

## **Serum Lactate Dehydrogenase Level in Acute Leukemias**

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### **Summary:**

#### **Background:**

Acute leukemias are clonal neoplastic proliferations of immature cells of the hemopoietic system. They are divided into acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and acute undifferentiated leukemia (AUL). LDH has been suggested as a possible non-specific tumor marker for many years, and total serum LDH is frequently elevated in neoplastic diseases. The aims of the study are to evaluate the significance of increased serum LDH levels in patients with acute leukemia and to determine the importance of serum LDH level in the follow up and assessment of treatment responses.

#### **Patients, Materials and Methods:**

This study was conducted at Baghdad Teaching Hospital in Medical City during the period of October 2003 till October 2004. It included 108 patients with acute leukemias. The patient groups were compared with 21 apparently healthy control subjects. All patients had full medical history, complete physical examination, and routine investigations and other specific investigations e.g. BM aspiration and biopsy. Serum lactate dehydrogenase LDH level was estimated in all patients serially during diagnosis and after chemotherapy as well as in control subjects.

#### **Results:**

Total serum LDH levels were significantly higher among patients with acute leukemias compared to that of the controls. Comparing the three types of leukemic patients, no significant difference was observed in total serum LDH levels between AML, ALL and AUL patients. Regarding treatment, levels of total serum LDH were significantly decreased in both remitter and non-remitter patients with acute leukemia with no significant difference between them.

#### **Conclusion:**

Although total serum LDH is higher in all acute leukemic patients, it is hardly discriminator between subsets of acute leukemia and is of little value in the prognosis and prediction of treatment response and outcome.

**Keywords:** LDH, acute leukemia.

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### **Introduction:**

The acute leukemias are defined as clonal, neoplastic proliferations of immature cells of the hemopoietic system, which are characterized by aberrant or arrested differentiation; they are divided into two main

groups: Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) (1).

The AML is a clonal, malignant disease of hemopoietic tissue that is characterized by proliferation of abnormal (leukemic) blast cells, principally in the bone marrow, and

impaired production of normal blood cells. The ALL, is a neoplastic disease that results from somatic mutation in a single lymphoid progenitor cell at one of several discrete stages of development. The proliferation and accumulation of blast cells in the marrow result in suppression of hematopoiesis and thereafter, anemia, thrombocytopenia and neutropenia (2).

For the last three decades, acute leukemia has traditionally been classified according to the French-American-British (FAB) classification, based on the cytomorphological examination of the peripheral blood and marrow smears supplemented by few essential cytochemical stains. In the FAB classification the diagnosis of acute leukemia is established if the marrow blast cell is >30%. Initially nine subtypes were identified, three lymphoid (L1 through L3) and six myeloid (M1 through M6) (6)

Lactate dehydrogenase (LDH) enzyme catalyses the reversible oxidation of pyruvic acid (PA) (4). Specifically, it is important in Embden Myerhof metabolic pathway of glycolysis, which plays a pivotal role in tissues, which use glucose (e.g. skeletal muscles) (5). LDH is ubiquitous cytoplasmic enzyme that is widely distributed, found in all cells in man, but is specifically plentiful in cardiac and skeletal muscles, liver, kidney, red

blood cells, brain, lung, lymph nodes and white blood cells (6).

Active LDH molecule has a molecular weight of 13000 Daltons. It is a tetramer composed of four polypeptide subunits of two types: H (Heart), and M (Muscle) (7). In man, as many as five physically distinct isoenzymes of LDH exist, and are known as LDH - 1, LDH - 2, LDH - 3, LDH - 4 and LDH - 5 (8) .

In patients with acute leukemias, serum LDH can show a moderate increase in only some cases of acute nonlymphoblastic leukemias with FAB M4 and M5 cytotypes, whereas in acute lymphoblastic leukemia. LDH level almost always increase, sometimes markedly, an event related to the number of white blood cells during remissions or relapses of the disease (9,10). On the other hand, it was suggested that elevated serum LDH may relate to total leukemia cell mass, although values did not correlate neither with initial white blood cells nor circulating lymphoblastic count (11). This lack of correlation between total serum LDH and lymphoblast count is consistent with the poor correlation noticed between serum and intracellular LDH isoenzyme pattern (12). This may be due to the fact that a significant contribution to serum LDH may come from non - leukemic source (13).

#### **Aims of the Study:**

The aims of the study are to evaluate the significance of increased serum LDH levels in patients with acute leukemias and to determine

the importance of the serum LDH level in the follow up and assessment of treatment responses.

#### **Patients, Materials and Methods:**

This study has been conducted during the period from October 2003 till October 2004 at Baghdad Teaching hospital in Medical City. Patients selected were newly diagnosed cases of acute leukemia. Patients who have been diagnosed previously and admitted because of relapses or other complications of acute leukemia were excluded.

The study included (108) patients with acute leukemias: of these, (74) patients were with AML, (44 male + 30 female), (26) patients with ALL (21 male + 5 female) and (8) patients with AUL (5 male + 3 female). The patient groups were compared with 21 apparently healthy control subjects (14 male + 7 female).

Full medical history and clinical examinations were taken from all patients. Investigations done in all patients were complete blood count and ESR, reticulocyte count, Coomb's test, renal function test, uric acid and electrolytes, liver function tests, total serum protein, serum albumin, general urine examination, chest X-ray, abdominal and pelvic ultrasound and bone marrow aspiration and trephine biopsy.

From each individual 2 ml of blood was harvested and centrifuged and the sera were immediately frozen at -80C till used to determine the serum LDH level. It was estimated in all patients as well as in control subjects. The range of serum LDH level estimated in control subjects was 80-185 U/L.

The cut off level of serum LDH was considered to be 200 U/L. Levels above that were considered to be elevated. Analysis of serum LDH isoenzymes was not done in this study.

Electrocardiography was done in all patients at risk of ischemic heart diseases to exclude acute myocardial infarction. Measurement of serum creatinine phosphokinase level was done in all patients with muscle weakness and/or muscle pain and tenderness to exclude muscle disease. Cases of hemolytic anemias were excluded by measuring of reticulocyte count and doing Coomb's test and megaloblastic anemia was excluded by blood film examination. Classification of AL was done according to FAB system.

### **Results:**

A total of 108 patients (70 males, 38 females), who fulfilled the criteria of acute leukemia were participated in the present study. Patients were classified according to FAB classification as 74 patients (68.5%) with AML, 26 patients (24.1%) with ALL, and 8 cases (7.4%) with AUL.

Twenty-one healthy (14 males, 7 females) persons were participated as a control group. Total serum LDH levels estimated in acute leukemia patients and control group are shown in table 1. Among the 74 AML patients who were assigned to the standard chemotherapy protocol of AML treatment, 2 patients died during the diagnosis and before receiving chemotherapy treatment, from septicemia and 7 patients died after the initiation of induction chemotherapy from severe infection septicemia and severe bleeding, thus were excluded from the study group. Among the remaining 65 patients, 13 (20%) passed into complete remission while the other 52 patients (80%) remained as non-remitter. The 26 ALL patients were assigned to the standard chemotherapy for ALL. Within the first few days of treatment, 4 patients died from severe bleeding and septicemia, and excluded from study group. The remaining 22 patients, 17

No patient included in the study has had acute myocardial infarction, pulmonary embolism, myositis and other muscle diseases, viral hepatitis and other causes of acute and chronic liver disease, acute and chronic renal diseases, acute pancreatitis, and megaloblastic and hemolytic anemia.

Statistical analysis was done by using statistical package for social science (SPSS 7.5). Associations between different variables were measured by using t-test and analysis of variance (ANOVA test) association between continuous variables was measured by using correlation test. P value < 0.05 was considered as the level of significance.

(77%) passed into complete remission while 5 (23%) remained as non-remitter. 8 AUL patients received chemotherapy. One patient died from septicemia and was excluded from study group, 2 (24%) patients passed into complete remission and the remaining 5 patients (71%) remained as non-remitter. Table 2 shows the distribution of AL patients according to the response to treatment.

Base-line total serum LDH levels were significantly higher (P value 0.0001) among acute leukemia patients compared to the control subjects (305.6 u/l  $\pm$  45.8 Vs 117.6 u/l  $\pm$  33.8 respectively). When comparing the three types of AL patients, no significant difference was observed in the base-line total serum LDH level between AML, ALL, and AUL patients (328 u/l  $\pm$  79, 300 u/l  $\pm$  74, 299 u/l  $\pm$  58 respectively) (P value 0.06) as shown in table 3.

In response to induction treatment, levels of total serum LDH levels significantly decreased (P value 0.001) in both remitter and non-remitter patients with acute leukemia and no significant difference between the three types of acute leukemia was observed (P value 0.065) as shown in table 3.

**Table 1: Sample distribution and S.LDH levels of AL patients and control subjects**

Sample	Total No. (%)	♂ (%)	♀ (%)	No. of patients with S.LDH ≥200 U/L (%)	No. of patients with S.LDH < 200 U/L (%)
AML	74 (68.5%)	44 (59.9%)	30 (40.5%)	56 (76%)	18 (24%)
ALL	26 (24.1%)	21 (80.7%)	5 (19.3%)	17 (65%)	9 (35%)
AUL	8 (7.4%)	5 (62.5%)	3 (37.5%)	6 (75%)	2 (25%)
Total	108 (100%)	70 (64.9%)	38 (35.1%)	79 (73%)	29 (27%)
Control	21	14 (66.7%)	7 (33.3%)	-----	21

S.LDH: serum lactate dehydrogenase  
 Normal range of S.LDH: 80-185 U/L

**Table 2: Distribution of AL patients according to the response to treatment**

Sample	Total	No. of dead patients (%)	No. of alive patients (%)	No. of remitter patients (%)	No. of non-remitter patients (%)
AML	74	9 (12%)	65 (88%)	13 (20%)	52 (80%)
ALL	26	4 (15%)	22 (85%)	17 (77%)	5 (23%)
AUL	8	1 (12%)	7 (87%)	2 (29%)	5 (71%)
Total	108	14 (13%)	94 (87%)	32 (34%)	62 (66%)

**Table 3: Total serum LDH enzyme concentration (U/L) at baseline and during induction chemotherapy among AL patients (AML, ALL, AUL) (remitters and non-remitters)**

Patient group		Baseline	2 WK	4 Week
<b>AML</b>	Remitter Range Mean ± SD	215-430 328 ± 79	205-310 250 ± 38	180-285 223 ± 31
	Non-remitter Range Mean ± SD	240-285 250 ± 20	140-220 180 ± 35	130-210 180 ± 33
<b>ALL</b>	Remitter Range Mean ± SD	230-420 310 ± 40	190-340 250 ± 31	160-285 215 ± 21
	Non-remitter Range Mean ± SD	210-400 300 ± 74	170-320 245 ± 25	165-215 190 ± 15
<b>AUL</b>	Remitter Range Mean ± SD	220-360 299 ± 58	210-260 235 ± 25	200-260 230 ± 30
	Non-remitter Range Mean ± SD	215-360 287 ± 59	200-280 240 ± 43	200-230 215 ± 18
<b>Control</b>	Range Mean	85-180 117 ± 34	-----	-----

Serum LDH levels for total AL patients vs control P value 0.0001.  
 Baseline serum LDH levels for AML vs ALL vs AUL P value 0.06.  
 Baseline vs post-induction serum LDH levels for AL patients P value 0.001.  
 Post-induction serum LDH levels for AML vs ALL vs AUL P value 0.065.  
 Total remitters vs non-remitters P value 0.07

### **Discussion:**

Lactate Dehydrogenase (LDH) is perhaps the most common enzyme used in cancer patients for prognostic purposes. It has an important role in germ cell tumors and in association with chorionic gonadotropin, can predict response to therapy and the prospects of remission. It is also a valuable prognostic marker in lymphoma, leukemia, and in colonic cancer (14).

In this study the total serum level of LDH has been serially determined in the sera of patients with acute leukemia at the diagnosis and during the course of induction therapy aiming to assess its diagnostic and prognostic significance.

Total serum LDH level was found to be elevated among acute leukemia (AML, ALL, AUL) patients in this study and the initial high levels of serum LDH in patients with acute leukemias were highly significant (P value 0.0001) when compared with control levels.

The mean serum LDH level was slightly higher in AML (328 u/l) compared to ALL and AUL; however, the difference was not statistically significant (P value 0.06).

The results of this study are similar to those found by Scott et al, Hisconmez et al and Ghosh et al who all found that serum concentration of LDH was increased in most cases of acute leukemia cases irrespective of the morphological type (15, 16, and 17).

In Iraq a study performed by Al-Dorri indicated that the mean serum LDH activity was found to be elevated among all leukemic patients and the mean serum LDH level was higher in ALL compared to AML cases; however, the difference was not statistically significant (18).

Pandit et al reported a significant rise in LDH enzyme in cases of acute leukemia at presentation with significant lowering of total

serum LDH with its LDH2 and LDH3 isoenzymes in patients responding to chemotherapy, while non-remitter had practically unaltered values (19)

Salem and Omer reported a high LDH and  $\alpha$ -hydroxybutyrate dehydrogenase in patients with acute leukemia upon presentation, and with the institution of induction therapy, enzymatic activities dropped gradually till normalization. This was coincidental with clinical and hematological remission. Furthermore, when the patients were followed during maintenance therapy, an increase in these two enzymes was found to be associated with relapse state (20).

In this study, with the use of serial estimation of LDH activity during induction therapy for patients included in this study, although there was a smooth and continuous decline in the enzyme activity in acute leukemia patients which reached levels significantly lower than baseline activity as early as 2 weeks, it was still higher than the normal controls, furthermore, there was no significant difference between remitters and non remitter patients. So, the total serum LDH enzyme activity was invalid in predicting responses to induction treatment and relapse-free survival in acute leukemia, and the proportion of cases entering remission, fail to remit or die during induction as well as duration of relapse-free survival, were clearly unrelated to serum total LDH activity.

Blatt J. et al found that LDH3 isoenzyme is the predominant isoenzyme in the lymphoblasts of ALL patients. These findings can provide supportive evidence to indicate LDH3 isoenzyme as the most probable specific isoenzyme for leukemic blast cells (21). Unfortunately our study did not include the LDH isoenzyme estimation.

probable specific isoenzyme for leukemic blast cells, the addition of serum LDH-3 isoenzyme measurement to the routine investigations performed for patients with acute leukemia is highly recommended.

3. It is recommended to study thoroughly the LDH isoenzymes pattern in leukemic blast cells in relation to disease activity and leukemia subtype.

### **Conclusions and Recommendations:**

1. Although total serum LDH is higher in all acute leukemia patients, it is hardly differential between subsets of acute leukemia. and of little value in the prognosis and prediction of treatment responses and outcomes.

2. Since the increase of total serum LDH concentration may be non-specific for acute leukemia and LDH-3 isoenzyme is the most

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