Low-Density Lipoprotein Cholesterol, Hypertension, Diabetes, but Not High-Density Lipoprotein Cholesterol as Predictors of Acute Coronary Syndrome in Northern Area of Japan: A Case-Control Study

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**Background:** Recent rapid change in life style has resulted in a gradual increase in coronary heart disease (CHD) in Japan, although its incidence is still one fourth of that in US. Mean total cholesterol (TC) level in Japan, for example, was far less than that in US 20 years ago, but now mean TC of Japanese females surpasses that of American females. However, since the chronological accumulation of such a risk factor (RF) in Japan is still lighter than that in US and Europe, RFs for CHD in Japan may differ.

**Method:** We conducted a retrospective case-control study enrolling 722 Japanese patients who suffered their first acute coronary syndrome (ACS) and were transferred to 24 hospitals in the northern island of Japan. As controls, 1748 age-, sex- and residence-matched subjects were randomly picked up from a data base of one regional health check-up organization. We assessed associations between premorbid variable and the RFs of HDL by conditional logistic regression analysis. Result: The most important predictor of ACS in men was low HDL cholesterol (C) (odds ratio, OR: 6.159, p<0.001). History of hypertension (HT) and that of diabetes (DM) were also independent RFs (OR: 2.727, p<0.001 and OR: 1.815, p<0.001, respectively). On the other hands, in women, HT was the most important RF (OR: 5.787, p<0.001). Low HDL-C, hyperglycemia and DM were also independent RFs (OR: 3.427, p<0.01, OR: 2.298, p<0.05 and OR: 2.42, p<0.05, respectively). However, OR of high TC was significantly less than 1.0 and, of that high LDL-C was not different from unity in both sexes. The reason why TC and LDL-C were not independent predictors of ACS in the present subjects was because there were many ACS patients whose TC and LDL-C were normal; however, of note, their HDL-C was low. Thus, in Japanese northern area, low HDL-C, HT, DM and hyperglycemia representing metabolic syndrome, were significant predictors of ACS. Conclusion: The present results indicate the importance of metabolic syndrome as the cause of CHD in the population whose LDL-C has not been high, and would further imply the future tendency of CHD risks in US and Europe where recent nutritional education programs for general population to lower LDL-C have been effective.

High-Density Lipoprotein-Mediated Cholesterol Efflux From Cells Is a Strong Independent Predictor of Cardiovascular Risk

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**Background:** Low levels of high density lipoproteins (HDL) are recognized as a risk factor for coronary artery disease (CAD), presumably related to the ability of HDL to mediate reverse cholesterol transport from cells. We aimed to determine whether this function of HDL was related to the presence of CAD or predicts a primary combined endpoint (CE), death, myocardial infarction, unstable angina, revascularization or stroke) or all-cause mortality (MAC).

**Methods:** 129 men (mean age 62.6 years) undergoing coronary angiography at the Miami VA Medical Center (10/98 - 05/99) were prospectively followed for 3 years. Blood samples were analyzed for lipid, lipoproteins and CRP levels. ATP binding cassette transporter 1 (ABCA-1) dependent cholesterol efflux was defined as the ability of serum to decrease the pool of cholesterol available for esterification by the acylCoA:cholesterol acyltransferase reaction after incubating cultured fibroblasts with medium containing 2% patient serum for 6 hours.

**Results:** 65% of patients had CAD and about 1/3 smoked or had diabetes. Efflux did not correlate with HDL levels or the presence of CAD. The mean follow up time was 1047 ± 42 days. 41% of patients reached the CE and 19% died. Patients in the highest efflux tertile had significantly higher risk of reaching the CE (p=0.007; HR = 1.57; 95%CI 1.12-2.2). Efflux was also predictive of MAC (p<0.001; HR: 2.27; 95%CI 1.21-4.3). After correction for age, body mass index, blood pressure, ejection fraction, smoking, diabetes, family history of CAD, triglyceride, HDL, LDL, CRP, apoA1, apoAII, apoB, and statin use, efflux remained predictive of the CE (p<0.001; HR: 3.19 95%CI 1.91-5.43) and MAC (p=0.006; HR:2.60; 95%CI 1.12-1.06). Stepwise Cox Regression Analysis selected the efflux tertile (p<0.001; HR: 1.94 9.4-2.38), HDL (p<0.001; HR: 1.61 99.26-2.06) and LDL cholesterol (p=0.14) as independent predictors of the CE.

**Conclusions:** Oxidized, an in vitro measure of HDL function, was a strong, independent adverse predictor of cardiovascular events and ACM. This predictive value is independent of classical risk factors, HDL lipid or apoprotein levels.

The Role of Triglycerides, Very Low-Density Lipoprotein, and Triglyceride Rich Atherogenic Lipoprotein in Predicting Premature Heart Disease

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**Background:** Meta-analysis of prospective studies indicates that triglycerides are independently predictive of coronary artery disease (CAD). The role of triglycerides may be more important in this era of increasing rates of obesity. We previously reported that current guidelines based on LDL cholesterol under-estimate disease risk in young adults. Our population was characterized by high rates of obesity and the role of triglyceride rich atherogenic lipoproteins was not examined.

**Objective:** To determine the role of triglyceride rich atherogenic lipoproteins in young adults evaluated for primary prevention.

**Method:** Young adults without any history of CAD or statin therapy undergoing elective coronary angiography were prospectively studied. Fasting blood samples were sent for lipid and advanced lipoprotein testing (LipoScience, Inc.). Framingham risk scores were calculated for each subject. CAD was defined as stenosis ≥ 50%.

**Results:** 254 young men and women, mean age 53 ± 6 were enrolled. Group 1 had CAD (n=73), Group 2 no CAD (n=181). Mean total (202 versus 193 mg/dL), LDL (128 versus 120 mg/dL), and HDL cholesterol (49 versus 53 mg/dL) were similar in group 1 and group 2. In contrast, triglyceride (170 versus 138 mg/dL, p = 0.002), VLDL (132 versus 140 mg/dL, p=0.003), large VLDL (68 versus 46 mg/dL, p=0.01), and VLDL particle concentration (4.5 versus 4.6, p=0.02) were significantly higher in group 1 compared to group 2. The odds ratios (OR) and confidence intervals (CI) for subjects in the highest as compared with the lowest quartile were as follows: triglyceride-2.5 (CI: 1.2-5.4, p=0.002), VLDL-2.5 (CI: 1.2-5.4, p=0.002), VLDL particle concentration- 2.3 (CI: 1.1-4.9, p=0.04), and large VLDL-2.4 (CI: 1.1-5.0, p=0.02). Large VLDL-CR (OR: 2.9, CI: 1.6-5.4) was the only independent predictor of CAD in the multivariate model.

**Conclusion:** In the evaluation of young adults in a population with high obesity rates, triglycerides and triglyceride rich atherogenic lipoprotein may be valuable in risk assessment.