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Research article

LIPID CHANGES OCCURING IN THE COURSE OF HEMATOLOGICAL CANCERS

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Abstract: The relationship between plasma lipid levels and mortality from cardiovascular diseases has been shown in many studies, but there has been far less investigation into their relationship to non-cardiovascular diseases. The aim of this study was to investigate the lipid profile of individuals with hematological malignancies and its relationship to disease activity. 238 patients were included in the study: 84 with acute leukemia, 62 with non-Hodgkin lymphoma, 35 with Hodgkin's lymphoma, 32 with multiple myeloma, and 25 with myeloproliferative syndrome. The HDL cholesterol level of the patients differed to that of the individuals in the control group in the active disease period for all the analyzed disorders, but only remained statistically significant in the acute leukemia and non-Hodgkin lymphoma groups during the remission period. Smaller differences were observed for the remaining lipid fractions, except for the triglyceride level, which increased in the active disease period in all the analyzed disorders except non-Hodgkin lymphoma. The most pronounced changes in the lipid fractions occurred in the HDL cholesterol level, and were the most remarkable for acute leukemia.

Key words: Lipid profile, HDL-C, Hematological cancers

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Abbreviations used: HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, TC – total cholesterol

INTRODUCTION

The relationship between plasma lipid levels and mortality from cardiovascular diseases has been proven beyond doubt in many studies [1]. Moreover, therapeutic interventions focusing on lipid levels (lowering TC and LDL-C concentrations and increasing HDL-C levels) are beneficial in the prevention of cardiovascular complications, especially ischemic heart disease [2].

The connection between the risk of death for non-cardiovascular reasons, particularly from neoplasmic diseases, has been the subject of far less investigation. An increased risk of colon cancer in men with a low cholesterol level was shown in one study [3]. Sherwin *et al.* [4] proved that individuals with very low cholesterol levels have a higher mortality from neoplasmic diseases than found for a control group. Since then, only a few studies on serum lipids in patients with neoplasms have been published. The aim of this study was to analyze the disease activity-dependent differences in the lipid profiles of patients with recognized hematological malignancies.

MATERIALS AND METHODS

238 patients (128 men and 110 women) aged 20 to 80 (mean 52 years old) with diagnoses of malignancy were included in the study. The study group comprised patients with acute leukemia (AL, 84 people), non-Hodgkin lymphoma (NHL, 62 people), Hodgkin's lymphoma (HD, 35 people), multiple myeloma (32 people), and myeloproliferative syndrome (MPS, 25 people). To prevent the influence of general condition on the lipid parameters, patients who had a Karnofsky scale score of 80% or less were excluded from the study. The clinical data was obtained from their case histories.

The control group (C) consisted of 110 healthy individuals (60 men and 50 women) aged 25 to 76 (mean 49 years old). The mean body mass did not differ significantly between the study and control groups, and was respectively 71 ± 11 kg and 76 ± 11 kg. None of the subjects from either group took medications which could influence their lipid profile (i.e. statins, fibrates, nicotine acid derivatives, thyroid hormones or megestrol). A similar percentage of people (20%) in each group were active smokers.

A venous blood sample was obtained from the subjects while in the fasting state, i.e. at least 12 hours after their last meal. After centrifugation, the concentrations of TC and triglycerides were determined using the enzymatic method (bioMerieux). The LDL-C level was calculated using Friedewald's formula. The HDL-C concentration was measured using a precipitation method, from lipoproteins containing apo-B (bioMerieux). In the control group, the HDL-C level was 58 ± 13 mg/dl, the LDL-C level was 139 ± 51 mg/dl, the TC level was 220 ± 53 mg/dl, and the triglyceride level was 121 ± 77 mg/dl.

The distribution values for the TC, LDL-C and HDL-C levels in the analyzed groups were normal. The triglyceride level had a normal logarithmic distribution. The distribution was analyzed using the Shapiro-Wilk test. The

mean value (x), median (M) and standard deviation (SD) for all the groups were calculated. The mean values for the study and control groups were compared using the t-student test (after logarithmic transformation with respect to triglycerides). A comparison of the mean values of the diagnostic entities was performed using the analysis of variance and LSD (least significance difference) tests. The difference was considered statistically significant if P was less than 0.05.

RESULTS

HDL-C level

At the time of diagnosis, the lowest HDL-C level was found for patients with acute leukemia (39 ± 16 mg/dl), then for those with Hodgkin's disease (40 ± 14 mg/dl), non-Hodgkin lymphoma (43 ± 16 mg/dl), myeloproliferative syndrome (44 ± 15 mg/dl) and multiple myeloma (50 ± 13 mg/dl). With the exception of that for multiple myeloma, all these values were significantly lower than those for the control group (in the AL, NHL and MPS groups, P = 0.001; in the HD group, P = 0.002).
In the active disease period, the lowest HDL-C concentration was found for patients with acute leukemia (26 ± 11 mg/dl), then for those with non-Hodgkin lymphoma (30 ± 12 mg/dl), Hodgkin's disease (33 ± 8 mg/dl), multiple myeloma (37 ± 12 mg/dl), and myeloproliferative sundrome (38 ± 14 mg/dl). In all the patients, the HDL-C level was significantly lower than that for the control group (P = 0.001; Fig. 1).

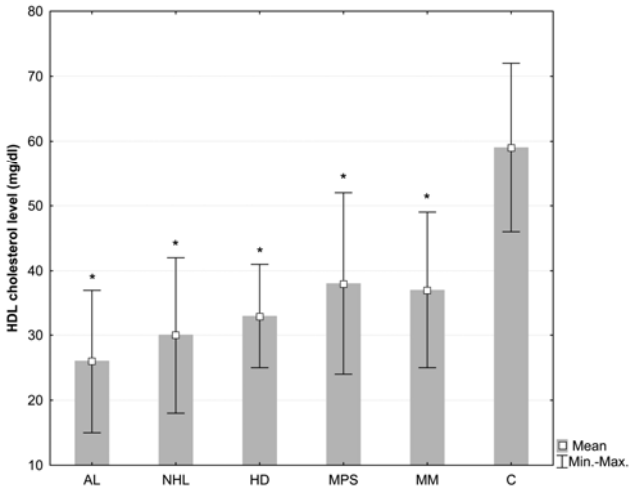

Fig. 1. The HDL-C cholesterol level in the active period of the studied neoplasmic diseases. * P < 0.001 compared to the control group; AL – acute leukemia, NHL – non-Hodgkin lymphoma, HD – Hodgkin's disease, MPS – myeloproliferative syndrome, MM – multiple myeloma, C – control.

During the remission of the disease, the lowest HDL-C level was also found for patients with acute leukemia (47 ± 14 mg/dl), then for those with non-Hodgkin lymphoma (49 ± 12 mg/dl), Hodgkin's disease (51 ± 10 mg/dl), multiple myeloma (55 ± 18 mg/dl) and myeloproliferative syndrome (56 ± 15 mg/dl). All the values were comparable to the control group, with the exception of those for acute leukemia ($P < 0.001$) and non-Hodgkin lymphoma ($P = 0.002$).

LDL-C level

At the time of diagnosis, the lowest LDL-C concentration was found for patients with acute leukemia (100 ± 39 mg/dl), then for those with myeloproliferative syndrome (122 ± 34 mg/dl), Hodgkin's disease (129 ± 55 mg/dl) and non-Hodgkin lymphoma (133 ± 37 mg/dl). The highest LDL-C level was found for patients with multiple myeloma (145 ± 47 mg/dl) and solid tumors (148 ± 41 mg/dl). In the active disease period, the lowest LDL-C level was also found for patients with acute leukemia (77 ± 29 mg/dl), then for those with myeloproliferative syndrome (99 ± 48 mg/dl), non-Hodgkin lymphoma (105 ± 34 mg/dl), and Hodgkin's disease (131 ± 38 mg/dl). The highest LDL-C concentration was found for patients with multiple myeloma (137 ± 59 mg/dl). All the values, with the exception of those for multiple myeloma and Hodgkin's lymphoma, were significantly lower than those for the control group (Fig. 2).

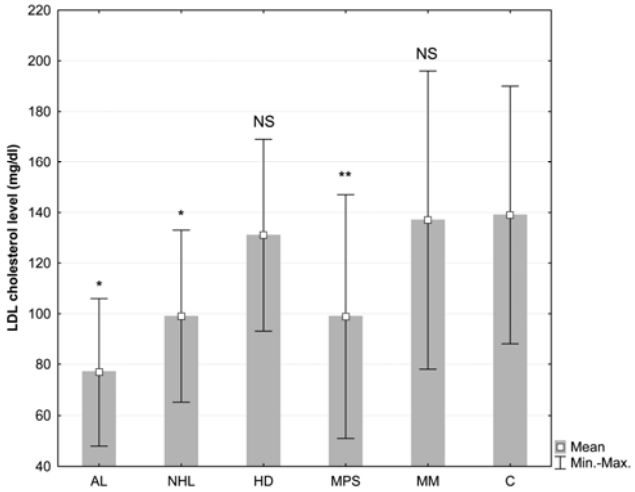

Fig. 2. The LDL-C cholesterol level in the active period of the studied neoplasmic diseases. * $P < 0.001$, ** $P < 0.01$, NS – non-significant, compared to the control group; AL – acute leukemia, NHL – non-Hodgkin lymphoma, HD – Hodgkin's disease, MPS – myeloproliferative syndrome, MM – multiple myeloma, C – control group.

During the remission of the disease, the lowest LDL-C level was found for patients with myeloproliferative syndrome (123 ± 43 mg/dl), then for those with acute leukemia (126 ± 43 mg/dl), non-Hodgkin lymphoma (143 ± 39 mg/dl) and Hodgkin's disease (144 ± 40 mg/dl). The highest LDL-C level was found for

the multiple myeloma group (163 ± 37 mg/dl). No differences between the analyzed groups and the control group were observed.

TC level

At the time of diagnosis, the lowest TC level was found for patients with acute leukemia (173 ± 49 mg/dl), then for those with myeloproliferative syndrome (194 ± 44 mg/dl), Hodgkin's disease (203 ± 61 mg/dl) and non-Hodgkin lymphoma (204 ± 49 mg/dl). The highest TC concentration was found for patients with multiple myeloma (216 ± 65 mg/dl). Only the acute leukemia group differed significantly when compared to the control group ($P < 0.001$).

In the active disease period, the lowest TC level was also found for patients with acute leukemia (141 ± 41 mg/dl), then for those with non-Hodgkin lymphoma (167 ± 45 mg/dl) and myeloproliferative syndrome (193 ± 80 mg/dl). The highest concentration was found for patients with Hodgkin's disease (209 ± 56 mg/dl) and multiple myeloma (213 ± 58 mg/dl). Only the acute leukemia and non-Hodgkin lymphoma groups differed significantly from the controls (Fig. 3).

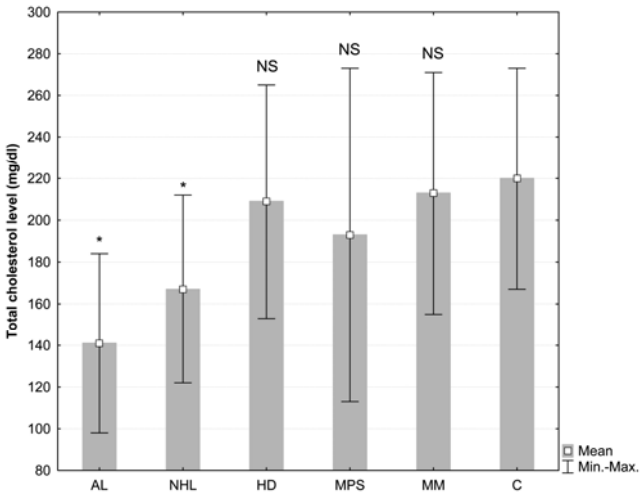

Fig. 3. The TC level in the active period of the studied neoplasmic diseases. * $P < 0.001$, NS – non-significant, compared to the control group; AL – acute leukemia, NHL – non-Hodgkin lymphoma, HD – Hodgkin's disease, MPS – myeloproliferative syndrome, MM – multiple myeloma, C – controls.

During the remission of the disease, an increase in TC level was found for all the analyzed disease entities. The values were: 204 ± 53 mg/dl for patients with acute leukemia, 204 ± 49 mg/dl for myeloproliferative syndrome, 218 ± 43 mg/dl for multiple myeloma, 219 ± 48 mg/dl for non-Hodgkin lymphoma, and 223 ± 45 mg/dl for Hodgkin's disease. No differences between the analyzed groups and the control group were observed.

Triglyceride level

At the time of diagnosis, the highest triglyceride level was found for patients with acute leukemia (172 ± 89 mg/dl), then for those with multiple myeloma (143 ± 98 mg/dl), non-Hodgkin lymphoma (140 ± 56 mg/dl), and myeloproliferative syndrome (134 ± 97 mg/dl). The lowest triglyceride concentration was found for patients with Hodgkin's disease (129 ± 90 mg/dl). All the values bar those for acute leukemia were significantly higher than those for the control group ($P < 0.01$).

In the active disease period, the highest triglyceride level was also found for patients with acute leukemia (195 ± 162 mg/dl), then for those with multiple myeloma (187 ± 121 mg/dl), Hodgkin's disease (181 ± 115 mg/dl), and myeloproliferative syndrome (164 ± 90 mg/dl). The lowest concentration was found for patients with non-Hodgkin lymphoma (156 ± 95 mg/dl). Only the non-Hodgkin lymphoma group's values did not differ significantly from the control values (Fig. 4).

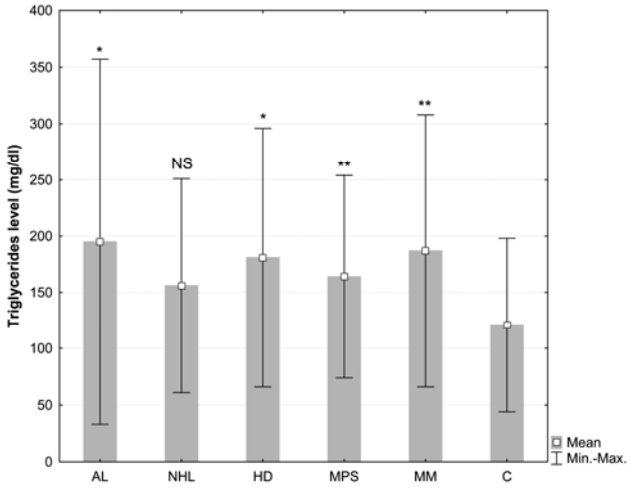

Fig. 4. The triglyceride level in the active period of the studied neoplasmic diseases. * –$P < 0.001$, ** $P < 0.02$; NS – non-significant, compared to the control group; AL – acute leukemia, NHL – non-Hodgkin lymphoma, HD – Hodgkin's disease, MPS – myeloproliferative syndrome, MM – multiple myeloma, C – controls.

During the remission of the disease, the highest triglyceride level was found for patients with multiple myeloma (166 ± 72 mg/dl), then for those with acute leukemia (160 ± 96 mg/dl), myeloproloferative syndrome (142 ± 63 mg/dl), non-Hodgkin lymphoma (135 ± 50 mg/dl) and Hodgkin's disease (117 ± 49 mg/dl). No differences between the analyzed groups and the control group were observed.

Summary
Tab. 1 shows the significant alternations in the lipid fractions in the analyzed groups. As can be seen, at the time of diagnosis, the HDL-C level was found to be lower in all the patients with neoplasms. In the active disease period, these differences became even more pronounced, while during the remission of the disease, only the values for the acute leukemia and non-Hodgkin lymphoma groups remained statistically significant. Less considerable differences were observed in the remaining lipid fractions, except for the triglyceride level, which increased in the active disease period in all the analyzed disorders except non-Hodgkin lymphoma.

Tab. 1. Statistically significant alterations in the lipid fractions in patients with hematological neoplasms, relative to the control group (↓ – decrease; ↑ – increase; • – statistically non-significant change).

	Acute leukemia	Non-Hodgkin lymphoma	Hodgkin's disease	Myeloproliferative syndrome	Multiple myeloma
At the time of diagnosis					
HDL-C	↓	↓	↓	↓	↓
LDL-C	↓	•	•	•	•
TC	↓	•	•	•	•
Triglycerides	↑	•	•	•	•
During active disease period					
HDL-C	↓	↓	↓	↓	↓
LDL-C	↓	↓	•	↓	•
TC	↓	↓	•	•	•
Triglycerides	↑	•	↑	↑	↑
During remission					
HDL-C	↓	↓	•	•	•
LDL-C	•	•	•	•	•
TC	•	•	•	•	•
Triglycerides	↑	•	•	•	•

The most significant alternations in the lipid profile were found for patients with acute leukemia, and were pronounced in all the disease phases with the exception of remission. The decrease in TC level and the increase in triglyceride level were connected with disease activity.

DISCUSSION

Some of the observed lipid level alterations presented above were mentioned in previous studies. Fiorenza *et al.* [5] analyzed the lipid profile in 530 patients newly diagnosed with cancer (of whom 97 had hematological malignancies) and

found significantly lower TC, HDL-C and LDL-C levels and a higher triglyceride concentration. Musolino *et al.* [6] reported a decrease in the total and HDL-C levels in 48 patients with newly diagnosed hematological malignancies; they even postulated that the lipid profile might be considered a useful biochemical and prognostic marker in hematological neoplasms. Dessi *et al.* [7] observed statistically important changes in the lipid profile in 66 patients with hematological malignancies with respect to the HDL-C level, while the TC level remained unaffected.

In this study, the most considerable changes in the lipid profile occurred in patients with acute leukemia, and comprised a decrease in the HDL-C, LDL-C and TC levels and an increase in the triglyceride level. Scribano *et al.* [8] found similar changes in 25 patients with acute lymphoblastic leukemia. The results of studies on children suffering from acute lymphoblastic leukemia have also been published [9]. Importantly, entering remission involved the normalization of the lipid profile, with the exception of the triglyceride level, as also observed in our previous study [10].

Alterations in the lipid profile also occur in hematological malignancies other than leukemia. Lorenc *et al.* [11] observed a decrease in TC and HDL-C levels in 128 patients with chronic lymphocytic leukemia, and these differences intensified together with disease progression. Studies by Ginsberg *et al.* [12] and Gilbert *et al.* [13] confirmed a decrease in the HDL-C, LDL-C and TC levels in patients with newly diagnosed myeloproliferative syndrome, which incresed significantly after chemotherapy [14]. Dessi *et al.* [7] only observed a lower HDL-C level in the presence of an unaltered TC concentration. In a study involving 43 patients with multiple myeloma, Hachem *et al.* [15] demonstrated a decrease in HDL-C, LDL-C and TC levels compared to the control group. Kuliszkiewicz-Janus *et al.* [16] observed a significant decrease on HDL-C, LDL-C and TC cholesterol concentrations in patients with newly diagnosed multiple myeloma, which seemed to normalize in the remission period. In this study, however, the changes in the lipid fractions in these patients were less pronounced and limited to the HDL-C level. We previously documented an increase in HDL-C and TC levels after effective chemotherapy in patients with malignant lymphomas [17].

It appears reasonable that these lipid profile alterations could serve as one of the prognostic factors for an answer to treatment and remission. In this study, people whose cancer went into remission were characterized by the normalization of their HDL-C and LDL-C cholesterol levels in the presence of an increased triglyceride concentration (except for acute leukemia, in which the triglyceride level remained increased).

Attempts have been made to elucidate the pathomechanism of lipid profile changes in the course of hematological malignancies. They resemble disturbances during the acute phase response [18] as a result of hypercytokinemia, and could theoretically be explained as affecting the activity of lipid metabolism enzymes, i.e. lecithin-cholesterol acyltransferase (LCAT)

and lipoprotein lipase. An increase in hepatic triglyceride synthesis may also play a role [8]. However, Sakashita *et al.* [19] demonstrated that the kinetics of chylomicrons was unaffected in patients with chronic lymphocytic leukemia. A low HDL-C cholesterol level can also be the result of infiltration by leukemic cells [20]. Experimental studies have demonstrated that leukemic cells secrete a leukemia inhibitory factor (hLIF), which reduces the plasma cholesterol level through upregulation of the LDL-C receptors on liver cells [21]. Conceivably, myeloid and lymphoid cells could take up high density lipoprotein (HDL-C) cholesteryl esters, most probably via the receptors SR-BI or LRP [22].

A better understanding through clinical and experimental studies of the alterations in the lipid profile of patients with malignancies is important from a practical point of view. Changes in lipid fractions may correlate with disease activity and be helpful for planning accurate treatment. Moreover, abnormally low total and LDL-C cholesterol levels in seemingly healthy people should always be investigated, and differential diagnosis of hypocholesterolemia should also comprise hematological malignancy.

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