Reduced high-density lipoprotein cholesterol: A valuable, independent prognostic marker in peripheral arterial disease

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ABSTRACT

Objective: The prognosis of patients with peripheral arterial disease (PAD) is characterized by an exceptionally high risk for myocardial infarction, ischemic stroke, and death; however, studies in search of new prognostic biomarkers in PAD are scarce. Even though low levels of high-density lipoprotein cholesterol (HDL-C) have been associated with higher risk of cardiovascular (CV) complications and death in different atherosclerotic diseases, recent epidemiologic studies have challenged its prognostic utility. The aim of this study was to test the predictive value of HDL-C as a risk factor for ischemic events or death in symptomatic PAD patients.

Methods: Clinical and demographic parameters of 254 symptomatic PAD patients were recorded. Amputation, ischemic coronary disease, cerebrovascular disease, and all-cause mortality were recorded during a mean follow-up of 2.7 years.

Results: Multivariate analyses showed that disease severity (critical limb ischemia) was significantly reduced in patients with normal HDL-C levels compared with the group with low HDL-C levels (multivariate analysis odds ratio, 0.09; 95% confidence interval [CI], 0.03-0.24). A decreased risk for mortality (hazard ratio, 0.46; 95% CI, 0.21-0.99) and major adverse CV events (hazard ratio, 0.38; 95% CI, 0.16-0.86) was also found in patients with normal vs reduced levels of HDL-C in both Cox proportional hazards models and Kaplan-Meier estimates, after adjustment for confounding factors.

Conclusions: Reduced HDL-C levels were significantly associated with higher risk for development of CV complications as well as with mortality in PAD patients. These findings highlight the usefulness of this simple test for early identification of PAD patients at high risk for development of major CV events. (J Vasc Surg 2017;■:1-7.)

The prognosis of patients with peripheral arterial disease (PAD), considered atherosclerotic occlusive disease of the lower extremities, is characterized by an exceptionally high risk for myocardial infarction, ischemic stroke, and death.[1-3] This is true for all PAD stages, besides the probability of deterioration of leg symptoms,[4] although 1-year mortality, which can be as high as 25% in patients with critical limb ischemia (CLI), might rise to 45% in subjects undergoing amputation.[5] The current challenge remains in the identification of markers able to discover patients who are at great risk for cardiovascular (CV) events before clinical syndromes develop as traditional atherosclerosis factors, such as diabetes mellitus, cigarette smoking, advanced age, hyperlipidemia, and hypertension, are poor predictors of ischemic events and mortality in lower limb arterial disease.[6]

Disorders of lipoprotein metabolism, in particular plasma triglycerides and reduced high-density lipoprotein cholesterol (HDL-C) levels, are established risk factors for CV diseases.[7,8] Numerous studies have shown that HDL-C levels are inversely associated with the development of atherosclerosis in patients free of CV disease[9] and with the risk of future events in the setting of secondary prevention.[7,10] This has recently been challenged by clinical trials showing that the inverse relationship of HDL-C levels with CV mortality was weaker in patients with established coronary artery disease (CAD) than in those without CAD.[11,12] The role of HDL-C as a prognostic marker of worse outcome in PAD is still unclear as few reports address this issue,[9,13] and in some, the definition of PAD might include abdominal aortic aneurysm and lower limb atherosclerosis subjects in the same group.[14] It has been suggested that the type of vascular disease

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and the extent of atherosclerosis can influence the relations between lipids and the risk of recurrent events.[15] Therefore, we decided to evaluate, first, the association between HDL-C levels and PAD severity, restricted to patients with atherosclerotic occlusive disease of the lower extremities, and second, the utility of HDL-C as a prognostic marker for the prediction of major adverse CV events (MACEs) and mortality in PAD.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, prospective, nonrandomized study
- **Take Home Message:** In 254 peripheral arterial disease patients with a mean follow-up of 2.7 years, there was a significant association between low high-density lipoprotein cholesterol levels and increased risk of cardiovascular complications and mortality.
- **Recommendation:** This study suggests a simple test, measurement of high-density lipoprotein cholesterol, to predict increased risk of mortality and cardiovascular complications in peripheral arterial disease patients.

METHODS

Baseline characteristics of patients. Patients (N = 254; mean age, 71 years (standard deviation [SD], 11 years); 88% men) were prospectively enrolled and blood samples collected at the time of clinical evaluation at the outpatient service of the Department of Vascular Surgery of the Complejo Hospitalario de Navarra between 2010 and 2016. No patient was included postoperatively. Patients were classified according to the severity of the disease into intermittent claudication (Fontaine class II, n = 139) diagnosed by hemodynamic study (Doppler ultrasound) and CLI (n = 115) with lower limb rest pain or trophic lesions (Fontaine class III-IV) confirmed by imaging studies (arteriography, magnetic resonance angiography, or ultrasound). Among those patients belonging to Fontaine class IV, the ones with infected lesions were excluded from the study, as were individuals who had evidence of neoplastic disease, had generalized or localized inflammatory disease (moderate or severe), had severe chronic kidney disease, were on hemodialysis, or were receiving anti-inflammatory drugs. Ankle-brachial index (ABI) was measured at rest, per standard technique, in the dorsalis pedis and posterior tibial arteries of both lower limbs. Patients were classified as high ABI with values ≥1.4 or noncompressible arteries.[16]

A thorough medical history was recorded for all patients, including details of previous myocardial infarction, nonischemic cardiomyopathy, arterial hypertension, cerebrovascular disease, smoking status, diabetes mellitus, body mass index (BMI), and medication. Patients were considered smokers (at least one cigarette daily on average during the past year), never smokers, and former smokers (no cigarette consumption in the past year). Diabetes was defined by history of diabetes mellitus or the use of antidiabetic drugs. Hypertension was defined by any history of hypertension or the use of antihypertensive drugs.

Follow-up. Patients were followed up for a mean period of 2.7 years (SD, 2.01 years) at the outpatient service of the Department of Vascular Surgery every 3 or 6 months, depending on the severity of PAD. At recruitment, patients were tested for biochemical parameters and underwent physical examination and ABI assessment. No patient was lost to the follow-up. For outcome evaluation of PAD patients, CV events and death were recorded at the exact date of the event. MACEs were defined, including amputation, ischemic coronary disease, cerebrovascular disease, and all-cause mortality as a composite end point.

The study was approved by the Institutional Review Board of the Complejo Hospitalario de Navarra, according to the standards of the Declaration of Helsinki on medical research, and written informed consent was obtained from all patients who were enrolled in this study.

Laboratory analysis. Serum total cholesterol, HDL-C, triglycerides, and glucose were measured in fasting blood samples by standard laboratory techniques. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald equation.

Statistical analysis. Continuous variables are presented as mean and SD. Categorical variables are presented as percentages. HDL-C levels were categorized in two groups based on the consensus for metabolic syndrome[17]: reduced HDL-C for <40 mg/dL in men and <50 mg/dL in women; and normal HDL-C for levels above those cutoffs.

Logistic regression models were used to assess the relationship between HDL-C and PAD severity after adjusting for relevant covariates (age, sex, BMI, creatinine concentration, cigarette smoking, diabetes mellitus, hypertension, LDL levels, triglyceride levels, high ABI, PAD severity, former history of chronic obstructive pulmonary disease, chronic kidney disease, acute myocardial infarction, cardiomyopathy and cerebral ischemia, and pharmacologic treatment [including anticoagulants, antiplatelets, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium antagonists, and statins]); odds ratios (ORs) and respective 95% confidence intervals (CIs) were obtained. Hazard ratios (HRs) and their 95% CIs for MACE and death were estimated using Cox regression models after adjusting for relevant covariates. Results of this analysis are displayed graphically as Kaplan-Meier survival plots adjusted by the inverse