Correlation of Serum Lipoproteins with the Activity of Acute Lymphoblastic Leukaemia

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ABSTRACT

Background: the activity of acute lymphoblastic leukemia had been observed to correlate with levels of serum lipoproteins

Objective: to evaluate the correlation of serum levels of different types of lipoproteins with activity of the disease in patients with acute lymphoblastic leukemia.

Type of the study: A prospective study.

Methods: A study included patients diagnosed as acute lymphoblastic leukemia, their serum levels of lipoproteins at time of diagnosis, and on relapse were obtained for comparison.

Results: there is significant inverse correlation of activity of acute lymphoblastic leukemia with serum total cholesterol, serum low density cholesterol levels, and serum high density lipoprotein level, but not with serum triglycerides level.

Conclusion:. The level of lipid profile is inversely correlated with activity of acute leukemia, and lipid profile assessment is recommended in evaluation of patients with acute leukemia .

Key wards: Dyslipidemia, Leukemia, Lipoprotein

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Lipoproteins are large macromolecular complexes that transport hydrophobic lipids (primarily triglycerides, cholesterol, and fat-soluble vitamins) through body fluids to and from tissues where they can be used as energy source or stored. (1, 2).The plasma lipoproteins are classified into five major classes based on their relative density: chylomicrons, very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), intermediate-density lipoproteins (IDLs), and high-density lipoproteins (HDLs) (1, 2). Acute leukemia is a malignant disorder which is created due to clonal expansion of lymphoid or myeloid progenitors where Instead of proliferating and differentiating normally, the affected cell gives rise to progeny that fail to differentiate but continue to proliferate in an uncontrolled fashion (2). As a result blast cells rapidly accumulate and progressively replace the bone marrow, diminishing the production of normal red cells, white cells, and platelets. This in turn gives rise to the common clinical complications of leukemia: anemia, infection, and bleeding. With time, the leukemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen, and other vital organs (2). In recent decades, the researchers' attention has been attracted towards studying the role of lipids in different types of malignancies. Decreased blood lipid levels have been observed in various forms of cancer including pancreatic, lung, ovarian and colon cancers and different hypothesis have been made to explain the pathogenetic mechanisms of these alterations (3, 4).It is believed that cholesterol is important for cell proliferation, because low serum cholesterol values may be the result of high cellular cholesterol need of cancerous cells (4). Attempts have been made to explain hypolipoproteinemia in patients with active acute leukemia and stated that due to high rate of expansion and metabolism in cancer cells, cholesterol and other intracellular lipids decrease in these cells, this may lead to over-expression of LDL receptors which causes the serum LDL to decline. For instance, in malignant cells of acute myeloid leukemia, LDL uptake increases up to 100 folds (5) .Low serum cholesterol values correlate with elevated levels of cholesterol in lymphocytes. Evidence of low levels of cholesterol in the culture medium is due to the development of lymphoma cells, which would consume more cholesterol for their own proliferation (5). Malignant, proliferative cells have an intense metabolism of cholesterol, while decreased intake of cholesterol is responsible for decreasing cell proliferation (5). It is known that cell membranes contain lipid layer, belonging to cholesterol-rich micro domains. These components of cell membrane are involved in intracellular signal transduction mediated by the receptor and in the self-renewal of cells (6). Many surveys have been performed considering the serum lipids abnormalities in acute leukemia and most of them have demonstrated decreased total cholesterol and elevated triglyceride in leukemic patients; nevertheless, changes of different cholesterol fractions are divers and contradictious (15,16,17). Limited studies have been performed in order to discover the correlation between abnormal lipids profile and disease activity in leukemic patients.Some research findings have demonstrated that lipid profile would get back to normal levels after

treatment and in complete remission phase which corroborates the correlation between abnormal lipid profile and disease activity. So the lipid profile of leukemic patients can be considered as a possible prognostic or diagnostic factor and might be used as a simple test for following up the patients response to chemotherapy (10,11).

Method: The study was conducted from April 1st 2014 to September 30th 2014, it included all patients diagnosed as acute lymphoblastic leukemia (ALL) at the hematology outpatient clinic or been admitted to the hematology ward in Baghdad teaching hospital. The patients were divided into two groups; first group included patients with disease not in remission (new cases or in relapse), and the second group included patients with disease in remission [during remission defined as blast cells are undetectable in peripheral blood, bone marrow examination shows blast cells less than 5%, the blood neutrophil count ≥1000/ᐧL and platelets count ≥ 100 000/ᐧL), or in consolidation phase. ALL was diagnosed by blood film and bone marrow examination reviewed by hematopathologists at teaching labs in Baghdad teaching hospital. Patients with one or more of the following criteria were excluded from our study: 1. known lipid abnormalities, or using lipid lowering agent. 2. Known to have type 2 diabetes mellitus, renal diseases, liver disorders, or thyroid diseases. 3. A family history of lipid disorders. After explanation and obtaining permission from each patient a 10 milliliters sample of venous blood were obtained after 10-12 hour fasting and sent to the laboratory in Baghdad teaching hospital for evaluation of lipid profile. Total cholesterol (TC), high density lipoprotein cholesterol (HDL) and triglycerides (TG) were assessed by enzymatic method using (Flex reagent cartridge) kit from Roch Company and analyzed by COBASS C311 machine from Roch Company. Low density lipoprotein cholesterol was calculated by using Frieldwald et al. formula (LDL=TC- (TG/5)-HDL) when S.TG < 400 mg./dl and by direct measurement when S. TG > 400 mg./dl. All values were represented in mg/dl. White blood cell count was determined by auto-analyzer CELL-DYN Ruby from Abbot Company while blood film and blast percentage were assessed by a hematopathologist. Mean and standard deviation were used to represent continuous variables, and t-test was used to assess the statistical significance among means of groups. Linear correlation was used to describe the relationship between continuous variables of interest and, correlation coefficient (C.C.) was found among them. C.C. was graded as weak, good, or strong when it is 0 – 0.25, 0.25 – 0.5, or >0.5 respectively. P. value was considered significant when it is < 0.05. Software package SPSS 20 was used for statistical analysis .

Results: The total number of the patients was (32) (16 patients of either gender. The age ranged from 17 to 36 years with a mean of 23.93 years. 17 patients were not in remission and 15 were in remission on admission to the study (table 1)

Table-. 1- patients characteristics

		No.	Percent (%)
Gender	male	16	50
	Female	16	50
Age groups (years)	<21	19	59.4
	21-30	5	15.6
	31-40	8	25
	41-50	0	0
	>51	0	0
Disease activity	Remission	15	46.9
	Not in remission	17	53.1

In patients not at remitting phase had total cholesterol (TC) level lower than patients with disease in remission level (mean = 149.1 ± SD 21 vs.195 ± SD 11.2 mg. /dl respectively) which was statistically highly significant (P. value <0.001). low density lipoprotein cholesterol (LDL) was also low in patient with disease not in remission when compared to that of patients with disease in remission (mean 91 ± SD 13.7 vs. 126.7 ± SD 29.7 mg./dl respectively), this difference was also statistically significant (P. value 0.005). HDL values were also different between patients group (mean24.9 ± SD 7.62 vs. 39.83 ± 6.31 mg. /dl. respectively) which was statistically very significant (P. value 0.001). While triglycerides level showed no statistically different values (tab. 2) The analysis of levels of different lipid with the percentage of blasts shows significant inverse correlation between the two variables (CO -0.437 with P. value 0.002 and CO -0.427 with P value 0.002, for total cholesterol and high density lipoprotein, respectively). LDL cholesterol was also inversely correlating but to a

lesser extent while triglyceride value was not; table (3). On the other hand total white blood cell (WBC) count did not show significant correlation with the level of different lipids (tab. 4)

Table-. 2 -correlation of serum lipids with the disease activity in ALL

S. Lipid profile	Disease not in remission	Disease in remission	P Value
TC (mg. /dl.)±SD	149.1±21	195 ± 11.2	<0.001
LDL (mg. /dl.) ± SD	91± 13.7	126.7 ± 29.7	0.005
HDL (mg./dl.) ± SD	24.9± 7.62	39.83 ± 6.31	0.001
TG (mg./dl.) ± SD	212.9 ± 46.8	203.3 ± 51.3	0.708

TC total cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TG triglycerides.SD standard deviation

Table (3): Person correlation between blast percentage and different lipid profile variables

Lipoprotein	Correlation coefficient	P. Value
TC	-0.437	0.002
HDL	-0.427	0.002
LDL	-0.345	0.014
TG	0.045	0.759

TC total cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TG triglycerides.SD standard deviation (P value is significant when < 0.05)

Table-. 4 -Person correlation between WBC count and different lipid profile variables

Lipoprotein	Correlation coefficient	P value
TC	0.123	0.397
HDL	0.084	0.563
LDL	0.133	0.358
TG	0.041	0.78

TC total cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TG triglycerides(P value is significant when < 0.05)

Discussion : Various epidemiological studies have found that there are some correlations between levels of serum lipids and various neoplastic diseases, In this study, we found that in patients with unremitting leukemia, the serum levels of TC, LDL, and HDL were lower than that in patients with disease in remission and values of TC, LDL and HDL had increased and reached to near normal values in patients with complete remission or their disease had controlled with chemotherapy. These results were consistent with Spigel et al. who studied changes in serum lipids in leukemia and lymphoma, they demonstrated decreased level of HDL and increased level of triglycerides in relapse phase, and return back to normal levels after remission (5). Favrot et al. and Budd et al. reported decline in TC, LDL and HDL among leukemic patients (12, 13). Similar results have been observed by Naik et al. in 55 leukemic patients, (14) and Tao et al. in 86 leukemic patients(8). Halton et al. studied lipid profile in children with ALL and realized that triglycerides levels are elevated and HDL levels are reduced but he found no significant increase in triglycerides levels after chemotherapy (9). Musolino et al evaluated the lipid profile in ALL patients and found that TC and LDL levels were lower than normal before chemotherapy and although they would increase after remission, they still be lower than normal (7). Although, many studies demonstrated that the triglycerides level was high in unremitting disease and before chemotherapy, other studies including this did not show this correlation, e.g. Goncalves et al. and Kornblau et al. who had shown that leukemic blood and bone marrow cells from ALL patients can uptake HDL with higher rate than normal cells, TC, LDL and HDL were lower than normal individuals but triglycerides and VLDL had shown no statistical difference (15, 16). It appears reasonable that these lipid profile alterations could serve as one of the biochemical markers for disease activity. A better understanding through clinical and experimental studies of alteration in

lipid profile of patients with malignancies is required for determination whether this correlation is caused by reliance of malignant cells on lipid, and lack of adequate lipids can interfere with their metabolism and proliferation. If this is the case it would be logic to expect a role of lipid lowering agents in managing acute leukemia.

Conclusion:

1. The level of lipid profile is inversely correlated with activity of acute leukemia, and lipid profile assessment is recommended in evaluation of patients with acute leukemia at time of diagnosis and in follow up.
2. Further studies are required to determine if these changes of lipid profile occur before relapse and so can be used as a predictor of early relapse. And if there are any dependency of malignant cells on lipids and any role of lipid lowering agents in treatment of ALL.

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