High HDL Cholesterol (Hyperalphalipoproteinemia)

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INTRODUCTION

Background

High-density lipoprotein (HDL) is positively associated with a decreased risk of coronary heart disease (CHD). As defined by the US National Cholesterol Education Program Adult Treatment Panel III guidelines, HDL cholesterol (HDL-C) level of 60 mg/dL or greater is a negative (protective) risk factor. On the other hand, a high-risk HDL-C level is described as one less than 40 mg/dL. Randomized controlled clinical trials have demonstrated that interventions to raise HDL-C levels are associated with reduced CHD events.

The major apolipoproteins of HDL are apolipoprotein (apo) A-I and apo A-II, the alpha-lipoproteins. Elevated concentrations of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP) which is associated with lower risk CHD. Conversely, hypoalphalipoproteinemia increases the risk of CHD. The levels at which HDL confers benefit or risk are not discrete, and the cut points are somewhat arbitrary, especially considering that HDL levels are, on average, higher in US women compared with men and higher in blacks compared with whites.

Elevated HDL levels are associated with low levels of very low-density lipoprotein cholesterol (VLDL) and triglyceride (TG) levels. Low-density lipoprotein (LDL) cholesterol levels may be within the reference range or elevated. Persons with HALP do not have any unusual clinical features, and the condition should not be considered a disease entity but rather a fortuitous condition that can increase longevity because of the associated decreased incidence of CHD in these persons.

HDL is more tightly controlled by genetic factors than the other lipoproteins (ie, LDL, very low-density lipoprotein or VLDL, intermediate-density lipoprotein or IDL, and chylomicrons). However, environmental factors also play an important role. These factors include chronic alcoholism, oral estrogen replacement therapy, extensive aerobic exercise, and treatment with niacin. In some families, a genetic deficiency of cholesteryl ester transfer protein (CETP) is associated with strikingly elevated HDL cholesterol levels, especially in some with Japanese ancestry.
Very high levels of HDL cholesterol has also been reported to be atherogenic. The mechanism of such paradoxical effect are not entirely clear.

Pathophysiology

HALP may be familial, primary, or secondary. Familial HALP is a well-documented genetic form of hypercholesterolemia characterized by deficiency of CETP, a key protein in the reverse cholesterol transport system that facilitates the transfer of cholesteryl esters from HDL to beta-lipoproteins. Primary HALP is a term used for familial elevated HDL cholesterol levels that are not due to CETP deficiency and for which the cause is unknown. Secondary HALP is due to environmental factors or medications.

Physiology

Plasma HDL is a small, spherical, dense lipid-protein complex that is half lipid and half protein. The lipid component consists of phospholipids, free cholesterol, cholesteryl esters, and triglycerides. The protein component includes apo A-I (molecular weight, 28,000) and apo A-II (molecular weight, 17,000). Other minor but important proteins are apo E and apo C, including apo C-I, apo C-II, and apo C-III.

HDL particles are heterogeneous. They can be classified as a larger, less dense HDL2 or a smaller, more dense HDL3. Normally, most of the plasma HDL is found in HDL3. To add to the complexity of HDL classification, HDL is composed of 4 apolipoproteins per particle. HDL may be composed of both apo A-I and apo A-II or of apo A-I only. HDL2 is predominantly apo A-I only, and HDL3 is made of both apo A-I and apo A-II. HDL particles that are less dense than HDL2 are rich in apo E.

The reverse cholesterol transport system

HDL serves as a chemical shuttle that transports excess cholesterol from peripheral tissues to the liver. This pathway is called the reverse cholesterol transport system. In this system, plasma HDL takes up cholesterol from the peripheral tissues, such as fibroblasts and macrophages. This may occur by passive diffusion or may be mediated by the adenosine triphosphate (ATP)–binding cassette transporter 1. The latter interacts directly with free apo A-1, generating nascent, or so-called discoidal, HDL. Cholesterol undergoes esterification by lecithin-cholesterol acyltransferase (LCAT) to produce cholesteryl ester, which results in the production of the mature spherical HDL. Cholesterol is also taken up from triglyceride-rich lipoproteins in a process mediated by a phospholipid transfer protein (ie, CETP).

Cholesterol is then returned to the liver by multiple routes. In the first route, cholesterol esters may be transferred from HDL to the apo B–containing lipoproteins, such as very low-density lipoprotein or intermediate-density lipoprotein, by CETP. These lipoproteins undergo metabolism and subsequent uptake by the liver, primarily by a process mediated by the B,E receptor. In the second route, HDL particles may be taken up directly by the liver. In the third, free cholesterol may be taken up directly by

the liver. Finally, HDL cholesterol esters may be selectively taken up via the scavenger receptor, SR-B1.

Cholesterol in very low-density lipoprotein and intermediate-density lipoprotein may also be delivered back to peripheral tissues if their hepatic uptake is impaired.

Frequency

United States

HALP is a common entity in the general population. A correct diagnosis would help avoid unnecessary treatment of hypercholesterolemia in 5% of the population. The overall prevalence rate is 7.8%. In those with HALP, primary HALP accounts for 92% of cases and secondary HALP accounts for 7.9% of cases.

International

Figures remain unknown. HALP has been described in most populations; however, few population-wide data are available.

Mortality/Morbidity

HALP may be associated with a decreased risk of CHD and reduced morbidity and mortality. Protective role in atherosclerosis: The plasma HDL level is inversely correlated with the prevalence and mortality rates for CHD. However, some patients may still develop lesions in their coronary arteries despite having HALP. HDL with apo A-I is considered the most reliable parameter for predicting a reduced risk of atherosclerosis.

Mechanism of atherosclerosis prevention: The most important mechanism by which HDL exerts its antiatherogenic role is the removal of excess cholesterol from peripheral cells and its transport to the liver, a process commonly termed the reverse cholesterol transport system. In this process, several proteins are involved, including ATP-binding cassette transporter 1, LCAT, CETP, and hepatic triglyceride lipase (see Physiology).

Other properties: HDL also has antioxidant properties that may directly slow the atherogenic process.

Race

A somewhat lower prevalence of HALP has been reported in Asian persons and Asian Indian populations. Population studies (Lipid Research Clinic data) in the United States demonstrate racial differences in the prevalence of HALP, as follows:

In randomly screened children aged 6-19 years who had age-, race-, and sex-specific total plasma cholesterol levels greater than or equal to 95th percentile levels, 7.8% of white males, 12.8% of white females, 25% of black males, and 17.2% of black females had hypercholesterolemia due to elevated HDL-C (but not LDL cholesterol) levels greater than age-, sex-, and race-specific 95th percentile levels (HALP).

For adults aged 20-79 years, 4% of white men, 6.9% of white women, 13.3% of black men, and 13.3% of black women had predominant HALP, which accounted for their hypercholesterolemia.

Sex

Population studies have demonstrated a female predominance (Lipid Research Clinic data).

Age

Incidence of HALP appears to decrease with age. In a population survey, the following rates were reported:

In persons aged 20-29 years, the prevalence rate was 15.8%.

In persons aged 30-39 years, the prevalence rate was 8.4%.

In persons older than 40 years, the prevalence rate averaged 7.8%.

CLINICAL

History

HALP has no specific symptoms. It is usually identified through the routine assessment of a lipid profile. Another family member may have been found to have elevated HDL cholesterol levels. Aside from its cardioprotective role, HALP is occasionally associated with the following symptoms and signs:

Juvenile corneal opacification

Multiple symmetric lipomatosis

History related to secondary causes

History of alcohol abuse

Treatment with medications such as oral estrogens, niacin (ie, nicotinic acid), phenytoin, or fibrates (eg, clofibrate, fenofibrate, gemfibrozil)

History of vigorous sustained aerobic exercise (eg, long-distance running)

Physical

Patients with asymptomatic HALP do not present with any significant physical findings. Rare patients may exhibit the following:

Juvenile corneal opacification: This is described in patients with marked HALP.

Multiple systemic lipomatosis: In rare patients, development of multiple lipomas has been reported.

Causes

Causes may be acquired (secondary) or primary. Primary factors can include familial syndromes of high HDL-C levels, which in some cases, may be associated with a decreased risk for coronary artery disease.

Primary causes

Primary HALP: This is a term used for familial elevated HDL-C levels that are not due to CETP deficiency. Epidemiologic studies have suggested that this syndrome is associated with a decreased risk for coronary artery disease and increased longevity. Primary HALP includes CETP deficiency, familial hepatic lipase deficiency, and familial HALP. Familial HALP can involve premature corneal opacity, reduced hepatic lipase activity, and reduced uptake of HDL by lymphocytes.

Familial HALP: A selective up-regulation of apo A-I production is one metabolic cause of familial HALP and results in high plasma concentrations of HDL-C, apo A-I, and lipoprotein A-I and, possibly, in protection from atherosclerotic CHD.

CETP deficiency: This asymptomatic hereditary syndrome is caused by low CETP levels. Decreased CETP activity slows the transport of cholesteryl esters from HDL to apo B–containing lipoproteins. The condition is frequently observed in Japanese Americans. Clinical features include marked elevations of plasma HDL-C in homozygotes (usually >100 mg/dL) and probably lower rates of CHD. In heterozygotes, the HDL levels are only moderately elevated. CETP deficiency has not yet been demonstrated to be associated with a decreased risk for atherosclerotic cardiovascular disease, and some experts do not consider this condition protective against cardiovascular disease.

LCAT overexpression: Rarely, HALP has been reported to be due to LCAT overexpression. The activity of LCAT is increased in blood plasma and is associated with high levels of HDL. Reduction in the fractional catabolic rate of HDL is considered to be the predominant mechanism by which LCAT overexpression modulates HDL concentrations. Such patients may have reduced risk of developing CHD.

Up-regulation of apo A-I production: Selective up-regulation of apo A-I production is another cause of familial HALP. Affected individuals have elevated HDL-C and apo A-I levels. Additionally, many patients have a reduced risk of atherosclerotic CHD.

Secondary causes

Vigorous and sustained aerobic exercise (eg, long-distance running)

Regular substantial alcohol consumption

Treatment with oral estrogens, particularly if not opposed by progestins

Treatment with nicotinic acid (niacin) at doses greater than 1 g/d

Treatment with phenytoin

Primary biliary cirrhosis

Treatment with fibrates (eg, bezafibrate, clofibrate, fenofibrate, gemfibrozil)

DIFFERENTIALS

Other Problems to be Considered

Longevity syndrome
Familial HALP
Primary HALP
CETP deficiency
LCAT overexpression
Frequent and vigorous sustained aerobic exercise
Heavy alcohol consumption
Use of oral unopposed estrogens
Use of high-dose nicotinic acid
Use of phenytoin
Primary biliary cirrhosis
Treatment with fibrates (eg, bezafibrate, clofibrate, fenofibrate, gemfibrozil)
Juvenile corneal opacification
Multiple systemic lipomatosis

WORKUP

Lab Studies

Plasma fasting lipid profile

Plasma fasting lipid profile measures LDL, HDL, total cholesterol, and triglyceride levels.

Lipids in plasma and in isolated lipoprotein fractions are quantified by enzymatic methods. HDL-C levels are determined using a phosphotungstic/magnesium chloride reagent to precipitate the apo B–containing lipoproteins; cholesterol is enzymatically measured in the supernatant. LDL cholesterol levels are calculated using the Friedewald formula or may be measured directly using enzymatic methods.

Plasma HDL apolipoproteins

Studies of HDL apolipoproteins are not routinely performed clinically, but they may be useful research assays. Some clinicians use ratios of apo A-I to apo B-100 for risk assessment, but these measurements are quite expensive and have been proven to be no more accurate than the ratio of total cholesterol to HDL-C. Measurement of apo C, apo D, and apo E concentrations is not clinically useful.

Apo A lipoproteins include apo A-I, apo A-II, and apo A-IV.

Apo C lipoproteins include apo C-I, apo C-II, and apo C-III.

Other apolipoproteins include apo D and apo E.

Imaging Studies

Whether or not imaging studies are appropriate depends on the clinical manifestations associated with HALP, if any.

Patients with corneal opacification may require ophthalmoscopic examination and corneal or intraocular imaging.

Other Tests

Studies to assess CTEP or hepatic lipase activity are not routinely performed clinically, but they may be useful research assays.

Density ultracentrifugation can be used to isolate and measure HDL levels directly.

Nuclear magnetic resonance measurements of HDL levels are used in some specialized laboratories.

HDL2 and HDL3 subfraction measurements can also be performed in the specialized laboratories involved in research studies.

Procedures

No procedures are usually required.

Histologic Findings

Histologic examinations may be performed on the biopsy specimens obtained from those rare patients with multiple lipomatosis syndrome. The findings are usually consistent with lipoma.

TREATMENT

Medical Care

Most patients with HALP are incidentally diagnosed following blood testing. Generally, patients are asymptomatic and no medical therapy is required.

Patients with corneal opacity may need an evaluation by an ophthalmologist.

Patients in whom excessive alcohol consumption is a cause of elevated HDL-C levels should be assessed for the possible consequences of this habit.

Surgical Care

Surgical care is not usually required.

Consultations

No consultations are usually required.

Diet

Certain forms of dietary therapy, including diets low in fat content, have been shown to influence the levels of alpha-lipoproteins and HDL-C in plasma. A low-fat diet may cause some reduction in HDL-C levels, while high-fat diets are associated with higher HDL-C levels.

Activity

Most patients are healthy and asymptomatic. No restrictions on activity are required.

MEDICATION

Persons with HALP are generally asymptomatic. It is associated with a lower prevalence of atherosclerosis and requires no treatment.

FOLLOW-UP

Further Outpatient Care

Outpatient care of patients with HALP may include periodic monitoring of the lipid profile and/or a determination of the lipid profile of the index patient's first-degree relatives.

Complications

Rarely, corneal opacity is associated with HALP.

Prognosis

The prognosis is excellent. In fact, HALP is associated with longevity.

Patient Education

The benefit of atherosclerosis prevention associated with HALP should be discussed with the patient. Any significant manifestations of ischemic heart disease must be evaluated seriously, despite the protective role of HALP.
If appropriate, the consequences of excessive alcohol intake must be discussed.

MISCELLANEOUS

Medical/Legal Pitfalls

Chest pain syndromes and other manifestations of ischemic heart disease in persons with HALP must be thoroughly evaluated in the usual manner.

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