Association of Peripheral Arterial and Cardiovascular Diseases in Familial Hypercholesterolemia

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Abstract

Background: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease characterized by an elevation in the serum levels of total cholesterol and of low-density lipoproteins (LDL- c). Known to be closely related to the atherosclerotic process, FH can determine the development of early obstructive lesions in different arterial beds. In this context, FH has also been proposed to be a risk factor for peripheral arterial disease (PAD).

Objective: This observational cross-sectional study assessed the association of PAD with other manifestations of cardiovascular disease (CVD), such as coronary artery and cerebrovascular disease, in patients with heterozygous FH.

Methods: The diagnosis of PAD was established by ankle-brachial index (ABI) values ≤ 0.90. This study assessed 202 patients (35% of men) with heterozygous FH (90.6% with LDL receptor mutations), mean age of 51 ± 14 years and total cholesterol levels of 342 ± 86 mg/dL.

Results: The prevalences of PAD and previous CVD were 17% and 28.2 %, respectively. On multivariate analysis, an independent association between CVD and the diagnosis of PAD was observed (OR = 2.50; 95% CI: 1.004 - 6.230; p = 0.049).

Conclusion: Systematic screening for PAD by use of ABI is feasible to assess patients with FH, and it might indicate an increased risk for CVD. However, further studies are required to determine the role of ABI as a tool to assess the cardiovascular risk of those patients. (Arq Bras Cardiol. 2014; 103(2):118-123)

Keywords: Peripheral Arterial Disease; Atherosclerosis; Ankle Brachial Index; Type II Hyperlipoproteinemia.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease characterized by an elevation in the serum levels of total cholesterol and of low-density lipoproteins (LDL- c)[1]. That elevation results from the absence of specific LDL-c receptors and/or their reduction, due to a familial defect in apolipoprotein B or to defects in proprotein convertase subtilisin/kexin type 9 (PCSK9)[1,2]. Currently, 10 million people are estimated to have FH worldwide[3].

Known to be associated with elevated cholesterol concentrations and closely related to the atherosclerotic process, FH can determine the development of early obstructive lesions in different arterial beds and a substantial increase in the relative risk of death due to coronary disease[1,4]. In addition, FH has been proposed to be a risk factor for peripheral arterial disease (PAD)[5], which results from the narrowing and stiffening of arterial lumina in lower limbs, as part of the systemic atherosclerosis process[6,7]. In the general population, PAD has a high prevalence, being associated with a high risk for fatal and non-fatal cardiovascular events (death, myocardial infarction and stroke)[6,7]. In Europe and North America, 27 million people are estimated to have PAD, and that figure might be underestimated[8], because most patients are asymptomatic or do not have the classic symptom of the disease, intermittent claudication[9]. A Brazilian multicenter study has reported a 10.5% prevalence of PAD[10]. In that study, PAD was associated with the presence of diabetes *mellitus*, total and abdominal obesity, stroke and ischemic heart disease.

Considering PAD as part of the systemic atherosclerosis process[11], several authors are currently discussing including its screening in populations at high cardiovascular risk, such as individuals with FH[3]. The progression of atherosclerosis in different arterial sites in individuals with FH is not uniform; previous studies have not shown the association of coronary atherosclerotic disease with carotid or aortic disease, at least in subclinical presentation[12,13]. Conversely, there is evidence of the high prevalence of PAD in the population with FH[5]; however, data on the association of PAD with other manifestations of cardiovascular disease in those individuals still lack.

The present study systematically assesses the association of PAD with other manifestations of cardiovascular disease (CVD) and with risk factors, such as sex, age, systemic arterial hypertension, diabetes *mellitus*, smoking, lipid profile, glycemia and serum creatinine levels.

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Methods

This study was performed in the outpatient clinic of the Lipid Clinical Unit of the Instituto do Coração (InCor) of the Medical School of the Universidade de São Paulo, from July 2009 to July 2013. This study was approved by the Ethics Committee of the Hospital das Clínicas of the Medical School of the Universidade de São Paulo. All participants provided written informed consent.

Study design

This is an observational cross-sectional study.

Patients

This study assessed a convenience sample of patients undergoing consecutive consultation at that outpatient clinic from July 2009 to July 2013, who met the inclusion criteria and provided written informed consent.

The inclusion criteria were as follows: age > 18 years and heterozygous FH clinically diagnosed according to the Dutch Lipid Clinic Network (DUTCH MEDPED) criteria[14] or to the genetic determination of pathogenic mutation in the LDL receptor, PCSK9 or ApoB-100. The DUTCH MEDPED criteria are based on family and clinical history of early vascular/coronary disease, in the presence of xanthoma and corneal *arcus*, high plasma LDL-c concentrations, and the determination of mutation of genes that encode LDL receptors, Apo B-100 or PCSK9. According to those criteria, the diagnosis of FH is considered as follows: definitive, for a score > 8 points; probable, for a score between 6 and 8 points; and possible, for a score between 3 and 5 points.

Patients with the following characteristics were excluded from the study: score ≤ 5 points; any condition that made the ankle-brachial index (ABI) measurement impossible (amputation, extensive ulcerations, fractures or revascularization of lower and upper limbs); and individuals with ABI values > 1.40.

This study selected 220 patients clinically diagnosed with FH, 8 of whom refused to participate in the study, and 10 were excluded because the diagnosis of FH was classified as possible according to the DUTCH MEDPED criteria, yielding, thus, a sample of 202 individuals. Of the patients studied, 195 (96.53%) had a definitive diagnosis, and 7 (3%) had it probable. The presence of mutations in the gene that encodes the LDL receptor was found in 183 patients (90.6%). Mutations in neither PCSK9 nor ApoB-100 genes were found.

Definition of cardiovascular disease

The following were considered previous clinical cardiovascular disease: acute coronary syndrome (acute myocardial infarction or unstable angina); ischemic stroke; and myocardial revascularization. Those events were assessed from the patients' medical records and adjudicated by one of the study's participants.

Assessment of clinical parameters

The following clinical parameters were assessed: family antecedents of early coronary artery disease (CAD - positive when a male first-degree relative had CAD manifestations before the age of 55 years, or before the age of 65 years for women); smoking habit (any individual currently smoking or who smoked regularly in the past was considered a smoker); systemic arterial hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg and/or use of antihypertensive drugs); diabetes *mellitus* (fasting glycemia ≥ 126 mg/dL and/or previous use of oral hypoglycemic agents/insulin). In addition, the following parameters were assessed: weight; height; body mass index (BMI); abdominal circumference; blood pressure; xanthomas (clinically determined via inspection and palpation of Achilles tendons, elbows, knees, and extensor tendons of the hands, and considered positive in the presence of diffuse thickening and focal nodules)[15]; and corneal *arcus* (distinct pigmentation in the periphery of the cornea in individuals younger than 45 years was considered positive)[3].

Assessment of laboratory parameters

In this study, the lipid profiles (cholesterol total, HDL-c, LDL-c, triglycerides) were retrospectively obtained from the patients' medical records of the InCor HCFMUSP. Either baseline values (prior to treatment with lipid-lowering drugs, when available) or the highest values during the use of lipid-lowering drugs were considered. In addition, glycemia and serum creatinine levels were retrospectively obtained from the latest exam performed.

Assessment of ankle-brachial index

Two skilled observers assessed ABI by using a handheld vascular Doppler device with no graphic recording (10 MHz, Medmega, Brazil) and aneroid sphygmomanometer. The cuff size was selected based on the right arm circumference (AC), which was measured on the middle point between the acromion and the olecranon: AC < 25 cm, small size; AC 25-32 cm, medium; AC 32-42 cm, large; and AC > 42 cm, thigh size. Systolic blood pressure was measured twice on each limb, on the arms (brachial artery) and ankles (dorsalis pedis artery and posterior tibial artery), with the individual resting in the supine position. The ABI was calculated by dividing the higher systolic reading at the ankle (dorsalis pedis artery or posterior tibial artery) by the higher systolic reading in the arm (right or left brachial artery). An ABI value was calculated for each lower limb, and the lowest value was used for analysis.

Definition of PAD

Ankle-brachial index values ≤ 0.90 were considered diagnostic for PAD[16]. Absence of PAD was defined as ABI values between 0.91 and 1.40. Ankle-brachial index values > 1.40, although pathological, were excluded from this analysis, because they do not define the diagnosis of PAD.

Screening for intermittent claudication

Intermittent claudication was defined according to the Edinburgh Claudication Questionnaire criteria validated to Portuguese[17].

Statistical analysis

The continuous variables were presented as mean and standard deviation, and the categorical variables, as absolute and percentage numbers. The chi-square, Fisher exact and likelihood ratio tests were used to analyze the categorical variables. The quantitative variables were compared according to the presence of CVD by use of Student *t* test (variables with normal distribution) or Mann-Whitney test (variables without normal distribution). Multiple logistic regression model was used to assess whether, after adjusting for the remaining variables that influence the presence of CVD, the change in ABI (≤ 0.90) associated with the presence of CVD. The analyses were performed by using the 20.0 version of the SPSS software (SPSS Inc., Chicago, IL, United States), and the 5% significance level was adopted.

This is a substudy of the project that assesses the PAD prevalence in individuals with FH as compared with the normolipemic population. The calculation of the sample size considered an ABI prevalence < 0.9 in 20% and 10% of the populations with and without FH, respectively. Thus, 199 individuals with FH had to be included considering an 80% test power with 5% significance. To study the association of variables with the presence of CVD, 5-15 individuals with CVD were required for each variable, a criterion that was met in this study, totaling 57 individuals with FH and previous manifestation of CVD.

Results

An ABI prevalence ≤ 0.90 was observed in 17% of the total study population, 31.6% in the group with CVD and 11.7% in the group without CVD (Figure 1). Tables 1 and 2 show the clinical and laboratory data of patients with FH with or without ABI < 0.90. Their mean age was 51 years, and 35% were men. Total cholesterol was 342 mg/dL. It is worth emphasizing that 95% of the patients studied were on statins at the time of the study assessment. The prevalence of previous CVD was 28.2%. The individuals with a history of CVD had the following characteristics: older age; predominantly of the male sex; active or non-active smokers; hypertension; diabetes; higher prevalence of corneal *arcus*; higher diastolic blood pressure levels; lower serum levels of HDL-c; and higher serum levels of glucose and creatinine ($p < 0.05$ for all parameters). The groups did not differ regarding total cholesterol and LDL-c levels. On univariate analysis, CVD was 3.5 times more frequent among those with an altered ABI ($p = 0.001$).

On multivariate analysis, the following parameters were independently associated with CVD: age increase; smoking; systemic arterial hypertension; lower HDL-c levels; and higher serum creatinine levels (Table 3). An altered ABI was associated with a 2.5 times higher odds ratio for the presence of CVD after adjusting for confounding factors ($p = 0.049$).

Discussion

This study shows that the ABI can be used in a practical way to detect PAD in patients with heterozygous FH. An independent association of PAD, represented by an altered ABI, with previous manifestation of CVD was observed in patients with heterozygous FH. That association was observed even after adjusting for factors classically related to atherosclerotic disease, such as diabetes, smoking habit, and systemic arterial hypertension. High total cholesterol and LDL-c levels could not identify the presence of CVD in that population. However, HDL-c levels were inversely associated with the presence of CVD.

Although FH is characterized by the early and important elevation of serum LDL-c levels and that alteration is the major cause of atherosclerosis in individuals with that condition[1], there was no association of cholesterol levels with previously diagnosed CVD in this study population. The variables independently associated with the presence of CVD in this study were similar to the already established risk factors for CVD in a normolipemic population[18]. This might be explained by the fact that, because all patients had high total cholesterol and LDL-c levels, those parameters had no discriminatory power

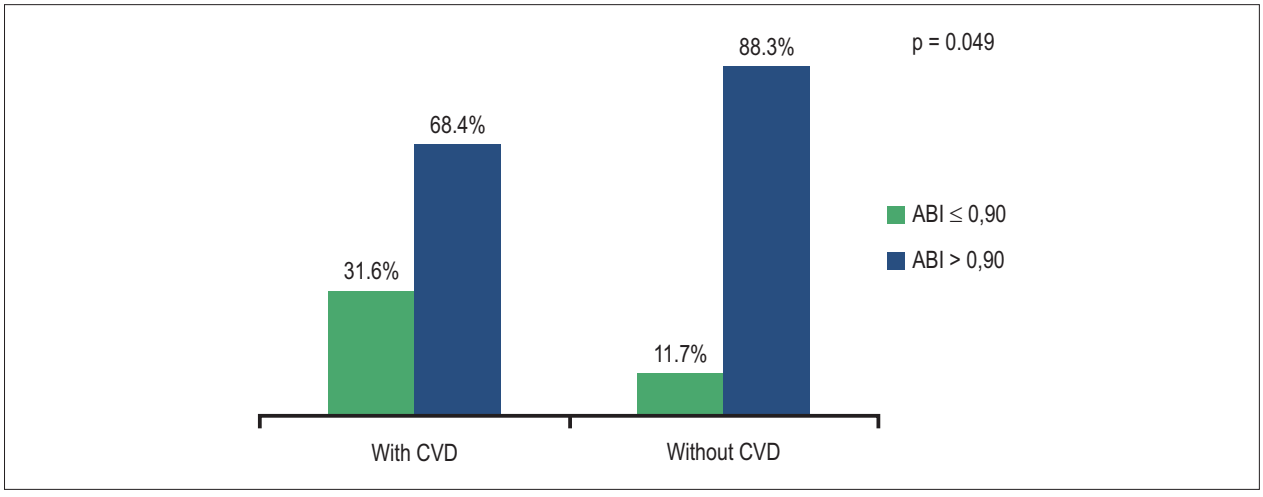

Figure 1 – *Prevalence of altered ankle-brachial index (ABI) in patients with and without cardiovascular disease (CVD - %).*

Table 1 – Univariate comparison of clinical parameters in individuals with familial hypercholesterolemia with and without previous cardiovascular disease (CVD)

Variable	Presence of CVD		OR (95% CI)	p
	No n = 145	Yes n = 57		
Age, years	48.2 (14.9)	57.6 (10.2)	1.05 (1.03-1.08)	< 0.001
Female sex, n (%)	103 (71)	28 (49.1)	0.39 (0.21-0.74)	0.004
Smoking, n (%)	40 (27.6)	31 (54.4)	3.13 (1.66-5.91)	< 0.001
SAH, n (%)	58 (40)	42 (73.7)	4.2 (2.14-8.26)	< 0.001
DM, n (%)	20 (13.8)	15 (26.3)	2.23 (1.05-4.75)	0.0370
Sedentary lifestyle, n (%)	88 (60.7)	36 (63.2)	1.11 (0.59-2.09)	0.746
Claudication, n (%)	19 (13.1)	13 (22.8)	1.96 (0.89-4.29)	0.093
BMI, kg/m^2	27.2 (4.6)	26.9 (4.6)	0.98 (0.92-1.05)	0.639
Xanthomas, n (%)	27 (18.6)	14 (24.6)	1.42 (0.68-2.96)	0.346
Corneal arcus, n (%)	32 (22.1)	28 (49.1)	3.41 (1.78-6.54)	< 0.001
ABI ≤ 0.90, n (%)	17 (11.7)	18 (31.6)	3.47(1.64-7.38)	0.001

Results of the chi-square, Student t and Mann-Whitney tests.
CVD: cardiovascular disease; DM: diabetes mellitus; SAH: systemic arterial hypertension; CI: confidence interval; BMI: body mass index; ABI: ankle-brachial index; OR: odds ratio. Continuous variables were expressed as mean (standard deviation).

Table 2 – Univariate comparison of laboratory parameters in individuals with familial hypercholesterolemia with and without previous cardiovascular disease (CVD)

Variable (mg/dL)	Presence of CVD		p
	No n = 145	Yes n = 57	
Total cholesterol	338 (81)	332 (103)	0.676
HDL-c	48 (12)	42 (12)	0.002
LDL-c	258 (78)	255 (103)	0.843
Triglycerides	133 (55)	147 (70)	0.163
Glucose	101 (22)	114 (48)	0.028
Creatinine	0.88 (0.12)	1.07 (0.56)	< 0.001

Data expressed as mean (standard deviation). CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 3 – Clinical and laboratory parameters related to the presence of cardiovascular disease in patients with familial hypercholesterolemia according to the multiple logistic regression model

Variable	OR (95% CI)	p
Age, years	1.05 (1.01-1.08)	0.010
Smoking	2.43 (1.12-5.28)	0.024
SAH	2.73 (1.17-6.36)	0.020
ABI ≤ 0.90	2.50 (1.004-6.225)	0.049
HDL-c (mg/dL)	0.95 (0.91-0.99)	0.008
Creatinine, (mg/dL)	1.62 (1.24-2.12)	< 0.001

SAH: systemic arterial hypertension; ABI: ankle-brachial index; HDL: high-density lipoprotein; CI: confidence interval; OR: odds ratio calculated to the 0.1-mg/dL increase.

to identify previous CVD. Obviously, the cross-sectional nature of this study, the use of statins by most patients, and not calculating the cholesterol burden throughout life, measured by the product "cholesterol X age", limit the value of that result.

Although the common process for the occurrence of PAD and other manifestations of CVD is atherosclerosis, previous studies have shown that there was no agreement between coronary atherosclerotic disease and carotid disease, at least in its subclinical form, in individuals with heterozygous FH previously studied by our team[12,13]. This suggests that atherosclerosis manifests differently in different arterial beds.

The association between PAD and previous CVD, even after adjusting for risk factors, such as diabetes, smoking habit, systemic arterial hypertension and low HDL-c levels, suggests that the presence of PAD can indicate a higher risk for cardiovascular events. The elevated prevalence of PAD in this study population, almost one in every five patients, suggests that the systematic screening for that disease by use of ABI can be useful for risk stratification of severe manifestations of atherosclerotic disease, such as CAD and cerebrovascular disease. Comparing that prevalence with that of individuals without FH, our results are consistent with data from a systematic review of small studies using different methodologies to detect PAD, in addition to ABI. That review has suggested that PAD is 5-10 times more frequent in individuals with FH than in controls without that disease[5].

Can PAD predict coronary and cerebrovascular events in patients with FH?

Although FH is clearly associated with early atherosclerotic disease, the course of clinical manifestations of the latter in individuals with FH varies. Many individuals will not have CVD, although exposed to high cholesterol levels for long periods[13,19]. Thus, PAD seems to depend on other factors, such as age, smoking habit, arterial hypertension and diabetes, to have manifestations other than elevated cholesterol levels[9].

The ABI is a specific marker of PAD, its alteration being associated with the risk of clinical manifestation of CVD and mortality in prospective studies[20]. However, it is worth noting that the present study has a cross-sectional design, which did not allow the confirmation of an association between PAD and the risk for cardiovascular events in FH. Thus, we cannot state that, in the long run, altered ABI values with consequent diagnosis of PAD will or will not indicate a higher risk for coronary or cerebrovascular events in the population with FH, as already reported for the normolipemic population[20,21]. That would require showing that systematic ABI measurement could discriminate and reclassify the risk for cardiovascular events in that population[21]. Prospective and longitudinal studies are necessary to determine the role of PAD detection as a predictor of the risk for cardiac and cerebrovascular events in heterozygous FH.

Study limitations

This cross-sectional study demonstrated only the association between PAD and previous CVD in patients with FH. The retrospective data collection from medical records might have led to bias in standardizing data registration, mainly regarding lipid profile values. Similarly, the use of statins by most patients did not allow calculating the cholesterol burden throughout life. Conversely, this was the first study that systematically assessed the ABI in a large population with a high likelihood of being diagnosed with FH.

Conclusions

An independent association of an altered ABI with the previous manifestation of DCV in individuals with heterozygous FH was found. This study results show that ABI can be used in a practical way to detect asymptomatic PAD. However, further studies are required to determine the role of ABI as a tool to assess the risk of cardiovascular events in individuals with FH.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Pereira C, Miname M, Makdisse M, Santos RD; Acquisition of data: Pereira C; Statistical analysis: Pereira C, Miname M, Santos RD; Writing of the manuscript: Pereira C, Miname M, Makdisse M, Santos RD; Critical revision of the manuscript for intellectual content: Pereira C, Miname M, Makdisse M, Kalil Filho R, Santos RD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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