**RESEARCH ARTICLE**

# Lipid profile of children with acute lymphoblastic leukemia during L-asparaginase treatment

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**Abstract**

**Background:** L-asparaginase is valuable in treating pediatric acute lymphoblastic leukemia (ALL), yet its use has been associated with lipid profile disturbances.

**Methods**: We compared the lipid profile [high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, apolipoprotein-α1 (Apo-A1), apolipoprotein-B100 (Apo-B100), lipoprotein-α (Lp-α), glucose, amylase, and lipase] between newly diagnosed ALL patients, ALL survivors, and healthy controls. We also assessed alterations of the parameters mentioned earlier during induction and consolidation treatment.

**Results:** We recorded significant differences in the lipid profile at diagnosis of children with ALL compared to controls (HDL cholesterol, triglycerides, Apo-A1, and Apo-B100 levels). HDL cholesterol, total cholesterol, and Apo-A1 levels increased significantly during induction at most time points. Levels of Apo-B100, triglycerides, and Lp-α exhibited a downward trend. During re-induction, no change was observed. During the treatment of high-risk patients, we found no statistically significant difference for any of the examined variables.

**Conclusion:** To confirm our preliminary results, the role of the administration of L-asparaginase and other medications in the variations in the lipid profile at diagnosis of children with ALL needs to be further elucidated with larger multicentre studies, including more patients from diverse ethnic backgrounds. HIPPOKRATIA 2023, 27 (2):41-47.

**Keywords:** Acute lymphoblastic leukemia, lipid profile, children, L-asparaginase

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## Introduction

The long-term outcomes for children who have acute lymphoblastic leukemia (ALL) have improved significantly with multiagent chemotherapy regimens, with overall survival rates reported to exceed 90 %[1]. One of the critical elements of childhood ALL treatment protocols is the use of L-asparaginase (L-ASP), which has increased survival rates since its introduction in the 1960s. L-ASP is a substantial and integral component of all protocols developed for children with ALL. Asparagine, a non-essential amino acid, can be synthesized from aspartic acid in healthy cells. Asparagine synthetase's enzymatic action facilitates the accomplishment of cellular synthesis of asparagine. Inadequate cellular asparagine levels lead to reduced deoxyribonucleic acid, ribonucleic acid, protein synthesis, cell growth inhibition, and, eventually, activation of the apoptotic cell-death mechanisms. Asparagine synthetase enzyme is lacking or in low levels in lymphoblastic leukemia cells; thus, they cannot produce asparagine independently and are highly dependent on deriving it from extracellular sources[2]. However, L-ASP is associated with severe toxicities such as hypersensitivity reactions, pancreatitis, thrombosis, encephalopathy, and liver dysfunction[3]. In addition, L-ASP has been reported to cause abnormalities in lipid metabolism[4]. This study aimed to evaluate alterations in the lipid profile of children with ALL during treatment with L-ASP in a cohort of Greek children. We could draw important conclusions about children receiving L-ASP and their lipid profile during treatment, their closer monitoring in the respective phases of treatment, and early therapeutic intervention to prevent its complications.

## Materials and Methods

The study was conducted at the Pediatric & Adolescent Hematology-Oncology Unit of the 2nd Department of Pediatrics in Northern Greece between May 2019 and September 2021. It was approved by the Bioethics Committee of the Aristotle University School of Medicine in Thessaloniki (decision No 6.321, dated: 29-07-2020). Parents/guardians of all participating children provided written informed consent, while patients over 12 years of

age provided written assent.

The participants enrolled in the study were divided into three groups. Group A comprised 30 children and adolescents with newly diagnosed ALL who had no history of autoimmune disease, previous malignancy, or recent infection. Group B included 30 children and adolescents with ALL who had completed chemotherapy more than six months previously ("survivors"), and Group C included 30 age- and sex-matched healthy children. The demographic characteristics of the three study groups were comparable. We excluded from the study patients with abnormal thyroid function tests, family history of hypercholesterolemia, Body Mass Index (BMI) equal or more than two standard deviations above the average as per World Health Organization (WHO) reference curves, corticosteroid treatment or total parenteral nutrition in the two weeks before enrolment.

*Clinical and Biochemical Parameters*

Whole blood was collected in plain tubes without anticoagulant. Demographic parameters (age, gender), clinical data (underlying disease, treatment phase), and laboratory test results [high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, apolipoprotein-α1 (Apo-A1), apolipoprotein-B100 (Apo-B100), lipoprotein-α (Lp-α), glucose, amylase, and lipase] were recorded on a predefined case report form (CRF). Information on liver, renal, and thyroid function was also collected to ensure no other disorder was present (data not shown).

*Check time points*

All patients with ALL received chemotherapy according to the ALLIC BFM 2009 treatment protocol[5]. Blood lipid profile was assessed before the administration of L-ASP on days zero and 11, as well as after L-ASP administration on days 15, 24, and 33 during the induction protocol (IA) for all patients. The lipid profile was re-assessed on day 60 [end of consolidation protocol (IB)] when patients were divided into intermediate and high-risk (IR and HR, respectively) based on disease characteristics and treatment response. The lipid profile was re-examined for patients with IR on days eight, 16, and 21 of re-induction (protocol II). For HR patients, the lipid profile was checked four days after the administration of L-ASP on day six of each of the first three HR blocks (HR-1, HR-2, HR-3). Values on day zero were also compared with the control groups.

*Statistical Analysis*

For the present study, we determined the sample size based on a previous pilot study in which an effect size of 0.5 was added to a power (1 - b) =0.95 and a significance level equal to α =0.05. We calculated the optimal sample size of up to 90 statistical units (30 for each group). Descriptive statistics for quantitative variables are presented as mean ± standard deviation. We used repeated measures ANOVA to explore statistically significant differences in the lipid profile variables at different time points during induction and at the end of consolidation. We performed pairwise multiple comparison procedures using Sidak's error correction methodology. Because IR and HR patients follow different treatment protocols, their data were analyzed separately. For both sub-groups and because each sub-group size was smaller than 30, we performed the non-parametric Friedman's test to examine for possible differences between time points. We applied the Wilcoxon test procedure with Bonferonni's error correction suggestion for pairwise comparisons. We applied the independent samples t-test to search for statistically significant differences in the lipid profile variables between patients and control groups (groups B and C). All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 28.0. (IBM Corp., Armonk, NY, USA) and all tests are provided at a 5 % level of significance.

**Results**

*Demographic characteristics*

A total of 30 patients (19 females) were recruited in group A with a mean age of 6.55 ± 4.63 years (range: 12 months-16 years). Twenty-four patients were diagnosed with B-ALL and six with T-ALL. Among them, 23 patients were classified as IR and seven as HR. In group B, 30 (19 females) off-treatment patients (i.e., "survivors") were recruited with a mean age of 7.06 ± 3.64 (range: 3-16) years. In group C, 30 healthy children (19 females) consented to participate with a mean age of 7.3 ± 4.06 (range: 1-16) years.

*Lipid profile*

*A. Comparisons between patients and controls*

Table 1 displays the descriptive measures for all parameters studied in patients and the two control groups. Total and LDL cholesterol did not differ in the two different sets of groups. On the contrary, triglyceride levels were significantly higher in patients than survivors and healthy children, whereas HDL cholesterol was lower in newly diagnosed patients, similar to Apo-A1. Apo-B100 was only marginally but significantly higher in newly diagnosed patients when compared to controls. All other parameters tested presented no significant differences.

*B. Lipid changes during induction and consolidation for all ALL patients*

The lipid profile was measured at six-time points during induction and consolidation, and the results are shown in Table 2. Total cholesterol levels increased after the beginning of treatment and declined to almost initial levels towards day 60, and these changes were statistically significant. Pairwise comparisons revealed several significant differences, as shown in Table 2. Regarding triglyceride levels, there was overall a significant fluctuation and, more specifically, a significant decrease on day 15 and day 60 in relation to day zero and day 11. HDL cholesterol levels significantly increased from day zero and remained elevated until the end of protocol IB. In

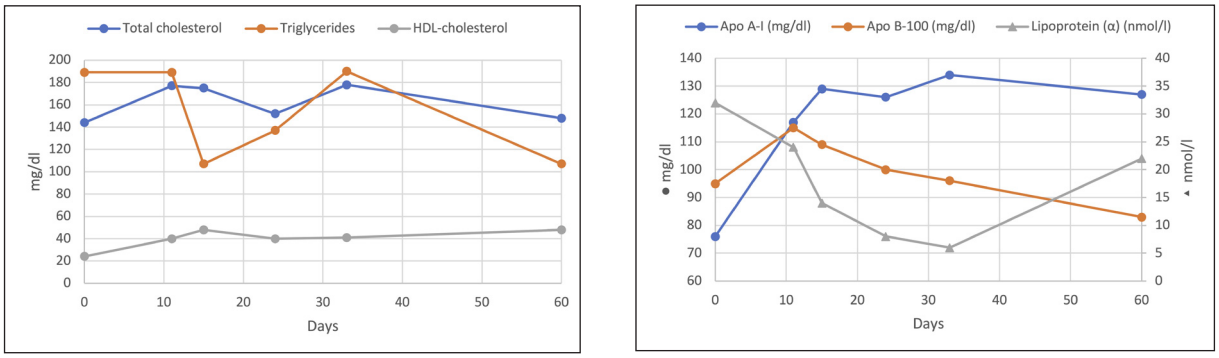


**Figure 1:** a) Total cholesterol, triglycerides, and high-density lipoprotein cholesterol and B) apolipoprotein-α1, apolipoprotein B100, and lipoptotein-α levels of children with acute lymphoblastic leukemia at successive time points during treatment from day zero (D 0) to day 60 (D 60).

HDL: high-density lipoprotein cholesterol, Apo A1: apolipoprotein-α1, Apo B-100: apolipoprotein B100, Lp-α: lipoptotein-α.

**Table 1:** Descriptive measures and comparisons for all studied lipid profile parameters in the three study groups: Group A, comprising 30 patients with B-and T- acute lymphoblastic leukemia; Group B, comprising 30 off-treatment patients; and Group C, comprising 30 healthy children.

| lipid profile parameter | group A*,# | group B* | group C# | p-value |
|---|---|---|---|---|
| total cholesterol (mg/dl) | 144 ± 40 | 160 ± 22 | 144 ± 34 | *: 0.075<br>#: 0.969 |
| triglycerides (mg/dl) | 189 ± 92 | 67 ± 23 | 74 ± 35 | *: 0.000<br>#: 0.000 |
| HDL cholesterol (mg/dl) | 24 ± 10 | 57 ± 11 | 49 ± 14 | *: 0.000<br>#: 0.000 |
| LDL cholesterol (mg/dl) | 84 ± 34 | 83 ± 25 | 77 ± 29 | *: 0.419<br>#: 0.895 |
| apolipoprotein A1 (mg/dl) | 79 ± 24 | 152 ± 22 | 133 ± 28 | *: 0.000<br>#: 0.000 |
| apolipoprotein B100 (mg/dl) | 95 ± 25 | 81 ± 16 | 80 ± 23 | *: 0.016<br>#: 0.016 |
| lipoprotein-α (nmol/l) | 32 ± 40 | 23 ± 41 | 23 ± 42 | *: 0.386<br>#: 0.385 |
| glucose (mg/dl) | 90 ± 24 | 90 ± 10 | 84 ± 7 | *: 0.908<br>#: 0.195 |
| amylase (U/l) | 52 ± 51 | 57 ± 25 | 63 ± 25 | *: 0.287<br>#: 0.642 |
| lipase (U/l) | 85 ± 2 | 20 ± 5 | 20 ± 5 | *: 0.116<br>#: 0.112 |

Values are reported as mean ± standard deviation, *: p-value for comparison of groups A and B, #: p-value for comparison of groups A and C, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

contrast, LDL cholesterol levels did not significantly differ between the various time points until day 60 (results not shown). Apo-A1 levels significantly increased during protocol IA from day zero and remained high until day 60. In addition, Apo-B100 levels showed a significant increase from the start of treatment until day 11 to day 15 and then dropped again, reaching initial levels on day 33 and remainind low. For Lp-α, levels gradually declined significantly throughout protocol IA (day 33) and then increased to normal at the end of protocol IB (shown in Figure 1). It is worth noting that glucose, lipase, and amylase levels did not show significant fluctuations during protocols IA and IB. All these changes in lipid metabolism induced by L-asparaginase were reversible at the end of the chemotherapy protocol.

*C. Re-induction protocol for intermediate-risk patients*

None of the lipid profile variables studied showed statistically significant variation during protocol II (re-induction) (on days: eight, 16, and 21).

**Table 2:** Total cholesterol, Triglycerides, high-density lipoprotein cholesterol, apolipoprotein-α1, apolipoprotein B100, and lipoptotein-α (Lp-α) levels of children with acute lymphoblastic leukemia at successive time points during treatment from day zero (D 0) to day 60 (D 60), and multiple comparisons with ANOVA repeated measures.

| | **time points** | **total cholesterol (mg/dl)** | **p-value ANOVA** | **pairwise comparisons** |
|---|---|---|---|---|
| | Day 0 | 144 ± 40 | | |
| | Day 11 | 177 ± 35 | | |
| | Day 15 | 175 ± 46 | 0.041 | D 0 vs D 11 (p <0.05)<br>D 0 vs D 15 (p <0.05)<br>D 11vs D 60 (p <0.05) |
| **protocol IA** | Day 24 | 152 ± 48 | | |
| | Day 33 | 178 ± 95 | | |
| **end of protocol IB** | Day 60 | 148 ± 36 | | |
| | **time points** | **HDL cholesterol (mg/dl)** | **p-value ANOVA** | **pairwise comparisons** |
| | Day 0 | 24 ± 10 | | |
| | Day 11 | 40 ± 15 | | D 0 vs D 11 (p <0.05) |
| | Day 15 | 48 ± 14 | | D 0 vs D 15 (p <0.05)<br>D 0 vs D 24 (p <0.05) |
| **protocol IA** | Day 24 | 40 ± 17 | 0.003 | D 0 vs D 33 (p <0.05) |
| | Day 33 | 41 ± 19 | | D 0 vs D 60 (p <0.05) |
| **end of protocol IB** | Day 60 | 48 ± 11 | | |
| | **time points** | **Apo A-I (mg/dl)** | **p-value ANOVA** | **Pairwise comparisons** |
| | Day 0 | 76 ± 24 | | |
| | Day 11 | 117 ± 32 | | D 0 vs D 11 (p <0.05) |
| | Day 15 | 129 ± 30 | | D 0 vs D 15 (p <0.05)<br>D 0 vs D 24 (p <0.05) |
| **protocol IA** | Day 24 | 126 ± 40 | 0.000 | D 0 vs D 33 (p <0.05) |
| | Day 33 | 134 ± 41 | | D 0 vs D 60 (p <0.05) |
| **end of protocol IB** | Day 60 | 127 ± 25 | | |
| | **time points** | **Apo B-100 (mg/dl)** | **p-value ANOVA** | **pairwise comparisons** |
| | Day 0 | 95 ± 25 | | |
| | Day 11 | 115 ± 30 | | D 0 vs D 11 (p <0.05) |
| | Day 15 | 109 ± 32 | 0.000 | D 11 vs D 60 (p <0.05)<br>D 15 vs D 60 (p <0.05) |
| **protocol IA** | Day 24 | 100 ± 34 | | D 24 vs D 60 (p <0.05) |
| | Day 33 | 96 ± 35 | | |
| **end of protocol IB** | Day 60 | 83 ± 27 | | |
| | **time points** | **lipoprotein-α (nmol/l)** | **p-value ANOVA** | **pairwise comparisons** |
| | Day 0 | 32 ± 40 | | |
| | Day 11 | 24 ± 33 | | |
| | Day 15 | 14 ± 25 | 0.001 | D 0 vs D 15 (p <0.05)<br>D 0 vs D 24 (p <0.05) |
| **protocol IA** | Day 24 | 8 ± 29 | | D 0 vs D 33 (p <0.05) |
| | Day 33 | 6 ± 16 | | |
| **end of protocol IB** | Day 60 | 22 ± 43 | | |

Values are reported as mean ± standard deviation, D: day, HDL: high-density lipoprotein, Apo A-1: apolipoprotein-α1, Apo B100: apolipoprotein-B100.

*D. HR blocks for high-risk patients*

There was no statistically significant difference for any measured variables at the predefined time points during HR treatment.

**Discussion**

The present study showed that ALL patients at diagnosis had elevated triglyceride and lower HDL cholesterol levels compared to survivors and healthy controls. In addition, Apo-A1 levels were lower, while Apo-B100 levels were slightly higher in patients than survivors and healthy children. Moreover, striking temporal associations between treatment and alterations in the lipid profile of children with ALL were demonstrated in this study.

It is known that in pediatric patients with neoplastic diseases, there are changes in lipid metabolism at the time of diagnosis[6-8]. In a study by Moschovi et al, serum lipids and lipoproteins were measured at diagnosis, before induction treatment, and every two months for the first 12 months of the maintenance phase of chemotherapy in 64 patients with ALL treated with the modified New York-II protocol. They showed lipid metabolism was abnormal at diagnosis, but this was reversed during remission[8]. In addition, Naik et al examined the lipid profile of pediatric patients with leukemia or Hodgkin's disease compared to age-matched controls[7]. The study included 52 healthy controls and 105 patients with leukemia or Hodgkin's disease. Serum total, HDL and LDL cholesterol were significantly decreased, whereas serum triglycerides were significantly elevated and outside the normal range[7]. These findings partially agree with ours, i.e., regarding triglycerides and HDL cholesterol. Similar changes are observed in adults. Fiorenza et al, compared total, LDL, and HDL cholesterol, as well as serum triglycerides in 530 adult patients with newly diagnosed cancer with those of 415 non-cancer subjects, and the outcomes were similar (i.e., low LDL cholesterol, low HDL cholesterol, and relatively high triglycerides, common for both hematological and solid tumors[6].

All the studies mentioned earlier confirm that the mere presence of malignancy alters the lipid profile even before the start of treatment, and this cannot be explained solely by poor nutrition. A possible explanation for the lipid profile abnormalities could be a change in lipid metabolism, i.e., decreased synthesis or increased catabolism. A possible mechanism for the reduced LDL cholesterol levels in leukemia patients would be the increased utilization of cholesterol for membrane synthesis by derepressed neoplastic cells[9].

Most importantly, this is the first study to report apolipoprotein levels in children with leukemia. Although apolipoproteins have been studied in various settings and in adults with myeloid leukemia as potential prognostic markers[10], to date, no studies have focused on the effect of leukemia on the level of Apo-A1, or Apo-B100, or Lp-α, in children, and that's what makes this study unique.

In the second arm of the study, we showed striking temporal fluctuations of various lipid profile parameters during induction and consolidation treatment in children with newly diagnosed ALL (shown in Figure 1). The changes in cholesterol levels we observed are consistent with the findings of other investigators who have previously reported an association between hypercholesterolemia and asparaginase[11,12]. More specifically, Steinherz et al were the first to show that 8 % of patients treated for leukemia (New York-II protocol) reported transient, severe, but benign hyperlipidemia (triglyceride level >1,000 mg/dl), while they observed no such issue in the 64 patients on the New York-I protocol[11].

In the literature, we found five similar cases during therapy with steroids, asparaginase, or both. No characteristics could distinguish these patients from most patients treated with similar protocols that did not present severe hyperlipidemia. In a study by Hasan, mean serum cholesterol and triglyceride levels were significantly higher during L-ASP therapy compared to pre-treatment levels[12].

Another study, however, by Parson et al, did not confirm temporal changes in serum cholesterol levels related to asparaginase therapy[4]. More specifically, 30 % of patients had cholesterol levels greater than 200 mg/dL during ALL therapy and before L-ASP administration[4]. This increased percentage of patients with elevated cholesterol levels before L-ASP therapy could be related to the effect of corticosteroids also given in high doses during induction.

Regarding triglycerides, we observed significant variations during induction, with two peaks (days zero to 11 and day 33). Corticosteroids increase triglyceride synthesis and lipoprotein lipase activity, while L-ASP inhibits lipoprotein lipase activity. When steroids and L-ASP are concurrently administered, triglyceride-rich lipoproteins may be formed rapidly, which are inadequately cleared, resulting in hypertriglyceridemia[13]. Numerous studies show an increase in triglyceride levels during therapy with asparaginase[4,14-17]. All these studies do not agree with our findings. However, one study found a reduction in triglyceride levels. Arzanian et al, studied the effect of L-ASP at a dose of 6,000 U/m$^2$ on the lipid profile in 82 Iranian children with newly diagnosed ALL. Triglyceride levels were assessed three times: before, during, and two months after L-ASP treatment. They concluded that L-ASP resulted in a reduction in triglyceride and an increase in HDL cholesterol levels[18].

The decrease in triglycerides observed in our study could be attributed to insufficient fat emulsification due to a deficiency of pancreatic lipase, particularly pancreatic fluid co-lipase. Other contributing factors to reduced triglyceride levels include the Mediterranean diet of Greek children and lipoprotein lipase polymorphisms that may act protectively against hypertriglyceridemia[19-25].

The direct and inverse relationship between triglyceride and HDL cholesterol levels is well-known. The decrease in triglyceride levels coincides with an increase in HDL[26]. The same result was found only by Arzanian et al, as mentioned above[18]. On the other hand, LDL did not

differ significantly at various time points, a finding which is in agreement with previous studies[18,27]. In the study by Madan et al, alterations in lipid levels in 82 newly diagnosed pediatric patients with ALL were studied, and no significant change was observed in LDL levels[26].

The decrease in the levels of triglycerides is in absolute agreement with the increase in Apo-A1 levels. The value of Apo-B100 increases with the increase of cholesterol and LDL, while the levels of Apo-A1 are reflected in the fraction of HDL[28]. In other studies, there were no statistically significant changes in Apo-A1 and Apo-B100 values[4,18].

The effect of treatment on Lp-α levels has only been analyzed by Arzanian et al, who demonstrated that its levels showed a statistically significant decrease during L-ASP treatment, which is in agreement with our results[18].

It is worth mentioning that no statistically significant changes were observed in HR patients for any of the measured parameters. The small number of patients in this risk group is a factor that may justify this.

Although the study sample size was calculated as adequate, ALL has many subtypes (according to immunophenotype, genetics, and risk group) that prevented further subanalyses and adjustments, and this could be considered a limitation of the current study. Also, our data were not adjusted for other factors influencing the lipid profile, such as dietary habits. On the other hand, an advantage of our study is that we report on apolipoprotein levels in children with leukemia, results that have not been previously examined, and we obtained some interesting and promising results.

## Conclusion

Lipid profile abnormalities in children with ALL during L-ASP therapy are relatively common. Determining various biochemical parameters before, during, and after administering asparaginase is essential in treating children with ALL. The evaluation of the described parameters was conducted for the first time in children of Greek origin.

Overall, our study showed significant differences in the lipid profile of children with ALL at diagnosis compared with controls. Significant fluctuations in most parameters studied were also shown during the induction and consolidation treatment. These changes were also seen for apolipoproteins (Apo-A1, Apo-B100, and Lp-α) in addition to well-studied variables. The role of L-ASP administration and other medications in these variations must be further elucidated. More extensive multicentre studies, including more patients from diverse ethnic backgrounds, are needed to confirm our preliminary results.

## Conflict of Interest

The authors declare no conflicts of interest.

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