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RETURN TO NORMAL VALUES OF LIPID PATTERN AFTER EFFECTIVE CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

In the present work we investigated HDL-C and its subfractions HDL_2 and HDL_3 as well as total cholesterol (TC), triglycerides (TG), LDL-C, VLDL-C, apolipoproteins A1 (ApoA1) and B (ApoB) and lipoprotein (a) (Lp(a) in 25 patients with newly diagnosed acute lymphocytic leukemia (ALL) before and after induction treatment. The mean basal plasma levels of TC, HDL-C and its subfractions, LDL-C, and ApoA1 were significantly lower than the mean values observed in normal subjects, whereas TG and VLDL-C were significantly higher. The patients (n = 22) who achieved complete remission after chemotherapy showed a significant increase of TC, HDL-C, HDL_2, HDL_3, ApoA1 and a significant decrease of TG and VLDL-C. These data suggest that ALL patients are characterized by a lipid metabolic derangement mainly of HDL and TG-rich lipoproteins, that is reversed by effective treatment of disease.

Key words: lipoproteins, ALL activity, induction treatment

Myeloid leukemic cells have been found to have low total cholesterol (TC) concentrations and elevated low-density lipoprotein (LDL) receptor activity;[1] cholesterol increased after effective chemotherapy. In acute lymphoblastic leukemia (ALL), LDL receptor activity was found to be low[1] and in a recent study[2] on ALL patients we found low concentrations of TC and HDL-C that significantly increased after remission, suggesting a correlation with disease activity.

The aim of this study was to confirm our previous data in a larger number of ALL patients and to shed some light on lipid change mechanisms by determinations of HDL subfractions (HDL_2 and HDL_3) and by a marker of liver involvement such as pseudocholinesterase activity (PCHE).

Patients and Methods

Twenty five patients, mean age 37 years (range 15.1-60.0), with newly diagnosed ALL admitted to our department of Hematology were studied. The patient and control groups were comparable with regard to number, mean age, sex distribution, body mass index (BMI) and dietary habits. The patients were classified according to FAB classification as: L1 14 patients, L2 8 patients and L3 3 patients. Eleven patients had a common phenotype, 3 a preT, 6 a T, 2 a preB and 3 a B phenotype. All patients but L3, underwent chemotherapy according to GIMEMA ALL 0288 protocol:[3] 9 patients were enrolled in Arm A and 13 in Arm B. The patients with L3 morphology were treated with conventional (Arm A) induction treatment, but including a higher dose of cyclophosphamide (1.5 g/m^2 vs 0.8 g/m^2). Twenty-two patients (*responders*) achieved complete remission[4] after induction treatment; only three patients were resistant (*non responders*) to therapy.

The following serum parameters TC, TG, HDL-C, HDL_2 and HDL_3, LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), ApoA1, ApoB, Lp(a) and PCHE were analyzed in the controls and in ALL patients at the diagnosis as well as six weeks after the end of the first

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induction phase.

All lipid parameters and PCHE were determined using standard laboratory techniques. In particular HDL_2 and HDL_3 were determined by PEG precipitation method.[5]

Statistics were performed using: unpaired and paired t-tests for non paired and paired data, non parametric tests for Lp(a) data, Kolmogorov-Smirnov test and Pearson correlation coefficient. Results were considered significant at $p < 0.05$.

Results

Nutritional status was normal in all patients and no BMI change was found after induction therapy. All lipid parameters but Lp(a), were normally distributed. Table 1 shows the comparison in baseline lipid parameters between ALL patients and control group. Patient mean values of TC, HDL-C, HDL_2, HDL_3 and ApoA1 and LDL-C were significantly lower while those of TG and VLDL-C significantly higher. Lp(a) and Apo B were not different from normals. No correlation ($r = 0.30$) was found between TC, LDL levels and WBC and number of circulating blasts.

Table 2 summarizes the serum levels of lipid parameters and of PCHE activity measured before treatment in resistant patients and before and after treatment in *responders*. In *non responders* no variation was observed. In *responders* we observed a significant increase of TC (25.6%), HDL-C (115%), HDL_2 (117%), HDL_3 (114%) and ApoA1 (67.5%), and a significant decrease of TG (–28.4%) and VLDL-C (–29%) while LDL-C, Apo B and Lp(a) were not modified in comparison with basal levels. Only in *responders* a significant increase of PCHE activity (+55%) was observed.

Discussion

The data we present demonstrate that ALL is associated with significantly low levels of TC, HDL-C and its subfractions, LDL-C and ApoA1 and significantly high levels of TG and VLDL-C. We can suggest different hypothesis explaining pathogenetic mechanisms of these alterations.

Table 1. Lipid baseline values (mean ± SD) in ALL patients and in control group

		ALL patients	*p*	*Control group*
TC	mmol/L	3.89±0.86	*	5.54±1.04
HDL-C	mmol/L	0.71±0.12	*	1.45±0.29
HDL_2	mmol/L	0.18±0.08	*	0.38±0.10
HDL_3	mmol/L	0.53±0.07	*	1.04±0.21
Apo A1	g/L	0.81±0.15	*	1.40±0.23
TG	mmol/L	2.20±0.75	*	1.52±0.37
VLDL-C	mmol/L	1.04±0.35	*	0.72±0.17
LDL-C	mmol/L	2.14±0.79	*	3.36±0.78
Apo B	g/L	0.93±0.24	ns	1.04±0.21
Lp(a)	mg/L	181± 170	ns	145±105

** = p < 0·01; ns = not significant.*

Hypocholesterolemia and low LDL levels could be due to an increased cholesterol requirement by leukemic cells primarily met by an increase in number and activity of LDL receptors. However, the known low activity of these receptors in ALL[1] and the lack of correlation in our patients between LDL and blasts do not support this hypothesis.

The significant increase of serum PCHE after complete remission suggest that hypocholesterolemia and low HDL-C levels might result from an impaired hepatic synthesis[6] of cholesterol and ApoA1, due likely to a blastic infiltration; high TG and VLDL-C concentrations

Table 2. Lipid and PCHE levels (mean±SD) in non responders and in responders pre- and post-therapy.

		Non responders (n=3)	*Responders* (n=22) pre	post	p
TC	mmol/L	4.16±0.72	3.75±0.87	4.71±1.05	*
HDL-C	mmol/L	0.65±0.08	0.72±0.14	1.55±0.40	#
HDL_2	mmol/L	0.17±0.05	0.17±0.09	0.37±0.17	#
HDL_3	mmol/L	0.47±0.12	0.55±0.06	1.18±0.38	#
Apo A1	g/L	0.75±0.20	0.80±0.16	1.34±0.33	#
TG	mmol/L	2.87±0.81	1.97±0.57	1.41±0.71	*
VLDL-C	mmol/L	1.49±0.41	0.93±0.27	0.66±0.34	*
LDL-C	mmol/L	2.03±0.58	2.09±0.75	2.47±0.81	ns
Apo B	g/L	1.20±0.12	0.90±0.21	1.01±0.24	ns
Lp(a)	mg/L	110±85	192±200	95±98	ns
PCHE	IU/L	3891±1468	3586±1679	5561±1778	#

** = p < 0·01; # = p < 0·001; ns= not significant.*

could be following from metabolic derangement of HDL.

HDL subfractions determination could help to understand the behaviour of enzymes modulating HDL levels and the interconversion of subfractions (lipoprotein lipase, LPL, lecitin: cholesterol acyl transferase, LCAT, hepatic lipase, cholesteryl ester transfer protein). In our patients we observed low HDL_2 and HDL_3 levels at the diagnosis and their parallel increase after complete remission without significant modification of the ratio HDL_3/HDL_2 before and after chemotherapy; moreover this ratio was not different from controls. The unmodified ratio may indicate that enzymes have exerted their influence in an abnormal way, but to an equal extent on both subclasses. An involvement of abnormally low LPL activity could not be excluded; in fact, an inefficient clearance LPL dependent on TG-rich lipoproteins may explain the hypertriglyceridemia and the reduction of both HDL subclasses through prevention of precursor formation. Also low LCAT activity might account for reduced HDL levels, but it should have exerted a greater effect on HDL_2 with consequent modification of the ratio. Moreover, no alteration in LCAT activity was observed by Ahaneku *et al.*[7] in ALL.

On the other hand, the pattern of lipid abnormalities described in our patients is very similar to changes induced by cytokines during acute phase response.[8] In fact, cytokines can determine hypocholesterolemia, hypertriglyceridemia and low HDL levels through reduction in cholesterol, ApoA1 and LCAT synthesis, inhibition of LPL activity and increase in hepatic TG synthesis. Cytokines could be produced by leukemic or by normal cells in response to leukemic invasion.[9]

In conclusion, our results show a correlation between TC, HDL-C, Apo A1, TG, VLDL-C and leukemic cell activity: the complete remission was always characterized by a return to normal values of lipid pattern.

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