HOSPITAL CHRONICLES 2020, 15(1): 3–6

EDITORIAL

Hypocholesterolemia: A Blessing or a Problem?

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We are all accustomed to face serum cholesterol as a potential threat for our health and so wish and try to have its levels as low as possible. So, in clinical practice we are rather indifferent or even satisfied when we find very low serum cholesterol levels -what we can call "hypocholesterolemia- in a certain individual. Is this practice right or it should be reevaluated? Since cholesterol is an important component of all cell membranes and its concentrations affect membrane permeability and fluidity it is highly probable that very low levels of it may disturb some cell functions and participate in the pathogenesis of diseases.

Let's start with a definition of the term, although this is not generally accepted. It can be described as a serum total cholesterol level under the fifth percentile of a general population adjusted for sex and age.[1] In a less complicated manner it can be defined as less than 115 mg/dl. In a study of 7,000 healthy blood donors, a percentage of 7.8% were found to meet the criteria for hypocholesterolemia.

Hypocholesterolemia may be congenital or acquired. Congenital conditions are either combined with low LDL- (low density lipoprotein) or low HDL- (high density lipoprotein) cholesterol levels.

1. Hypocholesterolemia with low LDL-cholesterol: it is due to a deficiency of apoprotein B, (apo-B), the main protein component of LDL. It can appear in:

i. **Abetalipoproteinemia**: this is a rare, autosomal recessive disorder characterized by a deficiency of microsomal triglyceride transfer protein. The result is malabsorption of fat and fat-soluble vitamins. It presents in the first few months of life with defective growth and steatorrhea. If untreated, it progresses to serious neurologic manifestations (ataxia, peripheral neuropathy, retinal degeneration) due to degeneration of the spinocerebellar and dorsal columns tracts.[2]

ii. **Familial hypobetalipoproteinemia**: this a rare autosomal codominant disorder. Its homozygous type is accompanied with severe fat malabsorption with consequences similar to the other here-described disorders. The heterozygous form is less rare (1:500 subjects) and is usually asymptomatic.[3]

iii. **Chylomicron retention disease**: this is a rare autosomal recessive disorder resulting in decreased intestinal absorption of triglycerides, cholesterol, and lipid-soluble vitamins. Clinical symptoms present in infancy or early childhood with slow growth and steatorrhea. Hepatic steatosis, neurologic disorders and amyotrophy can develop later in childhood.[4]

2. Hypocholesterolemia with low HDL-cholesterol: it is caused by a deficiency of apoprotein A, (apo-A), the main protein component of HDL. It can appear in:

i. **Tangier disease**: this is a rare autosomal recessive disorder characterized by a deficiency of ATP-binding cassette transporter, a protein that orients cellular cholesterol towards the cell surface and facilitates its transfer towards the core

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of HDL. As a result, cholesterol cannot be incorporated in the molecule of HDL and it is accumulated in several tissues, as peripheral nerves, dorsal roots, liver, spleen, tonsils, lymph nodes, cornea and intestinal mucosa. The clinical manifestations include neuropathy, hepatomegaly, splenomegaly, enlarged, orange-colored tonsils, corneal clouding, diabetes mellitus and increased risk of atherosclerosis.[5]

ii. **Familial hypoalphalipoproteinemia**: this is a rare autosomal dominant disorder caused by various deletions and mutations resulting in either decreased apo A-I production or function or increased apo A-I catabolism. Plasma HDL cholesterol concentrations are very low. Some patients may remain asymptomatic but in others may appear from adolescence corneal opacities or cataract, xanthomas or xanthelasmas and premature atherosclerosis. Neurologic symptoms (cerebellar ataxia, neurosensory hearing loss, proliferative retinopathy) or secondary amyloidosis leading to liver, renal or cardiac failure have also been described.[6]

iii. **LCAT deficiency**: this is a very uncommon autosomal recessive disorder. Lecithin-cholesterol acyl transferase (LCAT) is an enzyme that catalyzes esterification of free cholesterol in lipoprotein molecules. Its deficiency results to accumulation of free cholesterol in several tissues. Clinical manifestations include corneal opacities, anemia, renal failure and accelerated atherosclerosis.[7]

Acquired causes of hypocholesterolemia include:

1. **Hyperproliferative anemias** (e.g. hemolytic): increased erythropoiesis results in cholesterol consumption.
2. **Hyperthyroidism:** it is caused by increased expression of LDL-cholesterol receptors.
3. **Liver failure:** it is due to decreased synthesis of cholesterol esters.
4. **Malabsorption syndromes**
5. **Malnutrition**
6. **Chronic infections**, such as tuberculosis, chronic hepatitis, AIDS: hypocholesterolemia is probably caused by the action of cytokines. Its presence was found to be combined with lower levels of CD_4 and CD_8 lymphocytes, smaller thymus volume and increased ratio of antiretroic treatment failure.[8]
7. **Drugs**, including statins and several hypolipidemic substances. Recommended serum cholesterol levels for secondary prevention of cardiovascular diseases often are within the limits of hypocholesterolemia. Whether this represents or not an abnormal condition should be discussed. Of course, there are several clinical studies of long-term evaluation of patients under intensive statin treatment claiming that it is safe, e.g. the JUPITER study for primary[9] or the SATURN study for secondary prevention.[10] However, a clinical doctor must always have in mind that all biological parameters are usually fluctuating between a higher and a lower normal level and any deviation from them may have undesired consequences, either acute or delayed. Furthermore, one must not ignore some rather heretic studies, especially metanalyses, supporting that although cardiovascular mortality was significantly reduced after hypocholesterolemic treatment for primary prevention, the all-cause mortality remained unchanged. This finding obviously indicates that this treatment caused an increase of non-cardiovascular mortality.[11,12]

Hypocholesterolemia has often been related to several abnormal conditions. However, in most cases the existing data are rather conflicting.

1. **Malignant diseases**: Several studies have shown a decreased level of serum cholesterol (often at levels of hypocholesterolemia) in well-nourished patients with solid tumors (e.g. lungs, gastrointestinal tract) or hematologic malignancies.[13] It is not clear whether hypocholesterolemia participates in the pathogenesis of the malignancy or it is caused by it. In the SEAS study, combined administration of simvastatin and ezetimibe was accompanied with a significant ($p<0.01$) increase in cancer cases but it is not clear whether it should be attributed to the hypocholesterolemia or the action of the drugs.[14] A prospective study with a follow-up of 7735 individuals aged 40-59 for a median of 14.8 years showed an increased mortality due to cancer in patients with hypocholesterolemia. However, this effect was most pronounced in the first five years and became attenuated and non-significant with longer follow-up.[15] This may be an indication that some patients already had a preclinical malignancy during the beginning of the study and so hypocholesterolemia was a manifestation of the disease and not a factor contributing to it.

2. **Mental disorders**: There are numerous studies -mainly from psychiatric units- relating low serum cholesterol with depression and suicidality[16,17] and some with other psychiatric disorders, like schizophrenia[18] or antisocial personality.[19] A considerable number of them is based on a small number of patients or has several methodological problems.[20] Furthermore, there are some other studies that deny this effect.[21] In a large retrospective study, men with serum cholesterol values less than 160 mg/dl had a significantly higher ratio of deaths due to suicide.[22] The involvement of cholesterol in affective disorders remains a debated issue in current research but the results are controversial. On the contrary, the majority of literature shows a more consistent relationship between cholesterol levels and suicidality, with few studies that have found no relationships.[23] Concerning the possible mechanisms, one must keep in mind that cholesterol is an important component of cell plasma membrane. Due to its chemical composition it fits into the lipid bilayer and has a condensing effect on the packing of lipids. Its presence in cell membranes is involved with signaling in diverse cellular processes, such as immune regulation, cell cycle control, membrane trafficking and fusion events. Several recent studies have linked many of these functions with the effects of membrane cholesterol content.[24] Among

these functions is probably the regulation of serotonin reuptake in neurons, a procedure that is of main importance in the pathogenesis of mental disorders. Of course, such a link is not easy to be studied in humans. One animal study showed that lowering cholesterol levels resulted in lower central nervous system serotonergic activity and higher levels of aggression.[25] An additional point of view is that hypocholesterolemia may be sometimes associated with low levels of polyunsaturated fatty acids which are also implicated in the pathogenesis of several psychiatric disorders.[26]

3. **Hemorrhagic stroke**: Several studies have shown a statistically significant inverse association between serum total or LDL-cholesterol concentrations and the risk of hemorrhagic stroke. An increment of 1 mmol/l (39 mg/dl) in total cholesterol was associated with a 15% decreased risk of hemorrhagic stroke.[27] We must, however emphasize that in patients receiving hypolipidemic treatments, this risk is counterbalanced by the reduction of ischemic stroke cases.

4. **Critically ill patients**: There are considerable data indicating that in critically ill patients -such as with serious polytrauma, extensive surgery, sepsis or protracted hypovolemic shock- serum cholesterol levels are decreased and their levels may serve as a prognostic factor. In a study of critically ill trauma patients, mean cholesterol levels were significantly low (119 ± 44 mg/dl) and in those who died, they finally fell by 33% while on the contrary they had a 28% increase in survivors.[28] The underlying mechanisms of hypocholesterolemia in these patients are obscure. It is not clear whether the main disease causes hypocholesterolemia or hypocholesterolemia actively contributes to its deterioration. Both possibilities have been suggested. Proinflammatory cytokines may decrease cholesterol synthesis. On the other hand, since lipoproteins can bind and neutralize bacterial lipopolysaccharides, it is probable that cholesterol has a role in the inflammatory response against Gram-negative bacteria and its decreased presence may contribute to the deterioration of some infections.[1] New therapies directed at increasing low cholesterol levels are under consideration for the treatment of sepsis.

5. **Elderly people**: In a considerable number of elderly people serum cholesterol falls significantly with increasing age. However, many elderly people continue to receive hypocholesterolemic treatment for primary or secondary prevention of cardiovascular diseases. In a study of 724 individuals, aged 85 years and over, followed for 10 years it was found that mortality was higher in groups of lower serum cholesterol concentrations, mainly from cancer and infection. The authors concluded that each 1 mmol/l (39 mg/dl) increase in total cholesterol corresponded to a 15% decrease in mortality.[30] A study of 3572 men aged 71–93 years who were followed for over 20 years showed that relative risks for mortality were significantly lower in the second, third, and fourth quartiles of serum cholesterol as compared to the first (lowest) quartile. No significant difference of mortality was observed among these three groups. Such data cast doubt on the scientific justification for lowering cholesterol to very low concentrations (less than 180 mg/dl) in elderly people.[31]

In conclusion, hypocholesterolemia is an existing entity and clinical doctors should be familiar to it. If presenting in early life it may be due to several uncommon genetic disorders. Its appearance in adult life should be investigated as a secondary manifestation of an underlying disease. People with low serum cholesterol levels -either preexisting or caused by intensive hypocholesterolemic therapy- are exposed to possible health risks. A clinical doctor must have in mind that hypocholesterolemia may sometimes be equally harming to hypercholesterolemia. So, by adjusting all the existing data about his patients must at any case individualize his therapeutic interventions, trying to find the optimal levels of cholesterol than going towards either end of the cholesterol scale.[29]

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