



Prevalence, clinical features, and prognosis of patients with extremely low high-density lipoprotein cholesterol

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Lipids;
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BACKGROUND: Little data exist on the clinical features of patients with an extremely low level of high-density lipoprotein (HDL) cholesterol (<20 mg/dL).

OBJECTIVE: To assess the clinical characteristics of Japanese patients with extremely low HDL cholesterol levels.

METHODS: In this observational study of 429 patients with extremely low HDL cholesterol levels among 43,368 subjects whose HDL cholesterol was measured for any reason at Kanazawa University Hospital from April 2004 to March 2014, we investigated the presence of coronary artery disease, chronic kidney disease, the potential causes of reduced HDL cholesterol, their prognosis, and the cause of death.

RESULTS: Most patients (n = 425, 99%) exhibited secondary causes, including malignancies (n = 157, 37%), inflammatory diseases (n = 219, 51%), or other critical situations, such as major bleeding (n = 58, 14%). During the median 175-day follow-up period, 106 patients died. The causes of death in 80 (75%) patients were malignancies, inflammatory diseases, or major bleeding, in contrast to a relatively low incidence of death from atherosclerotic cardiovascular disease (n = 10, 10%). Multiple regression analysis showed that the presence of malignancy and HDL cholesterol was independently associated with death, in addition to age. The cumulative survival curve revealed that patients with an HDL cholesterol of <15 mg/dl, determined using the receiver-operating characteristic curve, had significantly higher mortality than those whose HDL cholesterol level was ≥15 mg/dL.

CONCLUSIONS: Extremely low HDL cholesterol levels could be a useful marker for poor prognosis, not necessarily related to cardiovascular diseases.

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Introduction

Decreased high-density lipoprotein (HDL) cholesterol levels are the most common lipoprotein abnormality in patients with premature coronary artery disease (CAD).¹

Epidemiologic studies have demonstrated that plasma HDL cholesterol concentration is inversely correlated with the incidence of CAD both in Caucasians and Japanese.^{2,3} However, recent Mendelian randomization trials as well as several intervention trials suggested that HDL cholesterol is merely a marker, casting doubt on the concept of “good cholesterol.”^{4,5} Uncommon encounters with subjects exhibiting extremely low HDL cholesterol provide an opportunity to directly observe the clinical impact of HDL cholesterol level. Such an extreme situation could be caused either primarily or secondarily. Indeed, such extreme cases are not always encountered in the clinical cardiology practice or in lipid clinics but rather in situations involving malignancies, inflammatory diseases, or major bleeding in hospital-based settings.⁶ However, little data exist regarding the clinical features of patients with extremely low levels of HDL cholesterol. We, therefore, investigated the potential causes of reduced HDL cholesterol and the prognosis in patients displaying such extreme conditions.

Methods

Study subjects and record review

We retrospectively investigated subjects with serum fasting HDL cholesterol concentrations <20 mg/dL among 43,368 subjects whose serum HDL cholesterol had been measured for any reason at Kanazawa University Hospital from April 2004 to March 2014. The inclusion criterion was fasting HDL cholesterol concentrations of <20 mg/dL. There were no exclusion criteria. Data were obtained from the hospital's information systems. We reviewed clinical diagnoses and their prognosis in addition to conducting a baseline examination that included a medical history review, physical examination, and blood analysis. Most of the study subjects were inpatients referred to our hospital, making it possible to assess the initial fasting blood samples.

Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University and was conducted in accordance with the [Declaration of Helsinki \(2008\)](#) of the World Medical Association. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Clinical evaluations

We assessed whether the subjects had consumed alcohol regularly by a medical interview. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic

blood pressure of at least 90 mm Hg, or use of antihypertensive medication. The presence of diabetes was defined as previously described by the Japan Diabetes Society⁷ or the use of diabetes medication. Body mass index (BMI) was defined as body weight in kilograms divided by the square of height measured in meters. CAD was defined by the presence of angina pectoris, myocardial infarction, or severe stenotic lesion(s) in the coronary artery, identified either by angiogram or by computed tomography. Chronic kidney disease (CKD) was assessed as CKD stage 3 or greater.⁸ Cirrhosis was assessed by liver histopathologic examination or pathognomonic results in ultrasound, computed tomography, or magnetic resonance imaging. Lipid-lowering therapy included the use either of statins, resins, ezetimibe, fibrates, or polyunsaturated fatty acids. Inflammation was defined as systemic fever (body temperature $\geq 37.5^{\circ}\text{C}$) with elevated serum C-reactive protein. Major bleeding was defined as previously described.⁹ All malignancies were diagnosed based on the Japanese guidelines for each disease by a board of certified specialists. Other critical situations, such as aortic dissection, Grave's disease, uremia, low birth weight, adrenal insufficiency, congenital biliary atresia, and VIPoma were diagnosed by specialists of each disease.

Potential secondary causes

We assessed the presence of potential secondary causes of extremely low HDL cholesterol, including (1) malignancies, (2) inflammatory diseases, or (3) other reasons that could cause such situations.

Cause of death

We assessed the cause of death based on the Japanese official death certificate in accordance with ICD-10 issued in 2003.

Biochemical analysis

Fasting blood samples were drawn for assays either before the lipid-lowering treatment or after discontinuation of medication for at least 4 weeks. Serum concentrations of total cholesterol, triglyceride, and HDL cholesterol were determined enzymatically, as previously described.¹⁰

Statistical analysis

Categorical variables were expressed as percentages. Fisher exact test or the chi-square test, whichever was appropriate, was used. Continuous variables with a normal distribution were presented as the mean \pm SD and were compared using unpaired Student *t* tests; otherwise, those values were shown as the median (interquartile range) and compared using the Mann-Whitney *U* test. Univariate and multivariate binary logistic regression analyses were used to evaluate the relationship between death and

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