressure index usefulness as predictor factor for coronary heart disease in diabetic patients

M. Filippella<sup>1</sup>, E. Lillaz<sup>1</sup>, A. Ciccarelli<sup>1</sup>, S. Giardina<sup>1</sup>, E. Massimetti<sup>1</sup>, F. Navaretta<sup>2</sup>, A. Antico<sup>2</sup>, M. Veronesi<sup>1</sup>, G. Lombardi<sup>3</sup>, A. Colao<sup>3</sup>, E. Ghigo<sup>4</sup>, A. Benso<sup>4</sup>, and G. Doveri<sup>1</sup>

<sup>1</sup>Unit of Diabetology and Endocrinology, <sup>2</sup>Unit of Vascular Surgery, Regional Hospital of "Valle d'Aosta", Aosta; <sup>3</sup>Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University of Naples, Naples; <sup>4</sup>Department of Endocrinology, University of Turin, Turin, Italy

**ABSTRACT.** Ankle brachial pressure index (ABPI) is a non-invasive marker of atherosclerosis, helpful to identify subjects at high-risk for coronary heart disease (CHD) among large populations with cardiovascular disease (CVD) risk factors. The diagnostic role of ABPI has been also recognized in patients with diabetes. In the present study, the role of an ABPI score <0.90 in predicting CHD has been evaluated in a large series of patients with Type 2 diabetes mellitus and compared to other known CVD risk factors. Nine hundred and sixty-nine (mean age was 66.1 yr) consecutive patients with Type 2 diabetes mellitus were evaluated. The patients were followed-up for 18.3±5.2 months (range 12-24) and all events of CHD, defined as myocardial infarction, unstable and resting angina or coronary atherosclerosis at the instrumental investigation (at the coronary angiography and/or perfusion stress testing) were recorded. A rate of 17.5% of CHD events were recorded in diabetic population during the follow-up period. The relative risk of

CHD was significantly increased for male patients [odds ratio (OR): 1.6; 95% confidence interval (CI): 1.1-2.2], patients with age ≥66 yr (OR: 1.8; 95% CI: 1.3-2.5), body mass index (BMI) >30 (OR: 1.5; 95% CI: 1.1-2.1), waist circumference >88 cm for females and 102 cm for males (OR: 1.5; 95% CI: 1.0-2.1), proteinuria ≥30 µg per min (OR: 1.6; 95% CI: 1.1-2.3), LDL-cholesterol ≥100 mg/dl (OR: 2.1; 95% CI: 1.5-3.0), glycated hemoglobin >7% (OR: 1.6; 95% CI: 1.1-2.3), insulin therapy (OR: 1.9; 95% CI: 1.3-2.9), and ABPI <0.90 (OR: 3.7; 95% CI: 2.2-6.2). BMI was higher in patients with ABPI <0.90 than in those with ABPI ≥0.90 ( $p<0.05$ ). At the multivariate analysis, ABPI <0.90 was the best factor independently associated with CHD ( $p<0.001$ ). ABPI <0.90 is strongly associated to CHD in Type 2 diabetic patients. We recommend to use ABPI in diabetic patients and to carefully monitor diabetic subjects with an ABPI lower than 0.90.

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## INTRODUCTION

The association between diabetes mellitus and cardiovascular disease (CVD) is well established (1-4). CVD is the primary cause of diabetes associated morbidity and mortality, as two-thirds of people with diabetes die of heart or vascular disease (5). The risk of developing a myocardial infarction in diabetic patients without known heart disease is equivalent to the risk observed in non-diabetic survivors of a prior infarction (6).

For this reason, an important challenge to decrease morbidity and mortality of diabetic patients is to detect CVD at an early asymptomatic stage. Although different methods have been employed to estimate the degree of atherosclerosis and to predict the risk for CVD, the best method of identifying high risk subjects has not been established. The ankle brachial pressure index (ABPI) is a non-invasive procedure helpful to evaluate peripheral artery disease (PAD) and more in general to screen for the presence of occlusive arterial disease. A low ABPI <0.90 was reported to be a marker of CVD risk and was an independent predictor of CVD and all-cause mortality (7, 8). Many prospective studies have shown that a low ABPI can predict CVD and all-cause mortality in general population and in patients with existing vascular disease such as hypertension or Type 2 diabetes mellitus, particularly in elderly men (9-11). In a large cohort of middle-aged

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Correspondence: G. Doveri, MD, Unit of Diabetology and Endocrinology, Regional Hospital of "Valle d'Aosta", Viale Ginevra 3, 11100, Aosta, Italy.

E-mail: doveri.giulio@uslaosta.com

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adults, individuals with ABPI <0.90 had an increased prevalence of coronary heart disease (CHD) (12). In patients with Type 2 diabetes, a rate of 71% of CVD has been found in subjects with ABPI score <0.90 and in this cohort of patients only ABPI was able to predict CVD while the traditional risk indicators such as age, blood pressure, left ventricular function, and exercise capacity failed to show any predictive value (13). This study confirms the usefulness of ABPI score as one of the main tool to reveal the cardiovascular compromising in patients with Type 2 diabetes mellitus and suggests to check for CHD in all patients with a ABPI score <0.90.

## PATIENTS AND METHODS

A total of 969 consecutive patients with Type 2 diabetes mellitus referred to the Unity of Diabetology and Endocrinology, Hospital of Aosta, between January and December 2003, and submitted to diabetic foot screening, were enrolled in this study. A subgroup of 799 patients was treated with hypoglycemic drugs whereas 170 patients were treated with insulin. All patients underwent a clinical and biochemical examination as well as an evaluation of ABPI and diabetic neuropathy. The follow-up time lasted for  $18.3 \pm 5.2$  months (range, 12 to 24 months). During this period all CHD events were recorded. CHD events were defined as myocardial infarction, unstable and resting angina or coronary atherosclerosis at the instrumental investigation (at the coronary angiography and/or perfusion stress testing) were recorded. Subjects with a history of coronary artery bypass grafting, coronary angioplasty, carotid surgery were excluded from the study. An informed consent had been read and approved by all patients entering the study.

### Clinical study

Height, weight, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP) were evaluated by standard methods. BMI was measured as the ratio between the weight and the square of the height. A BMI between 25 and 30 kg/m<sup>2</sup> was considered the index of over-weight, whereas BMI greater than 30 kg/m<sup>2</sup> was considered the index of obesity (14). Waist circumference was measured to the nearest 0.1 cm at the end of a normal expiration by measuring from the narrowest point between the lower borders of the rib cage and the iliac crest. The measurements were performed with the patients in standing position with relaxed abdomen, arms at sides, and joined feet (15). Blood pressure was measured in the right arm, with the subjects in a relaxed sitting position. The average of 6 measurements (3 taken by each of 2 examiners) with a mercury sphygmomanometer was used. Hypertension was diagnosed when DBP values were  $\geq 85$  mmHg and SBP values were  $\geq 130$  mmHg in line with Adult Treatment Panel III (16).

### Biochemical study

Glycated hemoglobin, HDL, and LDL cholesterol were measured at fasting by standard procedures. The urinary albumin excretion rate was measured from a single 24-h urine collection. A urinary albumin excretion rate of 30 to 300  $\mu\text{g}$  per min was defined as microalbuminuria; a rate greater than 300  $\mu\text{g}$  per min was defined as macroalbuminuria. Microalbuminuria and macroalbuminuria were defined together as proteinuria.

### Ankle brachial pressure index

The ABPI score was determined by using an 8-mHz Doppler (BI-DIDOP plus) that has a broad-beam ultrasound probe designed specifically for ABPI measurement. Scores were obtained while the subject being supine by recording the SBP in the upper extremities (brachial arteries) and in the lower extremities at the dorsalis pedis and posterior tibial arteries. The ABPI for each side was calculated by dividing the greater of the two ankle systolic readings in respective leg by the greater brachial pressure. An ABPI score less than 0.90 was considered abnormal (17).

### Michigan neuropathic diabetic scoring (MNDS)

MNDS was used for the diagnosis of diabetic peripheral neuropathy (18). This system provides a score in the range 0-8, based on evaluation of 4 different factors in the each leg. These factors are: appearance of foot (dry skin, callus, deformities, fissure, and infection), presence of ulcer, Achilles tendon reflex, and vibration perception in the great toe (measured with a 128 Hz tuning fork). Each component may be given a score of 0 or 1 on the basis of the relevant signs. This scoring system has sensitivity and specificity of nearly 95% (19). We used a cut-off point  $>2$  for the MNDS procedure like as recently suggested by Moghtaderi et al. (20). Patients with a clinical MNDS score  $>2$  had neuropathy.

### Statistical analysis

The statistical analysis was performed by Statistical Package for the Social Sciences for Windows version 9.0 (SPSS, Inc., Chicago, IL). The comparison between numerical data was performed by independent t-test. Univariate analysis was performed by using the Pearson's  $\chi^2$  test to evaluate the association between CHD and different risk parameters. The odds ratio (OR) for each parameter was also calculated. All parameters considered for the analysis were transformed in categorical data according to previously recognized cut-off levels:  $\leq 7\%$  for glycated hemoglobin (21),  $\geq 30$   $\mu\text{g}$  per min for proteinuria (16),  $>40$  mg/dl for HDL cholesterol (16),  $<100$  mg/dl for LDL cholesterol (16),  $\geq 130$  mmHg and  $\geq 85$  mmHg for SBP and DBP, respectively (16),  $>30$  kg/m<sup>2</sup> for BMI (16),  $>102$  and  $>88$  cm for waist circumference in male and in female respectively (16),  $<0.90$  for ABPI (17),  $>2$  for neuropathic diabetic score (NDS) (20). A logistic regression analysis was performed among the variables correlated at the univariate analysis. Numerical data were expressed as mean  $\pm$  SD. A *p*-value  $<0.05$  and 95% confidence interval (CI) were considered statistically significant.

## RESULTS

The clinical features of diabetic patients are summarized in Table 1. Of the 969 diabetic patients, 452 were males and 516 females. The mean age was 66.1 yr. As a whole, a CHD event occurred in 170 of 969 diabetic subjects (17.5%) during the follow-up period: 7 patients died from cardiovascular causes (0.7%), 7 patients had a non-fatal acute myocardial infarction (0.7%), 156 patients had coronary artery disease as suggested by angina or ecocardiogram abnormalities and confirmed by myocardial perfusion scintigraphy and/or coronary angiography (16.1%).

The relative risk of CHD was significantly increased for male patients (OR: 1.6; 95%CI: 1.1-2.2), patients

Table 1 - Study population parameters.

	Mean±SD	Range
Age (yr)	66.1±10.1	33-95
SBP (mmHg)	147.3±19.3	100-240
DBP (mmHg)	84.6±9.2	50-150
BMI (kg/m <sup>2</sup> )	29.3±5.2	16-61
Proteinuria (µg per min)	69.5±288.2	0-3597
LDL cholesterol (mg/dl)	118.3±34.7	25-288
HDL cholesterol (mg/dl)	54.4±16.5	17-191
Glycated hemoglobin (%)	7.5±1.1	4-13
WC (cm)	101.5±13.1	62-161
ABPI	1.0±0.1	0.36-2.14
NDS	1.7±1.2	0-12

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, WC: waist circumference, ABPI: ankle brachial pressure index, NDS: neuropathic diabetic score.

with age ≥66 yr (OR: 1.8; 95%CI: 1.3-2.5), BMI >30 (OR: 1.5; 95%CI: 1.1-2.1), waist circumference >88 cm for females and 102 cm for males (OR: 1.5; 95%CI: 1.0-2.1), proteinuria ≥30 µg per min (OR: 1.6; 95%CI: 1.1-2.3), LDL-cholesterol ≥100 mg/dl (OR: 2.1; 95%CI: 1.5-3.0), glycated hemoglobin >7% (OR: 1.6; 95%CI: 1.1-2.3), insulin therapy (OR: 1.9; 95%CI: 1.3-2.9), and ABPI score <0.90 (OR: 3.7; 95%CI: 2.2-6.2). No association was found between CHD and SBP, DBP, HDL-cholesterol, cigarette smoking, and neuropathic diabetic index (NDI) (Table 2).

At the logistic regression analysis, ABPI score <0.90 was the best factor independently associated to CHD (*p*<0.001). Twenty-nine of the 70 patients with abnormal ABPI score <0.90 developed a CHD event.

When patients were divided in two subgroups according to ABPI (<0.90/≥0.90), BMI was higher in patients with ABPI <0.90 than in those with ABPI ≥0.90 (*p*<0.05), whereas a slight significant increase of SBP and DNI was found in the former than in the latter subgroup. No significant difference for age, DBP, waist circumference, proteinuria, LDL- and HDL-cholesterol, glycated hemoglobin was found between the two subgroups (Table 3).

## DISCUSSION

This present study confirms in a large series of patients with Type 2 diabetes the ability of ABPI to identify those subjects who are at risk for CHD diabetes. In line with previous studies (12), a ABPI score <0.90 is able to identify CHD diabetic patients better than other conventional clinic-metabolic CVD factors. An

Table 2 - Prevalence of coronary heart disease (CHD) events during the follow-up period in diabetic patients according to different cardiovascular risk factors.

	CHD %	<i>p</i>
Gender (M/F)	21/15	<0.05
Age <66/≥66	15/22	<0.01
SBP <130/≥130	21/16	ns
DBP <85/≥85	19/17	ns
BMI ≤30/>30	14/21	<0.05
WC <88/>88 (F), ≤102/>102 (M)	15/21	<0.05
Proteinuria <30/≥30	14/21	<0.05
LDL cholesterol <100/≥100	15/27	<0.001
HDL cholesterol ≤40/>40	20/18	ns
Hemoglobin glycated ≤7/>7%	14/21	<0.05
Cigarette smoking (no/yes)	17/22	ns
Insulin therapy (no/yes)	16/27	<0.01
ABPI <0.9/≥0.9	41/16	<0.001
NDI ≤2/>2	16/19	ns

M: males; F: females; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference; ABPI: ankle brachial pressure index; NDI: neuropathic diabetic index.

ABPI index lower than 0.90 is strongly associated with CHD in diabetic patients. This finding, together with previous evidences of association between APBI and intima media thickness (IMT) as well as other indexes of early stage atherosclerosis in both diabetic and non-diabetic subjects (9-12, 22, 23), suggests that APBI is a helpful marker to identify diabetic patients who need a careful cardiovascular follow-up.

Patients with diabetes have a 200% higher risk of CHD than non-diabetic individuals (24). Numerous CVD factors have been studied in order to select patients who are at high risk to develop CHD (25-27), but none is yet considered ideal (25, 28, 29). Some well-established CVD factors are not so correlated to CHD in diabetic as in the general population. In the current study, CHD appears to be mainly related to ABPI and much less related to other CVD risk factors than you can expect. ABPI is a measure of peripheral arterial disease (PAD), a macroangiopathy complication typically affecting Type 2 diabetic patients. This could explain why CHD in the diabetic patients examined in the present study seems to be associated preferentially to ABPI and at a lower extent to other CVD risk factors as cigarette smoking and hypertension which greatly influences CHD in the general population.

ABPI is a simple, non-invasive, and inexpensive test which identifies patients who are affected with periph-

Table 3 - Cardiovascular risk factor values (mean±SD) according to ankle brachial pressure index (ABPI) &lt;0.9/≥0.9

	ABPI <0.9 / ≥0.9	p
Age (yr)	71.2±8.9 / 65.6±10.1	ns
SBP mmHg	149±16.1 / 147±19.5	0.06
DBP mmHg	81.6±7.8 / 84.8±9.2	ns
BMI ≤30/>30 (kg/m <sup>2</sup> )	29.6±5.3 / 27.8±4.0	<0.05
Waist circumference (cm)	99±14 / 97±13	ns
≤88/>88(F)	105±12 / 101±11	
≤102/>102 (M)		
Proteinuria <30	20±29 / 19±40	ns
≥30	1276±1142 / 712±758	
LDL cholesterol (mg/dl)	112±35.9 / 119±34.8	ns
HDL cholesterol (mg/dl)	53.2±14 / 54.6±17	ns
Glycated hemoglobin (g/dl)	7.7±1.1 / 7.5±1.2	ns
NDI	2.2±1.0 / 1.7±1.2	0.06

ABPI: ankle brachial pressure index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; NDI: neuropathic diabetic index.

eral atherosclerosis. The ABPI is essentially a screening level assessment for anatomic PAD in the legs, and when <0.90, it is quite sensitive and specific for obstruction compared with a full vascular laboratory evaluation (30). A low ABPI is more prevalent in patients with CVD risk factors such as smoking, diabetes, and hypertension and is inversely correlated with other measures of vascular disease, including microalbuminuria (31) and carotid intima medial thickness (12, 22). Several studies have demonstrated that after adjusting for conventional CVD risk factors, a low ABPI is an independent predictor of cardiovascular risk in general population (9, 23, 32-35). The American Heart Association Prevention Conference V described the ABPI as a strong and independent risk factor for cardiovascular mortality and recommended it to be used to detect subclinical disease in the prevention of cardiovascular mortality and stroke (23). Among 165 patients undergone elective coronary angiography, an ABPI score <0.90 was shown to be related to the extent of CHD and was an independent predictor factor for cardiovascular events after adjustment for age, LDL cholesterol, carotid, and femoral IMT and Gensini score (36). Dieter and co-workers observed that 40 of 100 hospitalized patients with CHD had PAD at the ABPI evaluation. Patients with PAD were older, had a greater smoking history, and were more likely to have diabetes, hypertension, and dyslipidemia (37). The prevalence of ABPI score <0.90 in diabetic subjects ranged between 14 and 21% (38, 39). This rate increases with age but still remains higher in diabetic than in non-diabetic subjects (40). In Fremantle Diabetes Study, Norman and co-workers

found that an ABPI <0.90 was independently associated with an increased risk of cardiac death of 67% in Type 2 diabetic patients (41).

The present study highlights that an ABPI score lower than 0.90 is able to predict CHD occurrence in patients with Type 2 diabetes. This association is independent by age, gender, type of anti-diabetic treatment and the CVD risk factors evaluated in the multivariate model.

By a practical point of view, Type 2 diabetic patients with ABPI lower than 0.90 are at high risk of CHD and need to be carefully monitored to prevent myocardial infarction or other CHD events.

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