Association of Cholesterol Subfractions and Carotid Lipid Core Measured by MRI

To the Editor:

A strong relationship exists between cholesterol and atherosclerosis,1 with low density lipoprotein (LDL) being a major risk factor.2 However, 50% of patients with acute coronary events have “normal” cholesterol, and 75% patients with premature coronary heart disease (CHD) have normal LDL.3 Thus, contribution of other lipoproteins has been explored. High density lipoprotein (HDL), comprised primarily of 2 subfractions, HDL$_{3}$ (large buoyant) and HDL$_{2}$ (small dense), has a protective role in CHD.4,5 LDL can be dense or buoyant, and dense LDL is highly atherogenic, associated with 4-fold increased CHD risk.6 Lipoprotein, [Lp(a)], is a strong risk factor for CHD and stroke.7

MRI can noninvasively visualize arterial wall remodelling and atherosclerotic plaque components (lipid core, fibrous cap, and calcium).8,9 However, in vivo relationships between plaque components and cholesterol subfractions have not been demonstrated in humans. We examined in vivo relationship between cholesterol subfractions and atherosclerotic plaque, measured by MRI, in internal carotid arteries (ICA) of atherosclerotic patients.

This was an exploratory cross-sectional study of consecutively enrolled initial 28 patients who were part of an ongoing randomized trial testing the effects of extended release Niacin versus placebo treatment on top of baseline therapy on carotid plaque regression, analyzed at baseline. All patients signed written informed consent and had documented atherosclerosis in at least one vascular territory: >3.9 mm aortic atherosclerosis on transesophageal echocardiography, >50% lesion in one coronary artery at cardiac catheterization, >50% carotid lesion on ultrasound or peripheral arterial disease (PAD). We excluded patients with pacemakers, defibrillators, aneurysm clips, elevated liver transaminases (>2 X normal), significant medical event within 3 months, decompensated heart failure, or inability to consent. The types and dosages of statins, alcohol intake, and abdominal girth were recorded. To account for different statins, a dose standardization model was developed (10 mg Atorvastatin = 20 mg Simvastatin = 40 mg Pravastatin = 80 mg Fluvastatin).10

After an overnight fast, patients had chemistries and lipid profile drawn. Subsequently, serum was separated, frozen at −70°C, and analyzed by ultracentrifugation for cholesterol subfractions [HDL$_{2}$, HDL$_{3}$, Dense LDL, Lp(a)] using the validated11,12 vertical auto profile II technique by a certified laboratory (Atherotech, Inc.).

On the same day, an MRI was performed on a 1.5-T magnet (GE Healthcare) using a dual 3-inch immobilized surface coil.9 Images from 5 randomly selected patients were reanalyzed by a certified radiologist (Atherotech, Inc.) using customized software (University of Leiden, The Netherlands). High resolution MR images of the right internal carotid artery (ICA) of a 70-year-old man with advanced atherosclerosis. T1-weighted (A), T2-weighted (both precontrast; B) and T1 weighted (postcontrast; C) fast spin echo images of the right internal carotid artery demonstrating arterial wall remodelling caused by atherosclerotic plaque (AP). Note the lipid core (LC) within the atherosclerotic plaque on T2-weighted and postcontrast T1-weighted images. L indicates lumen.

Univariate regression analyses relating vessel wall volume and serum dense LDL, triglycerides, Lp (a), HDL$_{2}$, HDL$_{3}$, and HDL were not significant (r = −0.19, 0.21, −0.05 to 0.2, −0.13 and −0.2, respectively). A significant relationship existed between ICA lipid core volume and total HDL (r = −0.5, P = 0.01) as well as HDL$_{3}$, (r = −0.57, P = 0.003). The association between lipid core and HDL$_{2}$ was borderline significant (r = −0.35, P = 0.08) and not significant for dense LDL, Lp(a), or triglycerides (r = −0.14, −0.002, and −0.13). Multivariate analysis revealed significant relationships between lipid core and total HDL (adjusted R$^2$ = 58% for the model, P for HDL$_{2}$ <0.05) and HDL$_{3}$, (adjusted R$^2$ = 63% for the model, P for HDL$_{3}$ <0.001) and nonsignificant with HDL$_{2}$ (adjusted R$^2$ = 50% for the model, P for HDL$_{2}$ = 0.29) and other cholesterol subfractions. The ICCs for intraobserver and interobserver concordances for vessel wall volume (0.93 and 0.83, respectively) and lipid core volume (0.90 and 0.93, respectively) by MRI were high.

Our preliminary findings demonstrate a significant inverse association between lipid core measured in vivo by MRI and serum HDL and HDL$_{3}$ in patients with advanced atherosclerosis. There was no association between lipid core and other cholesterol subfractions, including HDL$_{2}$. HDL$_{2}$ is thought to be more effective than HDL$_{3}$ in inhibiting LDL oxidation, a major determinant of atherosclerosis progression and lipid core.16 However, it is possible that some findings were affected by small sample size and baseline statin usage. Further longitudinal studies are needed to elucidate the role of cholesterol subfractions in atherosclerosis.

Acknowledgments

This work was supported by the National Institutes on Aging RO1-AG021570-01 grant, and by the Johns Hopkins Reynolds Cardiovascular Center, D.W. Reynolds Foundation. The authors thank R.J. Van der Geest, PhD for providing us with the vesselmass software used for analysis of the MR data. The authors also thank Tramaine Marshall for her help with MR image analysis for assessment of reproducibility.

The study population consisted of 21 males and 7 females (mean age 73±4 years, 77% hypertensives, 27% diabetics, 20% smokers, 34% with a history of stroke, 31% with history of myocardial infarction, 12% with PAD, and 70% with regular alcohol intake). Twenty four patients took baseline statins (12 Atorvastatin, 5 Simvastatin, 4 Pravastatin and 3 Fluvastatin). Mean abdominal girth was 39±5 inches, systolic blood pressure 131±17 mm Hg, and heart rate was 69±17 beats. Mean cholesterol subfraction values (mg/dL) were: total HDL 49±11; HDL$_{3}$, 11±5; HDL$_{2}$, 37±7; LDL, 86±25; Dense LDL, 49±15; Lp(a), 6.4±2.4; and triglycerides, 137±104.

Mean vessel wall and lipid core volume of ICA were 0.45±0.11 cm$^3$ and 0.03±0.03 cm$^3$, respectively.

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Arterioscler Thromb Vasc Biol. 2005;25:e110-e111
doi: 10.1161/01.ATV.0000166599.78182.6c
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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