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VERY HIGH HDL CHOLESTEROL LEVELS - BOON OR BANE

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Abstract: *A 50 year old patient cam to Sampurna Sodani Diagnostic Clinic, Indore for routine tests including CBC and Lipid profile. CBC was WNL while chol (211 mg/dl), Triglyceride (109 mg/dl) and HDL was unusually high (113 mg/dl). On further investigations and detailed history it was found that he was a farmer, was nonalcoholic, non-diabetic, normotensive, nonsmoker and had not received any medications for reducing his lipids . He had never undergone any blood tests previously. He complained of headache off and on for which a CT scan was performed and which revealed focal area of hypoattenuation in right anterior centrum semiovale, corona radiate and right lentiform nucleus suggestive of recent right MCA territory infarct. High density lipoprotein or HDL is often called the good cholesterol. It has long been accepted that the HDL is more tightly controlled by genetic factors than are the other lipoproteins (ie, LDL, VLDL, intermediate-density lipoprotein [IDL], and chylomicrons). For example, in certain families, especially some families with Japanese ancestry, a genetic deficiency of cholesteryl ester transfer protein (CETP) is associated with strikingly elevated HDL cholesterol levels. However, environmental factors also have a significant impact on HDL levels. Factors that elevate HDL concentrations include chronic alcoholism, treatment with oral estrogen replacement therapy, extensive aerobic exercise, and treatment with niacin, statins, or fibrates. On the other hand, smoking reduces levels of HDL cholesterol, while quitting smoking leads to a rise in the plasma HDL level. Very high levels of HDL cholesterol have been reported to be atherogenic. The mechanism of this paradoxical effect is not entirely clear.*

Conclusion: *While the epidemiology indicates a strong inverse association between HDL-C and CVD risk, at both extremes of HDL-C distribution, genetic conditions that influence HDL metabolism have a far less predictable relationship to atherosclerosis. Ongoing studies of genetic causes of very high HDL-C also promise to provide similarly important insights on the complex relationship between HDL metabolism and atherosclerosis that could lead to new therapies for the treatment of atherosclerotic CVD.*

Key words: *HDL, good cholesterol, CETP (Cholesteryl Ester Transfer Protein), HL (Hepatic Lipase), EL (Endothelial Lipase). Scavenger receptor class B type I(SRB 1). RCT (Reverse cholesterol Transport) HALP (hyeralphalipoproteinemia)*

Introduction

A 50 year old patient cam to Sampurna Sodani Diagnostic Clinic,Indore for routine tests including CBC and Lipid profile. CBC was WNL while chol (211 mg/dl), Triglyceride (109 mg/dl) and HDL was unusually high (113 mg/dl). On further investigations and detailed history it was found that he was a farmer doing rigonous hard work in his farm,was nonalcoholic,non diabetic,normotensive, nonsmoker and had not received any medications for reducing his lipids. He had never undergone any blood tests previously. He complained of headache off and on for which a CT scan was performed and which revealed focal area of hypoattenuation in right anterior centrum seniovale, corone radiates and right lentiform nucleus suggested of recent right MCA territory infarct.

If his HDL (good) cholesterol was high, and all other risk factors were negative,what led to his developing a Right MCA territory infarct?

Discussion

The major apolipoproteins of HDL are apolipoprotein (apo) A-I and apo A-II, the alpha lipoproteins. An elevated concentration of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP), which is associated with a 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

HDL is more tightly controlled by genetic factors than are the other lipoproteins (ie, LDL, VLDL, intermediate-density lipoprotein [IDL], and chylomicrons). For example, in certain families, especially some families with Japanese ancestry, a genetic deficiency of cholesteryl ester transfer protein (CETP) is associated with strikingly elevated HDL cholesterol levels. However, environmental factors also have a significant impact on HDL levels. Factors that elevate HDL concentrations include chronic alcoholism, treatment with oral estrogen replacement therapy, extensive aerobic exercise, and treatment with niacin, statins, or fibrates. On the other hand, smoking reduces levels of HDL cholesterol, while quitting smoking leads to a rise in the plasma HDL level. Very high levels of HDL cholesterol have been reported to be atherogenic. The mechanism of this paradoxical effect is not entirely clear.

Pathophysiology

Hyperalphalipoproteinemia (HALP) may be familial, including primary (without CETP deficiency) and otherwise (with CETP deficiency), or secondary. Familial HALP (aside from the primary form) is a well-documented genetic form of hypercholesterolemia characterized by a deficiency of CETP, a key protein in the reverse cholesterol transport system that facilitates the transfer of cholesteryl esters from high-density lipoprotein (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, denser 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 apo A-I and apo A-II or of apo A-I alone. HDL2 is usually made up only of apo A-I, while HDL3 contains a combination of apo A-I and apo A-II. HDL particles that are less dense than HDL2 are rich in apo E.

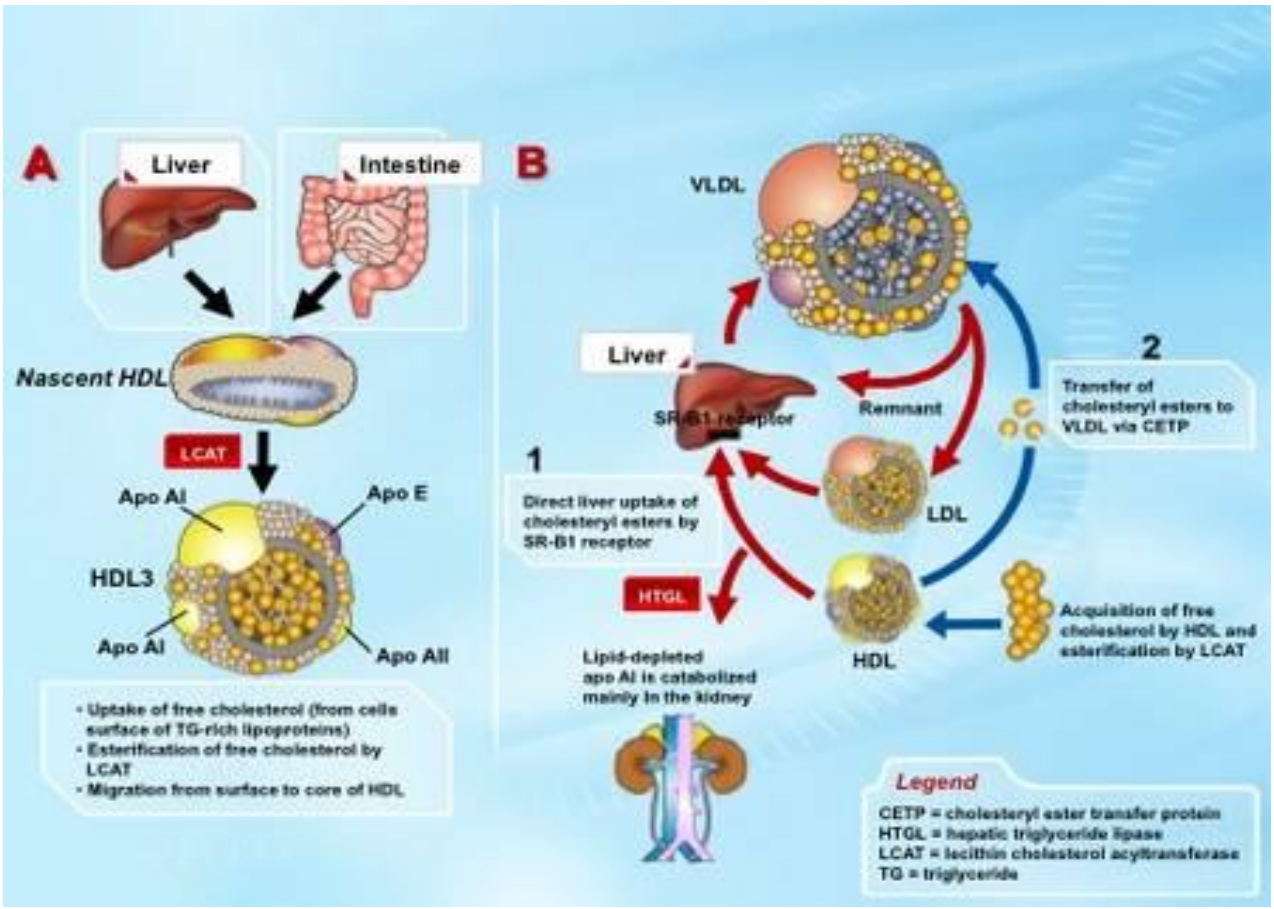
The Reverse Cholesterol Transport System

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 (VLDL) or intermediate-density lipoprotein (IDL), 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.
If the hepatic uptake of VLDL and IDL is impaired, their cholesterol may be delivered back to peripheral tissues. (TABLE I).

Table I:
HDL METABOLISM



In persons with HALP, primary HALP accounts for 92% of cases, and secondary HALP accounts for 7.9% of cases.

The incidence of hyperalphalipoproteinemia is unknown. The condition has been described in most populations, but few population-wide data are available. Despite having HALP, however, some patients may still develop lesions in their coronary arteries.or may present with

- Juvenile corneal opacification
- Multiple symmetric lipomatosis
- History related to secondary causes
- History of alcohol abuse

- Treatment with medications such as oral estrogens, statins, niacin (ie, nicotinic acid), phenytoin, or fibrates (eg, bezafibrate, clofibrate, fenofibrate, gemfibrozil)
- History of vigorous, sustained aerobic exercise (eg, long-distance running)

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

- **Primary causes**
  - Familial HALP - Familial HALP includes CETP deficiency, familial hepatic lipase deficiency, and primary HALP. A selective up-regulation of apo A-I production is one metabolic cause of familial HALP and leads to high plasma concentrations of HDL cholesterol, apo A-I, and lipoprotein A-I. It possibly may also result in protection from atherosclerotic coronary heart disease (CHD).Familial HALP can involve premature corneal opacity, reduced hepatic lipase activity, and reduced uptake of HDL by lymphocytes.
  - Primary HALP - This is a term used for familial elevated HDL cholesterol 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 with increased longevity.
  - 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 cholesterol 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 cholesterol 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 statins

- 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)

High density lipoprotein or HDL is often called the good cholesterol. It has long been accepted that the more HDL cholesterol a person has the better off he is with regard to risk for coronary artery disease. However, review of the data from original Framingham study which just solidly identified the importance of HDL, or of the data from the placebo group in another large study reveals that many heart attacks and strokes occurs in persons with perfectly normal or even raised HDL cholesterol levels[1]

Now, a new study that makes use of powerful databases of genetic information has found that raising HDL levels may not make any difference to heart disease risk. People who inherit genes that give them naturally higher HDL levels throughout life have no less heart disease than those who inherit genes that give them slightly lower levels. If HDL were protective, those with gives causing higher levels should have had less heart disease[2].

HDL hypothesis seems to be on the ropes right now and It is for the scientists to figure out where HDL fits in the puzzle just what exactly it is a marker for.

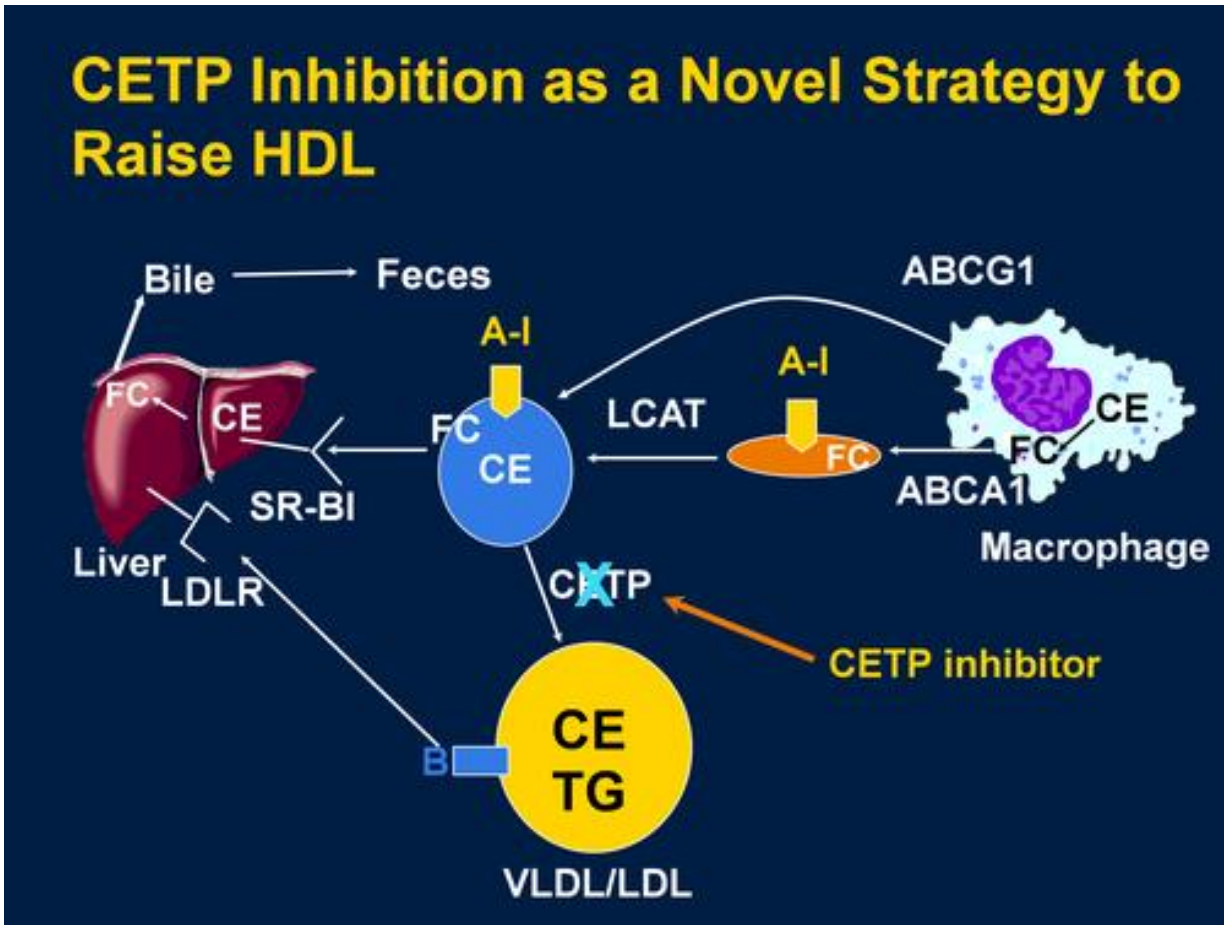
The revelation that HDL is the good cholesterol has suffered a major blow in recent times. Past studies have shown that much of what increases our risk for heart disease like obesity, lack of exercise smoking and insulin resistance, is correlated with low HDL. It was a logical conclusion then that by increased HDL levels, the risk of cardiac problems would decrease.

In the most recently published study researches used genetic, lipoprotein and heart attack outcome data from some thirty old studies to see if a genetic mutation known to increase HDL levels decreased the chance of heart attack. They focused on the gene for endothelial lipase. Past research has shown that when endothelial lipase has certain single nucleotide polymorphisms (SNPS) it leads to increased levels of HDL. Looking at a study data for 116000 participants they saw that 2.6 % of them had the SNPs and informed that their HDL levels were significantly higher than average. But when they compared the incidence of heart attack between the two groups they found no difference whatsoever. Motazacter MM et.al[3] inducted a study to assess the evidence of a polygenic origin of extreme HDL cholesterol levels.

Marina cuchel et.al[4] studied the genetics of increased HDL cholesterol levels. Insights into the relationship between HDL metabolism and atherosclerosis. A strong inverse association exists between plasma HDL cholesterol levels and incidence of CAD[5]. Although environmental factors play a role, variation in HDL-C levels are at least 50% genetically determined[6]. The genetics of syndromes of very low HDL-C have been extensively studied.

Syndromes of inherited high HDL-C also exist, but have been much less studied. The only known monogenic cause of inherited high HDL-C in humans is deficiency of the cholesteryl ester transfer protein (CETP), which transfer HDL- C out of HDL to apoB- containing lipoproteins. CETP deficiency results in markedly reduced rates of turnover of apo A-1[8]. CETP deficiency occurs primarily in Japan, where its relationship to cardiovascular risk is still under debate.Some investigators believe it is associated with protection from CVD[9] whereas other contend that it increases CVD risk [10,11]. This topic is not merely academic, as inhibitors of CETP are under development as novel HDL- raising therapies [12].(TABLE2)

Table 2:
CETP INHIBITION



Outside Japan, most subjects with inherited High HDL-C do not have CETP deficiency, and the genetic etiology of their high HDL-C is unknown. Hepatic lipase deficiency may be causative for increased HDL-C levels . Patients with HL deficiency also have dyslipidemia and increased risk of CVD. Genetic variations of another member of lipase gene family, endothelial lipase (EL), might be also associated with elevated HDL-C levels. Finally scavenger receptor class B type 1 (SR-BI) is another candidate gene in which loss of function might be expected to result in high HDL-C levels. Action and colleagues [16] described on cell surface receptor capable of binding HDL and mediating selective uptake of HDL into cells[14].

Conclusion

In summary, while the epidemiology indicates a strong inverse association between HDL-C and CVD risk, at both extremes of HDL-C distribution, genetic conditions that influence HDL metabolism have a far less predictable relationship to atherosclerosis. Ongoing studies of genetic causes of very high HDL-C also promise to provide similarly important insights on the complex relationship between HDL metabolism and atherosclerosis that could lead to new therapies for the treatment of atherosclerotic CVD.

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