

## **Glucose, lipids and proteins abnormalities accompanying acute-phase response of the hematological malignance disease: a pilot study**

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### **ORIGINAL ARTICLE**

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**Sources of funding:** None

**Conflict of interests:** None

## **ABSTRACT**

**OBJECTIVE:** to study the triglycerides, glucose, albumin and lipoproteins profile and their correlation with a biomarker of hematological malignance disease in pediatric cancer patients at admission.

**DESIGN AND SETTING:** Cross-sectional study carried out at Pediatric Oncology Institute of Federal University of São Paulo, Brazil.

**SUBJECTS AND METHODS:** The study was performed from October 2003 to June 2005. Fasting blood lipids, lipoproteins, serum glucose and proteins levels and serum lactate deshydrogenase (disease biomarker) were obtained in newly diagnosed patients in a cross-sectional study. Exclusion criteria: previous anticancer treatment, non-collected blood sample and patients who refused the protocol.

**RESULTS:** Thirty-three patients with leukemia and lymphomas were analyzed. Thirty-two out of 33 (97%) and 7/30 (23%) demonstrated HDL and albumin below normal value. Hyperglycemia was observed in 14% of the patients, hipertriglyceridemia in 66% and hipercholesterolemia and high LDL levels in 3% and 6%, respectively. Eight patients colleted C-reactive protein; 50% presented values above quintile 3. Serum lactate deshydrogenase correlated with triglycerides ( $r= 0,44$ ;  $p=0,02$ ) and with HDL ( $r= -0,16$ ;  $p=0,002$ ). The HDL tended to correlate with albumin ( $r= 0,56$ ;  $p=0,09$ ). However, there was not correlation between serum lactate deshydrogenase and glucose. C-reactive protein showed a positive correlation with triglycerides and serum lactate deshydrogenase, without correlation with others.

**CONCLUSIONS:** This study demonstrated abnormalities in lipids and protein profile in patients with hematological malignance disease. The relationship between serum lactate deshydrogenase, C-reactive protein, triglycerides and HDL suggests association with inflammation status induced by cancer. However, low prevalence of hyperglycemia and the lack of relation of the fasting glucose with C-reactive protein and serum lactate deshydrogenase need to be more studied, in order to clarify this hematological cancer response. Considering that these results are of a pilot study, a larger number of patients are required to establish a more precise conclusion.

**KEY WORDS:** Triglycerides. Lipoprotein. Protein. Cancer. Hematological disease. Inflammatory response.

## **INTRODUCTION**

Some evidence pointed that cancer patients demonstrate metabolic changes because of the disease, as well as its treatment and complications. Lipid profile changes, that are characterized by high triglycerides have been described, as well as hyperglycemia, insulin resistance and catabolism of muscle protein<sup>1</sup>. These changes seem to be associated with inflammatory response due to malignance tumor and/or to infectious or organic complications during anticancer therapy. This situation leads to the anorexia-cachexia syndrome<sup>2,3</sup>.

Hyperglycemia, hypertriglyceridemia and decrease in albumin synthesis are expected in inflammatory response because of the increase in pro-inflammatory cytokines production<sup>4</sup>. Studies have shown an inverse correlation between HDL-C and C-reactive protein (CRP), pointing to HDL-C as a negative indicator of acute inflammatory response<sup>5</sup>. In adults with cancer, Fiorenza et al. (2000) observed low levels of HDL-C and moderately high levels of triglycerides. The authors suggested an association with cell cytokines production in response to an inflammatory status due to malignance or with a direct cytokines produced by tumor cells<sup>6</sup>. A more recent finding is that the presence of an inflammatory response identifies patients with more aggressive disease and may also compromise the pharmacokinetics pharmacodynamics of anticancer drugs. Raised concentrations of some cytokines and phase acute positive proteins seem to be strong independent prognostic factors for survival in several malignant disorders. Thus, it is

believed inflammatory response is a potentially important factor in the interindividual variability of response and toxic effects to cancer chemotherapy<sup>7</sup>.

Halton et al. (1998) demonstrated an altered blood lipid profile in children with acute lymphoblastic leukemia (ALL) at diagnosis and after remission induction therapy associated with the administration of L-asparaginase<sup>8</sup>. Previous studies have reported marked lipoproteins and lipids abnormalities in patients with leukemia and lymphoma, specifically low levels of HDL-C and elevated levels of triglycerides<sup>9,10</sup>. High level of serum lactate deshydrogenase (LDH), a malignance biomarker, is found in higher risk patients, identifying those with a more aggressive cancer<sup>11</sup>. However, we cannot find any study about the relationship between lipids profile and LDH. Thus, the aim of the study was to evaluate the lipoproteins, triglycerides, glucose and proteins levels and their correlation with LDH in patients with hematological malignance disease.

## **SUBJECTS AND METHODS**

The study was carried out at the Pediatric Oncology Institute of Federal University of São Paulo from October 2003 to June 2005. The sample was composed of children and adolescents with newly diagnosed hematological malignancies followed by a cross-sectional study. The exclusion criteria was directed to patients that had used previous anticancer therapy, those who did not provide a blood sample or refused to participate the protocol study.

Blood sampling for laboratory analysis was performed at diagnostic after an overnight fast (12 hours) at admission and was colleted in EDTA or heparin anticoagulated tubes to be immediately centrifuged. Serum cholesterol was measured by calorimetric

method and HDL-C was measured enzymatically by immunoinhibition method Sera-Pak Plus. Serum triglycerides were determined by enzymatically method too, and LDL-C was calculated from measured values of total cholesterol, triglycerides, and HDL-C using the Friedewald equation:  $LDL-C = \text{total cholesterol} - HDL-C - (\text{triglycerides}/5)^{12}$ . LDH was determined by its activity in human serum and plasma on ADVIA 1650 Chemistry System. Glucose Hexokinase II (GluHII) (Bayer) was used to determine blood glucose and turbimetric method was used to measure serum albumin. Reference values of lipids were based on Guidelines of the National Cholesterol Education Program<sup>13</sup> (NCEP, 1992) and albumin and glucose were considered abnormal when below 3,5mg/dl and above 110mg/dl, respectively<sup>14</sup>.

C-reactive protein is a non-specific acute phase-reactive protein, which appears in the blood during an inflammatory process. Its measurement is performed by means of the antigen-antibody reaction by the end-point method. Reference values were in accordance with the quintile distribution, which considers high risk when values are above quintile 3 (1.9 mg/dl)<sup>15</sup>.

Medical Ethics Committee of Federal University of São Paulo approved the nutritional protocol which this analysis was part. The correspondent consent from all parents or guardians was obtained after the study protocol was explained to them.

### **Statistical analysis**

The analysis was performed to study prevalence of abnormalities in lipids, lipoproteins, glucose, albumin and C-reactive protein metabolism at diagnosis, mean and

median of the variables and their association with serum lactate deshydrogenase. For this purpose, Spearman test, a non-parametric analysis, was performed.

## RESULTS

Thirty-three patients with leukemia and lymphomas were analyzed; 25 males and 8 females. The median of age was 5.7 years (0.18 – 16.7); 26 children (below 10 years) and 7 adolescents (10 years or above). Diagnostics of cancer are demonstrated in table 1.

Thirty-two out of 33 (97%) and 7/30 (23.4%) demonstrated HDL and albumin below normal range, with medians of 20 mg/dl (3 – 37) and 3,65 g/dl (2,8 – 5,1), respectively. Glucose levels above normal were observed in 14.3% of the patients (median: 91.5 mg/dl; 61 – 149). Hipertriglyceridemia was detected in 66% (median = 133.5 mg/dl; 49 – 493) and hipercholesterolemia and high LDL levels in 3% (median = 129mg/dl; 72-233) and 6.3% (median = 77.5mg/dl; 31-167), respectively. In 8 patients C-reactive protein was collected; 50% of them (4/8) presented values above the 3<sup>d</sup> quintile.

Serum lactate deshydrogenase correlated with triglycerides ( $r= 0,44$ ;  $p=0,02$ ) and with HDL ( $r= -0,16$ ;  $p<0,003$ ). There was not a significant correlation between HDL and triglycerides ( $r= -0,20$ ;  $p=$ not significant) and between HDL and albumin ( $r= 0,56$ ;  $p=0,09$ ). However, there was not any correlation between serum lactate deshydrogenase with LDL and between and serum lactate deshydrogenase with glucose. C-reactive protein showed a positive but non-significant correlation with triglycerides ( $r=0,76$ ;  $p=0,10$ ) and significant correlation with serum lactate deshydrogenase ( $r=0,62$ ;  $p<0,01$ ), without correlation with others.

## DISCUSSION

The results of this study confirmed the lipid abnormalities observed in others, and demonstrated only a mild alteration in glucose levels. The primary change found in this study was the lipids and lipoprotein changes: high triglycerides levels and low HDL-C levels. They were associated with LDH and PCR. Three other studies with leukemia and/or lymphoma patients have showed very low levels of HDL-C, corroborating our results<sup>6,9,10</sup>. The rates of elevated levels of triglycerides in the present study also corroborate others that have previously reported a pattern of high triglycerides in cancer patients<sup>16</sup>, even though it remains controversy in some studies<sup>17</sup>.

Thus, like this, other studies have demonstrated changes in lipids and lipoproteins profile in patients with several malignancies<sup>8</sup>. However, in the present study we observed an association with the disease and inflammatory response.

Although many authors have reported abnormalities in lipid profile, studies of association of this pattern with other variables are scarce in medical literature. In the present study, when a correlation test was performed, we could observe statistical significance of the LDH with triglycerides, HDL-C and CRP levels. On the other hand, there were not any correlation of the LDH with both glucose and LDL-C levels.

There was also an association between HDL-C and albumin. It may be hypothesized that HDL-C, like albumin, behaves as a negative acute phase proteins, which are modified due to cytokines action<sup>4</sup>. Serum amyloid A (SAA) is an acute phase protein that is associated with HDL-C. SAA is one of the three major acute phase proteins, produced predominantly in the liver by hepatocytes in response to cytokines IL-1, IL-6 and TNF- $\alpha$ . Like CRP, serum levels may increase 1000 fold over normal levels during acute phase response. During inflammation, SAA readily associates with HDL, displaces apoA-1 and

becomes the predominant apolipoprotein of HDL. This process causes a remodeling of HDL to yield particles of higher density (HDL3) and larger size (HDL2) that are relatively depleted of apoA-1. The plasma clearance of SAA is more rapid than any of the other HDL apoproteins and HDL particles containing SAA have a greatly reduced half-life in the circulation<sup>18</sup>. The changes in HDL particles caused by inflammation reduce HDL-C levels and alter antioxidant properties of HDL and LDL protection from oxidation<sup>19</sup>. That condition is believed to play a role in the pathogenesis of organic toxicities<sup>20,21,22</sup>. For this reason, HDL-C levels should be better studied in cancer patients, because they could be related with organic failure and mortality. These data suggest that the prognosis significance of serial determination of HDL-C level in leukemia and lymphoma patients should be explored. In this aspect, studies about the association of the HDL-C with other biological markers, as well as disease markers are important in order to establish a prognosis condition.

On the other hand, high triglycerides could be deleterious to immune function, increasing the risk of infection. Nieman et al. (1999) demonstrated that serum triglycerides levels were elevated in obese subjects and were related to impairments in some aspects of immunity<sup>23</sup>. Other studies have demonstrated that a reduced clearance of triglycerides, specially related to high load of fat emulsion in parenteral nutrition led to a partial blockage of both macrophage and granulocyte function, resulting in a higher incidence of infectious complications and morbidity<sup>24,25,26,27</sup>.

Protein synthesis changes and high triglycerides levels observed in this study are expected in the metabolic response to stress, because of the increase in pro inflammatory cytokines induced by malignance disease. Concurrently, these data could suggest that an inflammatory response associated with cancer is responsible for these metabolic

disturbances. The importance of the correlations found in this study is that high levels of LDH identify high-risk patients in terms of complications and identify a more aggressive disease, which leads to a worse prognosis<sup>11</sup>.

However, the low prevalence of hyperglycemia and the lack of relation between glucose and C-reactive protein and glucose and serum lactate deshydrogenase were not a expected response. If this could be an uncommon behavior in inflammatory response induced by hematological malignance disease should be better studied. Thus, it is important to study glucose metabolism, since only fasting glucose was studied, in order to elucidate whether glucose present a different response and the involved mechanisms in this population. Considering that these results are generated of a pilot study, a larger number of patients are required to confirm these data and establish a conclusion, as well as to elucidate the mechanisms related to these responses.

## **CONCLUSIONS**

The findings of this study demonstrated a relationship between serum lactate deshydrogenase, C-reactive protein, triglycerides and HDL-C, suggesting an association with inflammatory status induced by cancer, and identified a different profile in the fasting glucose response.

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Table 1. Diagnostics of hematological cancers

<i>Diagnostic</i>	<i>Number</i>	<i>Percentage</i>
ALL	26	78.8
AML	2	6.1
NHL	2	6.1
HL	3	9.1
Total	33	100

ALL: acute lymphoblastic; AML: acute myeloblastic leukemia; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma.