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REVIEW

Hypocholesterolemia: A Neglected Laboratory Finding

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ABSTRACT

Although there is an increased awareness against hypercholesterolemia to prevent its hazardous effects on health, the physicians may neglect hypocholesterolemia that has been associated with various pathological situations. Hypocholesterolemia is defined as a total serum cholesterol level lower than 120 mg/dl whereas some authors suggest a cut-off level to be 160 mg/dl. Primary hypocholesterolemia is observed due to genetic mutations leading to hypobetalipoproteinemia and abetalipoproteinemia and Tangier disease. Secondary hypocholesterolemia is more common and observed in patients with anemia, infection, inflammation, sepsis, malabsorption, hyperthyroidism, myeloproliferative diseases, leukemias and other malignancies as well as in hospitalized patients. Each of the above pathological states may present with hypocholesterolemia either individually or as combinatory entities. Serum cholesterol level is an important laboratory parameter in monitoring disease progression and determining severity of the clinical condition.

Key words: Hypocholesterolemia, anemia, infection, hyperthyroidism, cancer, hospitalized patient

Introduction

Thirteen Nobel Prizes had been awarded to scientists who devoted major parts of their careers to cholesterol. Cholesterol was introduced as *the most highly decorated small molecule in biology* by Michael Brown and Joseph Goldstein in their Nobel Laureate lecture in 1985. Cholesterol needs at least 30 enzymatic steps for its synthesis whereas various metabolites such as prenyl groups (geranyl and farnesyl), ubiquinone and oxysterols are synthesized via certain intermediate steps in cholesterol biosynthesis.

Cholesterol is an important component in the cell membrane. It is essential for the appropriate membrane composition needed by a certain cell type. Signal transduction is especially intense in the areas where cholesterol and sphingolipids form special areas of membrane communication, namely membrane rafts. This membrane cholesterol is in equilibrium with the unesterified cholesterol in the plasma pool. Cholesterol is carried mainly by the low-density lipoprotein (LDL) fraction in the plasma.

Although there is an increased awareness against hypercholesterolemia to prevent its hazardous effects on health, the physicians may neglect hypocholesterolemia that has been associated with various pathological situations.

Hypocholesterolemia and underlying clinical situations

Hypocholesterolemia is defined as a total serum cholesterol level lower than 120 mg/dl [1]. However, some authors suggest a cut-off level to be 160 mg/dl [2-3].

Primary hypocholesterolemia is observed due to genetic mutations leading to hypobetalipoproteinemia and abetalipoproteinemia [4] and Tangier disease [5].

Secondary hypocholesterolemia is more common and observed in many clinical situations. For example, hypersplenism is associated with hypocholesterolemia and splenectomy resulted with an increase of serum cholesterol levels [6]. Polycythemia vera is also characterized by hypocholesterolemia [7].

Hypocholesterolemia may be associated with low serum antioxidant reserve that increases susceptibility to oxidative stress [8].

The largest study investigating serum cholesterol and overall mortality followed up 5941 men without a history of prior disease at the beginning of the study [9]. A decline in total cholesterol levels was associated with a subsequent increased risk of death caused by some types of cancer and by liver disease. However, there was no significant increase in all-cause mortality among men with stable low total cholesterol levels. This study concluded that a decreasing total cholesterol level in time indicated a catabolic disease

The most common clinical situations related to hypocholesterolemia will be reviewed below.

Anemias

Hypocholesterolemia has been described in various types of chronic anemia which include: congenital dyserythropoietic anemia [10], congenital spherocytosis [10], sickle cell anemia [11], beta thalassemia [12-13], aplastic anemia [10], and sideroblastic anemia [14-15]. However, the underlying mechanism that produces hypocholesterolemia has not been elucidated at all.

Increased erythropoietic activity in various anemias is proposed as a mechanism that consumes plasma pool of cholesterol for the construction of cell membranes of the young erythrocytes [10]. Low levels of serum cholesterol and other lipids suggested severe bone marrow failure and irresponsiveness to therapy in aplastic anemia patients [16]. Decreased in vivo hepatic cholesterol synthesis was found in a mouse model, with inherited iron deficiency anemia [17]. Hypocholesterolemia is also observed in malaria infection which is characterized by increased hemolysis [18]. Anemia induces stress erythropoiesis in the bone marrow which is characterized by an extensive consumption of blood cholesterol pool in membrane synthesis for the production of new erythrocytes [19].

Infection, inflammation and sepsis

Transient hypocholesterolemia and hypertriglyceridemia are observed at the initial phase of bacterial infections of various origin [20]. Hypocholesterolemia was reported in malaria infection and has the strongest positive predictive value (96%) among parameters for malaria diagnosis [21]. Severity of hepatic amebiasis was predicted by the degree of hypocholesterolemia [22]. Hypocholesterolemia is a typical laboratory finding in severe chronic hepatic insufficiency due to viral cirrhosis [23].

It was found that serum cholesterol levels were low in tuberculosis infection and diet high in cholesterol helped the patients to recover from the disease [24]. Patients develop hypocholesterolemia during sepsis possibly because lipids and lipoproteins bind to bacterial lipopolysaccharide and neutralize the endotoxin [25]. Correcting hypocholesterolemia, observed in sepsis patients, is a target to increase the survival of these patients [26]. Hypocholesterolemia has been observed in several inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and sarcoidosis [27-28]. Hypocholesterolemia is part of the inflammatory response in these patients [29]. Declining blood cholesterol levels were reported to predict the subsequent relapse in patients with Takayasu arteritis [30].

Malabsorption

Hypocholesterolemia is observed in celiac disease [31]. There was hypocholesterolemia in 35% of pediatric patients with celiac disease [32]. Reduced intestinal lipolysis observed in pancreatitis also results with hypocholesterolemia [33].

Hyperthyroidism

Hyperthyroidism is associated with hypocholesterolemia characterized by a reduction in total cholesterol, HDL and LDL [34]. There is an upregulation of LDL receptor gene expression as well as increased lipoprotein lipase activity that results with increased lipoprotein clearance from the plasma [35]. Thyroid hormones stimulate cholesterol ester transfer protein, an enzyme that transports cholesterol esters from HDL to VLDL which is metabolized by lipoprotein lipase in adipose tissue and muscle [36]. All of these factors promote a lower blood cholesterol level.

Myeloproliferative diseases, leukemias and other malignancies

Hypocholesterolemia is also a prominent finding in multiple myeloma and progression of the disease is characterized by a further decrease of cholesterol [38]. Hypocholesterolemia is also typical in acute myeloid leukemia as well as in other malignancies as a result of rapid cell proliferation [37]. Increased LDL receptor activity in leukemia cells was shown in patients with acute leukemia and elevated LDL consumption was suggested to produce

hypocholesterolemia in their serum [39]. Serum cholesterol levels in leukemia patients increased in complete remission where nonresponders to chemotherapy continued to have lower serum cholesterol levels [40]. Therefore serum cholesterol is suggested as a prognostic marker in these patients.

Hypocholesterolemia in hospitalized patients

Hypocholesterolemia has been established as a bad prognostic marker in hospitalized patients with severe illness [41-42]. Severity of the acute phase response, liver dysfunction, and hemodilution from blood loss have cumulative impacts in decreasing cholesterol in post-operative patients or intensive care unit patients especially with sepsis [43]. Mortality of patients who had been hypocholesterolemic during admission was reported to be ten times higher and was inversely correlated to serum cholesterol levels. Occurrence of hypocholesterolemia during hospitalization may be among the first signs of further deterioration of the disease [44].

Concluding remarks

The physician should be alert that severe hypocholesterolemia is a serious finding that is associated with a wide variety of diseases and may result with a high mortality rate. Each of the above pathological states may present with hypocholesterolemia either individually or as combinatory entities. Serum cholesterol level is to be regarded as an important laboratory parameter in monitoring disease progression. Additionally if the factors that produce hypocholesterolemia are thoroughly understood, new therapies can be developed in modulating serum cholesterol levels and treating hypercholesterolemia. Serum cholesterol levels were found to be lower in blood donors [45]. This is a result of stimulation of erythropoiesis and consumption of plasma cholesterol pool for the membrane synthesis of young erythrocytes. Patients with hypercholesterolemia can be encouraged to donate blood as an alternative to pharmacotherapy in decreasing their blood cholesterol level.

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