Cholesterol Levels in Patients with Chronic Lymphocytic Leukemia

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Abstract: Low cholesterol levels may be accompanied by solid tumors or hematological malignancies such as multiple myeloma. Decreased cholesterol levels have been reported in some experimental studies about chronic lymphocytic leukemia (CLL). It may be associated with tumoral cell metabolism. Herein, we examine blood lipid profiles of patients with newly diagnosed CLL (284 male, 276 female, mean age 64 ± 11 years) as defined by National Cancer Institute criteria. The control group consisted of 71 healthy subjects with mean age 55 ± 9 years (28 male, 43 females). 60% of patients with Binet A, while 25% were Binet C. Decreased levels of total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) were observed in patients with CLL than control group ($p < 0,001$). There was no statistical significance between CLL and control group for triglycerides (TG) and very low density lipoprotein (VLDL), also between HDL-C, VLDL, TG and grades. Cholesterol may metabolized by abnormal lymphocytes in CLL patients.

Keywords: Blood lipid profiles■Cholesterol levels■Chronic lymphocytic leukemia

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is most common type of adulthood leukemias characterized by increased lymphocyte counts and clonal expansion of $CD5^+$ B cells in peripheral blood, bone marrow, lymph node, spleen or other organs.[1] Cholesterols play an important role on cancer cells' growth and proliferation. Especially, mevalonic acid is involved in the transition from G1 to S phase.[2] Hypocholesterolemia have been described as laboratory abnormality for pyelonephritis, pneumonia or hyperthyroidism.[3] Also, it may present during the course of malignant disorders such as hematological (acute/chronic leukemia, lymphoma, multiple myeloma, etc.) and solid (gastrointestinal, squamous cell and small cell lung cancer, etc.).[4–7] Cancer cells may lead low density lipoprotein (LDL)/LDL receptor-related protein overexpression. The other factors such as increased uptake of LDL, high density lipoprotein or cholesterol ester have been implicated. Also, suppressing the synthesis of cholesterol was reported in leukemic cells.[8,9] In literature, there were limited clinical studies about hypocholesterolemia and CLL.[10–13] We aimed here to determine correlation between cholesterol levels and its relationship in patients with CLL.

MATERIAL AND METHODS

Patients

Five hundred and sixteen patients who admitted to 9 different hematology centers with the diagnosis of CLL according to the criteria of "National Cancer Institute criteria" were enrolled to this study. Patients with medical history of hypo-hyperthyroidism were excluded from the study. Also, there was no medical history about gastrointestinal absorption disorder, malnutrition and hereditary lipidosis diagnosed by symptoms and physical examination. The control group composed of healthy adults without malnutrition, renal failure, nephrotic syndrome/proteinuria,

hypo/hyperthyroidism, chronic diarrhea/malabsorption, familial hypercholesterolemia, and drugs affecting cholesterol or bile acid metabolism. Seventy one (28 male and 43 female with mean age 55 ± 9 years) healthy subjects were included to this retrospective study as control group. The control group was paired for age, sex, and body mass index.

Methods

CLL was diagnosed with the presence of at least 5×10^9 B lymphocytes/L (5000/μL) on peripheral blood and the clonality of the circulating B lymphocytes were confirmed by flow cytometry. Venous blood samples were taken under the supervision of medical personnel. Whole blood cell count was measured by Coulter Gene-S instrument (Beckman Coulter, California, USA), and the level of total cholesterol (TC), HDL, triglyceride (TG) by Architect C8000 instrument and kits (Abbott, Illinois, USA). Also, LDL-C levels were calculated according to Friedewald Formula ($C_{LDL} = C_{plasma} - C_{HDL} - TG/5$).[14]

Statistical methods

Demographical data about CLL and lipid parameters were recorded. Student's t-test was used for comparison of the normally distributed parameters between the groups in addition to descriptive statistical methods (mean ± standard deviation) during the assessment of the study data. Student's t-test, One-way ANOVA test were used in statistical evaluations. Tukey and Dunnett tests were performed as post-hoc tests. The statistical analysis was performed by using SPSS (Statistical Package for the Social Sciences).[15] The results were evaluated in 95% confidence interval and at a significance level of $p < 0,05$.

RESULTS

Patients

Five hundred and sixteen (284 male and 276 female) patients with mean age with 64 ± 11 years were enrolled to this study. According to Binet classification, 60% of patients were in stage A, while 25% of them were in stage C. Mean laboratory test results were as follows: hemoglobin: 9.9 ± 2.2 g/dL, hematocrit: 30.2 ± 3.7%, platelet counts: 110 ± 89 × 10^3 mm^{-3}, leukocyte counts: 29 ± 8 × 10^3 mm^{-3}, and lymphocyte counts: 21 ± 7 × 10^3 mm^{-3}. There were 71 healthy subjects as control group (43 female and 28 male with mean age 55 ± 9 years). There was no significant difference in gender and age within 2 groups. Serum TSH, AST and ALT were within normal ranges in CLL and control group. Also there were no statistical differences for these parameters between CLL and control group. The characteristic features of the patients with CLL are shown in Table 1.

Table 1. The characteristic features of the patients with chronic lymphocytic leukemia.

Sex (M/F)	284/276
Age (years)	
Mean	64 ± 11
Grade (Binet staging system)	
A	255
B	61
C	104

Lipid parameters

There was significant difference within 2 groups for TC, LDL and HDL levels ($p < 0,001$), and these parameters were significantly lower in CLL group. But, there was no significant difference between 2 groups for the level of VLDL and TG. The lipid parameters are shown in Table 2.

There was no significant difference between lipid parameters and grade. The levels of TC and LDL in the patients with Binet A were higher than Binet B and Binet C ($p < 0,001$). There were no statistical significant differences for HDL, VLDL, and TG between grades. The level of HDL in the patients with Binet C was lower than control groups ($p < 0,001$). The comparison of lipid parameters between Binet staging system in the patients with CLL chronic lymphocytic leukemia is shown in Table 3.

Table 2. Lipid parameters between the patients with chronic lymphocytic leukemia and control group.

	Chronic lymphocytic leukemia (n = 560)	Control group (n = 71)	P value
Total cholesterol (mg/dL)	175 ± 42	217 ± 36	<0.001
HDL-cholesterol (mg/dL)	37 ± 11	53 ± 14	<0.001
LDL-cholesterol (mg/dL)	107 ± 31	131 ± 29	<0.001
Triglyceride (mg/dL)	140 ± 71	147 ± 68	>0.05
VLDL-cholesterol (mg/dL)	30 ± 17	31 ± 17	>0.05

Table 3. The comparison of lipid parameters between Binet staging system in the patients with chronic lymphocytic leukemia.

	Binet A (n = 301)	Binet B (n = 101)	Binet C (n = 158)	P value
Total cholesterol (mg/dL)	182 ± 38	178 ± 43	154 ± 40	<0.001
LDL-cholesterol (mg/dL)	113 ± 28	109 ± 33	98 ± 30	<0.001
HDL-cholesterol (mg/dL)	40 ± 12	36 ± 14	29 ± 12	<0.001
Triglyceride (mg/dL)	142 ± 76	136 ± 53	141 ± 68	>0.05
VLDL-cholesterol (mg/dL)	30 ± 15	34 ± 33	31 ± 13	>0.05

DISCUSSION

We have shown that lower total cholesterol, HDL and LDL levels in newly diagnosed CLL patients when compared with the control group. However, the levels of triglyceride and VLDL were not different in CLL.

In literature, there are limited studies investigating the cholesterol levels in patients with CLL.[10–13] The lipoprotein consists of phospholipids, triglycerides, and esterified-free cholesterol. Cholesterol synthesis and transduction of cell signals are regulated by free cholesterol.[10] Unesterified cholesterols are located on surface, while hydrophobic triglycerides and cholesterol esters in the core of lipoprotein. The fluidity of cellular membrane is associated with phospholipids and cholesterol. Chylomicrons are synthesized from dietary triglycerides which are absorbed from epithelial cells of small intestine. VLDL is a result of increased triglyceride synthesis in the liver. Lipoprotein lipase (LPL) catalyzes the hydrolysis of chylomicron, VLDL triglycerides, and converts VLDL to LDL.[16–18] Cholesterols play an important role on cancer cells' growth and proliferation. The patients with malignancies have altered cholesterol levels. Hypocholesterolemi may present during the course of oncohaematologic disorders such as hematological (acute/chronic leukemia, lymphoma, multiple myelom, etc.) and solid (gastrointestinal, squamous cell and small cell lung cancer, etc.).[4–7] The lipid profiles were analyzed in 18 patients aged 45−65 years with newly diagnosed CLL by Mulas et al,[10] 530 patients newly diagnosed with cancer (of whom 97 had hematological malignancies) by Fiorenza et al[3] and 128 patients (59 female, 69 male with mean age of 65,7 ± 8) with CLL by Lorenc et al[11] decreased cholesterol levels have been reported in some experimental studies about CLL. In our retrospective multicenter study, as not to be found in the literature on the frequency 420 (264 male and 256 female with mean age 64 ± 11 years) newly diagnosed CLL patients were evaluated. Although there is many information about lipid profile in malignancies, the pathophysiologic relationship between cholesterol and malignancies is still unknown.[10] It may be associated with cholesterol synthesis and tumoral cell metabolism.[19] Cytokines may affect the enzymes such as lecithin-cholesterol acyltransferase or LPL.[20] Elevated LPL levels is correlated with shorter survival of CLL cells, and reported as prognostic indicator in B-CLL.[21] Cancer cells may lead LDL receptor/LDL receptor-related protein overexpression. CLL cells express lower LDL receptor activity, and also the proliferation may be regulated by these receptors.[22] Serum triglycerides and LDL may be with normal or increased level in patients with CLL.[10–13]

Increased risk for hematological cancer has been shown with LDL levels below ≤70 mg/dL. Lower LDL degradation rates have been reported in CLL cells. Shor et al[23] reported each 1 mg/dL increase in LDL was associated with 2.4% relative reduction in odds of hematological cancer. VLDL triglycerides are secreted by liver and converted to intermediate-density lipoproteins (IDL) and then to low-density-lipoprotein cholesterol (LDL) cholesteryl esters. High-density-lipoprotein cholesterol (HDL) removes cholesterol from vascular endothelial to liver. Decreased plasma HDL levels are commonly observed in cancer patients, and also reported in leukemic patients.[9,10,24,25] Lymphoid cells could take up HDL cholesteryl esters, via the receptors scavenger receptor class B type 1 (SR-BI) or LRP.[26] SR-BI may mediate cholesterol efflux across cellular membrane.[27] Musolino et al[19] reported decreased HDL levels in 48 patients with newly diagnosed hematological malignancies (5 with B-CLL). Leukemic cells were found with increased levels of cholesterol esters, but decreased free cholesterol.[10] Increase cholesterol ester levels were observed in rapidly proliferating tissues.[28] Mulas et al[10] studied with phytohemagglutinin that activated mitosis on ALL and CLL cells' growthing, and reported as a result of increased cholesterol levels. Increased triglyceride, VLDL and normal levels for HDL, LDL and chylomicrons were reported of 9 newly diagnosed children with acute lymphoblastic leukemia in another study.[29] Chylomicron lipolysis is not affected in CLL patients according to Sakashita's study.[13]

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme of cholesterol synthesis. Mevalonic acid (cholesterol precursor) is involved in the transition from G1 to S phase, and related to cell proliferation.[2] Farnesyl/geranylgeranyl pyrophosphate and associated signal transduction proteins such as ras and rho are synthesized from mevalonic acid pathway. However, which cholesterol levels modulate cell signaling is still unknown.[10] HMG-CoA reductase is expressed in many tissues, cells also on lymphocytes. CLL cells express higher HMG-CoA reductase activity than normal mononuclear blood cells.[30] More rapidly proliferating CEM cells from acute T-cell leukemia patients had lower expression for HMGCoA-reductase and LDL receptors.[31]

Liver X receptors are important for lipid and cholesterol metabolism, and associated with increased HDL levels and cholesterol excretion.[32] The cell proliferation is inhibited by activated liver X receptor in CLL cells.[33] Some studies have shown that cholesterol depletion from the plasma membrane may result ligand-independent activation of the epidermal growth factor receptor.[34] According to other study, responsibility of cells to mitogens was inhibited with cholesterol depletion. Plasma cholesterol levels are affected with leukemia inhibitory factor by inhibiting LPL enzyme and hepatic LDL receptors.[35]

Lorenc et al[11] evaluated the association between Rai classification stage of CLL and lipid parameters. Decreased HDL levels (but not total cholesterol) were found as dependent with stage or disease progress. Decreased HDL levels were suggested as generalized phenomenon related to massive cellular growth in normal and malignant processes by Dessì et al.[36] Sherwin et al[37] have been also reported lower cholesterol levels with higher mortality for neoplastic diseases. In our study, according to Binet classification, 60% of patients were in stage A, while 25% of them were in stage C. The levels of triglyceride, LDL, and HDL in the patients with stage C were lower than those of both stage A and stage B.

Onat et al[38] evaluated serum TC and trigliseride levels in adults. The results were as follows: the average TC level was 177,14 ± 42,41 for male, 184,38 ± 38,97 mg/dL for female, and the average trigliseride level was 146,65 ± 81,83 for male, 131,83 ± 66,18 mg/dL for female. The lipid parameter results of control group were similar to those obtained in other studies in Turkey, but significantly lower in patient group.

The limitation of our study that we have no information about cholesterol levels of patients before diagnosis. But, patients with disorders that might affect the cholesterol levels were no included in the study. Also, we have no further information about cytogenetics, molecular genetics, and cholesterol levels in patients with Binet C after treatment due to retrospective multicenter study design. The lipid and lipoprotein disorders are reversible by effective chemotherapy in cancer patients.[39] Decreased LDL and HDL cholesterol levels were reported in breast cancer patients treated with chemotherapy.[40] So, normalize lipid levels is expected after negative effects of chemotherapy on nutrition.

In conclusion, hypocholesterolemia may be accompanied by newly diagnosed CLL patients. Hypocholesterolemia may be as a result of increased LDL clearance or utilization of cholesterol by CLL cells. The stage and activity of disease may be affected by the levels of cholesterol. In addition, clinicians should be careful in term of another diseases such as hematological or solid malignancies, when total cholesterol, HDL and LDL levels were lower. Also, these parameters could be accepted as useful biochemical or prognostic markers for patients with newly diagnosed CLL patients.

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