High density lipoprotein cholesterol in coronary artery patients: is it as low as expected?

Koroner arter hastalarında yüksek dansiteli lipoprotein kolesterol: Beklendiği kadar düşük mü?

In the December 2005 issue of the Anatolian Journal of Cardiology, Uzunlulu and colleagues (1) reported high density lipoprotein cholesterol (HDL-C) levels in a series of 420 men and women, 40 years or older, who underwent coronary arteriography to establish the presence or absence of any atherosclerotic lesions. This test was used to classify individuals as coronary artery disease ("CAD") or "non-CAD" patients. The article raises a critical question: do Turks really have low HDL-C?

Studies were done to assess each patient's risk factor status including age, gender, blood pressure, smoking habit, and fasting levels of glucose and lipids. There was a significant difference ($p<0.05$) in fasting glucose levels between the CAD and non-CAD groups (111±40 mg/dl vs. 122±50 mg/dl, respectively), and the average values of both groups were in the impaired range (≥100-125 mg/dl). The CAD patients had an average total cholesterol level that was 10 mg/dl greater than the non-CAD group. This difference was primarily due to the higher levels of very low density lipoprotein cholesterol in the CAD group (34 mg/dl) than in the non-CAD group (25 mg/dl) as assessed by the Friedewald equation (very low density lipoprotein cholesterol = triglyceride level/5). The average levels of low density lipoprotein cholesterol were not different between the groups. The HDL-C levels were slightly lower in the CAD group vs. the non-CAD group (45±11 mg/dl vs. 48±9 mg/dl, $p<0.05$). The authors correctly point out that lower average HDL-C levels of the CAD group would be expected to be responsible to some extent for the presence of CAD. The most interesting point of the paper is the authors' conclusion that the average HDL-C levels of these CAD and non-CAD patients were in the 45-48 mg/dl range, values that are substantially higher than the mean levels of HDL-C (36 mg/dl for men; 42 mg/dl for women) determined in large, population-based studies of the Turkish people. What accounts for these relatively high HDL-C levels, especially in the CAD patients?

Numerous well-controlled studies have established that Turks have uniquely low HDL-C (males, 32-38 mg/dl; females, 37-46 mg/dl), including data from large surveys of the population in Turkey (2-12) and of Turks living in other countries (3, 13, 14). In our studies, the conclusion that Turks have low HDL-C did not rely only on measurements of HDL-C. We demonstrated that Turks have a significant reduction in apolipoprotein AI (the major apoprotein of HDL) and in the HDL2 and LpAI subclasses of HDL (4). Furthermore, Turks have hepatic lipase levels that are elevated by 25-30% compared to controls in the United States, and these high levels of hepatic lipase serve as a surrogate established by many studies as predictive of low HDL-C (3). Recently, extensive family studies have shown that the heritability of HDL-C is 80% in Turks, a genetic predisposition far greater than seen in other populations (15). Furthermore, a genome-wide scan linked low HDL-C in Turks to a locus at chromosome 15q22 in the vicinity of the hepatic lipase gene (15).

There are several methodological issues that may explain the discrepancy between the HDL-C levels of the subjects in this study and those reported in the epidemiologic studies. First, it is important to know the conditions under which the fasting blood samples were obtained. The authors excluded patients with a recent myocardial infarction (within two months prior to phlebotomy), but we are not told if the study subjects were hospitalized because of their angiographic procedure or if they were sampled as outpatients with stable symptoms or if there were individuals included in both circumstances. Hospitalization often is associated with dietary changes that affect lipid levels, especially when the hospitalization is of several days duration. However, it is unlikely that this issue could totally account for the observed HDL-C levels in the 45-48 mg/dl range.

Second, all subjects in this study underwent angiography presumably because they had chest pain that was suspected to be due to atherosclerosis. The authors do not define the angiographic criteria used to classify patients with CAD and without CAD other than the presence or absence of "any atherosclerotic lesions." It is common to define being CAD positive based on at least one vessel with a 50% stenosis. What is the authors' definition of "any atherosclerotic lesion?" Does the absence of "any atherosclerotic lesion" mean that persons in the non-CAD group were truly free of atherosclerosis? Probably not. All of the persons in this study had a sufficiently compelling history suggesting the presence of CAD such that they were admitted to and underwent coronary angiography in a tertiary care center specializing in management of patients with CAD. The pre-angiography probability of CAD in their carefully screened patients is high. Intravascular ultrasound and necropsy studies indicate that CAD is diffuse, not focal. A person without "any atherosclerotic lesions" may have diffuse CAD, but lack a 50 percent, or greater, stenosis which is a common definition of CAD in many angiographic studies (16, 17). Use of intravascular ultrasound demonstrates CAD in the 10-15% of patients undergoing angiography and whose angiographic studies are reported as "normal" (16). In the current study it is possible that many of the patients in the non-CAD group had CAD not detected by angiography. The high levels of fasting glucose, 111 mg/dl, in the non-CAD group support the contention that a significant number of

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patients had type 2 diabetes mellitus or impaired fasting glucose. Both of these conditions are associated with increased CAD risk and diffuse atherosclerosis of the coronary arteries. Perhaps a better control group would be age-matched subjects without a history that would lead to any consideration of performing coronary angiography. The similarity of HDL-C levels in the CAD and non-CAD groups supports the contention that insulin resistance was prevalent in both groups of patients.

Third, the authors discuss the average HDL-C levels of male CAD patients in the United States and point out that the average value for white persons was 38 mg/dl and that the average value in blacks was 45 mg/dl. A value of 45 mg/dl for male black patients is substantially below the average value of 52 mg/dl for adult black males (18). If Turks with CAD are truly like African Americans because the HDL-C levels of blacks with coronary heart disease is similar to the HDL-C levels of Turks with CAD in the present study, then a logical assumption might be that Turks without CAD would have average HDL-C values of 50-55 mg/dl, similar to those of black Americans without coronary heart disease. However, there are no data to support this contention. Perhaps the Turkish men in this study are affected by CAD because of other risk factors than low HDL-C levels, and the average value of ~45 mg/dl is truly representative of the mean HDL-C value of all Turkish men. The putative culprit risk factor(s) would not be elevated total cholesterol or low density lipoprotein cholesterol. The ratio of total cholesterol/HDL-C is the sensitive indicator of CAD risk caused by dyslipidemia (7, 19-22). In Turks the average (or median) value of the total cholesterol/HDL-C is ~5.2 for men (2, 21). In the present study the total cholesterol/HDL-C ratio of men with CAD was 4.6 (although this value is lower than it would have been had 38.1% of the CAD patients not been taking statins).

Fourth, and most important, is the issue of documentation of the precision and accuracy of the cholesterol measurements, especially HDL-C levels. The authors provide data indicating that the precision of their HDL-C assay is good, but they do not provide data regarding the accuracy of their HDL-C determinations. It is not sufficient to document accuracy of cholesterol (either total cholesterol or HDL-C) measurements simply by employing the standard solutions supplied by the manufacturer of the cholesterol testing reagents. This is especially true for methods used in research studies. Testing of samples supplied to laboratories by a worldwide cholesterol reference method laboratories network (CRMLN) provides external verification of the accuracy of total cholesterol and HDL-C determinations (23). The Turkish Heart Study and TEKHARF, epidemiologic studies of Turkish lipid levels, participated in external laboratory monitoring programs tied to the CRMLN and its predecessor. It is incumbent upon the authors of the present study to demonstrate the accuracy of their HDL-C method. Until that is done the significance of the results is in question. International sites in the CRMLN network may be accessed at http://www.cdc.gov/labstandards/crmln_member_labs_international.htm. Participation in outside monitoring programs that certify the accuracy of all laboratory tests is an important issue for medicine in Turkey (24).

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Author`s reply

Dear Editor,

We would like to thank the author of the Letter to the Editor for comments on our manuscript.

In our study the control group was not a healthy control group. They had had some clinical signs of coronary artery disease, so they needed to have a coronary angiographic procedure. Their angiograms were described as normal if there was no sign of any stenotic lesion in coronary angiograms. We agree that normal coronary angiograms do not necessarily indicate completely healthy coronary arteries. But as in many other studies, these patients can represent a good control group for severe coronary artery patients. Our patients were not hospitalized before angiographic procedures.

After we presented the results of our study in the First Metabolic Syndrome Symposium in Antalya, Dr. Mahley asked about the method of high density lipoprotein (HDL) cholesterol measurement and he advised us to check our method with the Turkish Heart Study method, which was done in American Hospital in Istanbul by Dr Palaoğlu. We did it and Dr. Palaoğlu confirmed the accuracy of our method . We agree with the authors that national monitory procedure should be done in the laboratories where this kind of investigations are performed.

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