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Low High-Density Lipoprotein Cholesterol, Hypertension, Diabetes, but Not High Low-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 of 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 pre-morbid variable and the RFs of ACS 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: 5.767, p<0.001). Low HDL-C, hypertriglyceridemia 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, that of high LDL-C was not different from unity in both sexes. The reason why TC and LDL-C did not become the 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 hypertriglyceridemia, 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.

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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 (ICE), death, myocardial infarction, unstable angina, revascularization or stroke) or all-cause mortality (ACM).

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

69% 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 1.12-2.22). Efflux was also predictive of ACM (p=0.009; HR 2.27; 95%CI 1.21-4.23). After correction for age, body mass index, blood pressure, ejection fraction, smoking, diabetes, family history of CAD, triglyceride, HDL, LDL, CRP, apoA-I, apoA-II, apoB, and statin use, efflux remained predictive of the CE (p<0.0001; HR 3.19 95%CI 1.91-5.34) and ACM (p=0.006; HR=2.60; 95%CI 1.12-1.06). Stepwise Cox Regression Analysis selected the efflux tertile (p<0.0001; HR 2.63 95%CI 1.69-4.08), CRP (p=0.0001; HR=1.61 95%CI 1.26-2.06) and LDL cholesterol (p=0.14) as independent predictors of the CE.

Conclusions

Cholesterol efflux, 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.

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The Role of Triglycerides, Very Low Density Lipoproteins, 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 cur-

rent 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 ± 8 were enrolled. Group 1 had CAD (n=73). Group 2 had 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 (133 versus 102 mg/dL, p=0.003), large VLDL (68 versus 46 mg/dL, p=0.01), and VLDL particle concentration (79 versus 69 mg/dL, p=0.01) were significantly higher in group 1 versus 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=0.02), VLDL-2.5 (CI: 1.2-5.4, p=0.02), 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 (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.

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Impaired Reverse Cholesterol Transport in Asian Indian Males Compared With Females Assessed by Nuclear Magnetic Resonance Spectroscopy

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Background: Asian Indian (AI) males have higher incidence of CAD compared to females. Large size HDL (LHDL) offers CAD protection and reflects reverse cholesterol transport. Heterogeneity with respect to size, density & composition of HDL may explain higher incidence of CAD in males. **Methods:** Cohort: 407 relatively healthy AIs. Nuclear Magnetic Resonance Spectroscopy (NMRS) was used to determine the concentrations of 5HDL subclasses of different particle sizes. HDL was subdivided in two categories, LHDL & Small HDL. Subjects (n=77) on anti-lipid, thyroid or hormone replacement therapy were excluded. **Results:** Among remaining 330 subjects, 119 (mean age 48±11) were females and 211 (mean age 50±11) were males. CAD was twice as common in males, 8% compared to 3.8%. Risk factors for CAD were similar in both genders: Age, DM, HTN, h/o high cholesterol, & smoking. Total cholesterol (205 ± 39 vs. 209 ± 40, p=0.38) & LDL cholesterol (135 ± 31 vs. 137 ± 33, p=0.58) were nearly identical. HDL by NMRS are tabulated. **Conclusions:** Despite twofold higher CAD among AI males, both genders AIs have similar risk factors for CAD, total cholesterol & LDL levels. However males exhibit significantly impaired reverse cholesterol transport as reflected by significantly lower HDL concentrations, smaller HDL particle sizes, reduced levels of LHDL & higher levels of Small HDL, which may partly explain higher rates of CAD among males. Further studies are warranted to determine that these differences can be extended to other race, sex groups.

| | HDL lipoproteins by NMRS | | |
|----------------------------------|--------------------------|------------------|------------|
| HDL by NMRS | Males (N = 211) | Females (N =119) | P Value |
| HDL Levels (mg/dl) | 40.7 ± 9.7 | 52.5 ± 12.1 | <0.0001 |
| HDL Size (nm) | 8.5 ± 0.31 | 8.9 ± 0.35 | <0.0000001 |
| LHDL Levels (mg/dl) (H3+H4+H5) | 21.4 ± 13.9 | 38.3 ± 15.0 | <0.0000001 |
| Small HDL Levels (mg/dl) (H1+H2) | 19.7 ± 6.5 | 14.8 ± 6.7 | <0.0000001 |

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Long-Term Effectiveness of the Management of Dyslipidemia With a Planned Strategy of Management

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Background: Despite unequivocal reduction in mortality/morbidity with lipid lowering therapy (LLT) in patients with coronary artery disease (CAD), a substantial proportion remain un/under-treated. A previous study demonstrated the short-term effectiveness of a planned strategy of management using a cardiac rehabilitation nurse (CRN) as an integral mediator in achieving the recommended goals in dyslipidemia.

Methods: Pts with CAD enrolled in the cardiac rehabilitation program (CRP) had their lipid profiles arranged and followed by the CRN with up-titration of drugs to achieve an LDL less than 2.6mmol/l. Pts received a booklet tabulating their lipid values with the goals (for LDL, HDL etc) identified, as well as instructions to follow these up with their family physicians. Pts were contacted 12-18 months later. All data were collected prospectively.

Results: Of the 1100 consecutive pts (M=864; F=236; Age- Mean 60.0±0.1 SEM yrs; H/O AMI=24.5%; DM=20.4%; HT=44.0%; F/H of CAD=38.3%), 1040 pts (94.5%) were contacted 15.5±0.4 months after completion of the CRP. 60 pts (5.5%) could not be contacted despite numerous attempts. 867 pts (83.4%), 793pts(78.7%), 580pts(57.7%), 936 pts (92.8%) and 159pts(15.8%) were on LLT, beta-blockers, ACE-inhibitors, ASA and calcium antagonists respectively.

Conclusions: A planned strategy of management using a CRN is effective in achieving lipid targets and the appropriate use of medications on a long-term basis. However attempts at weight reduction appear sub-optimal