# Serum lactate dehydrogenase level in hodgkin's disease relationship to certain features at the time of diagnosis

Mutaz F. AL-hadithi* FICMS,CABM
Fuad M. AL-Kasab* MRCP, FRCP
Khalid A. AL-Khazraji* CABM

## Summary:

***Background:*** *lactate dehydrogenase (LDH) has been suggested as a non-specific marker in many tumors including Hodgkin's disease (HD). The aim of this study is to verify the relationship of serum LDH level to certain features at the time of diagnosis of HD.*

***Patients, Materials and Methods:*** *This study was conducted at the Medical City-Baghdad during the period of October 2000 till April 2002. The study included 54 patients with HD and 55 healthy control subjects. For all patients routine investigations and other specific investigations for staging purposes were done when possible. Serum LDH level was estimated in all patients and control subjects.*

***Results:*** *High serum LDH levels were significantly related to advanced stages of disease (III and IV), presence of mediastinal and/or hilar tumors, splenomegaly, and liver and bone marrow involvement, but not significantly related to histological types, B-symptoms, bulky disease, intraabdominal lymphadenopathy and disease relapse.*

***Conclusion:*** *The serum LDH concentration, at the time of diagnosis of HD, is significantly related to several features, many of them are well known poor prognostic features in HD.*

***Key words:*** *Lactate dehydrogenase, Hodgkin's disease*

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## Introduction

Hodgkin's disease (HD) is a malignant lymphoma that is distinguished from other lymphomas by the presence of large binucleated or multinucleated cells (i.e. Reed–Sternberg cells) [1]. Lactate dehydrogenase enzyme (LDH) catalyses the reversible oxidation of pyruvic acid (PA) and lactic acid (LA). 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) [2]. LDH has been suggested as a possible non-specific tumor marker for many years [3]. Serum LDH has the advantage of being a simple inexpensive hospital test that is easily available with quick result [2]. Elevations of serum LDH levels have been found to reflect growth and regression of various malignant neoplasms[3]. The serum LDH level determined at the time of diagnosis provides important prognostic information in patients with Hodgkin's disease. The median survival of patients with normal values was significantly more than that of patients with elevated values [4]. The prognostic power of LDH persisted after adjustment for age, sex, symptom class, stage, histology, or type of therapy [5].

* *Dept of Medicine, College of Medicine, University of Baghdad*

The aim of this study was to find out the relationship of the increase in serum LDH level to certain features at the time of presentation of patients with HD. These features are the histological type of HD, the clinical stage, the presence of B-symptoms, bulky disease, splenomegaly, liver and bone marrow involvement, mediastinal and/or hilar tumors, intraabdominal lymphadenopathy and disease relapse.

## PATIENTS, MATERIALS AND METHODS:

This study has been conducted during the period of October 2000 till April 2002 at the Medical City, Baghdad, Iraq. 54 patients with new diagnosis or recent relapse of Hodgkin's disease were interviewed and examined before treatment together with 55 apparently healthy subjects (control subjects) in Baghdad teaching hospital and Nursing Home hospital. Table (1) shows the characteristics of the study populations. 47 patients were new cases and 7 patients were relapsed cases after complete remission. The mean duration of disease in patients with HD was 5.7 months. Full medical history was taken from all patients and specific questions were asked about the presence of B-symptoms (fever, night sweating, or weight loss of more than 10 % of original body weight within 6 months), the presence of ischemic

chest pain , muscle pain and/or weakness and various symptoms regarding involvement of various organ systems. Clinical examination included examination of all lymph node areas, abdominal examination for hepatomegaly, splenomegaly, and other abdominal masses and examination of various organ systems. Investigations included in all patients complete blood count, reticulocyte count, routine biochemical tests, chest X-ray, abdominal and pelvic ultrasound, and bone marrow aspirate and trephine biopsy. From each individual in the study 2 milliliters of blood was harvested and centrifuged, and the sera were immediately frozen at – 80 °C till used. Serum LDH level was estimated in the teaching laboratories of the Medical City using the colorimetric method. The kit for estimating serum LDH level was supplied by the Randox Laboratories Ltd., United Kingdom. The range of S.LDH level estimated in control subjects was 80-185 U/L. The upper normal level of S.LDH was considered to be 200 U/L, and values above that level were considered to be elevated. Histological confirmation of the diagnosis was established mostly by lymph node biopsy, less commonly by bone marrow biopsy, and occasionally by other tissue biopsies. CT scan of chest and abdomen was not done in all patients. Laparoscopy with liver and/ or lymph node biopsy and laparotomy with splenectomy and/or lymph node biopsy were done in some patients. Other causes of increased serum LDH levels were excluded from the study by history, clinical examination, and appropriate investigations. Lymphangiogram was not done in our patients. Staging was done according to the Ann Arbor staging system. Bulky disease was defined as medistinal tumor width on chest X-ray more than one-third of the chest width and/or lymph node size more than 10 cm in maximum dimension.

All data were arranged and tabulated in numbers, means ± SD, and percentages. Associations between different variables were measured by using Chi-Square test and Fisher's test as appropriate. P value< 0.05 was considered as the level of significance.

## RESULTS:

The range of S.LDH level was 110-520 U/L in patients with HD, and 80-185 U/L in control subjects. The mean S.LDH level ± SD was 284 ± 105.5 in patients with HD, and127 ± 21.3 in control subjects. S.LDH level was elevated in 21 patients (38.8%) with HD (Table1). High serum LDH levels were significantly related to advanced stages of disease (III and IV), the presence of mediastinal and/or hilar tumors, splenomegaly and liver and bone marrow involvement by HD, but not significantly related to histological types, B-symptoms, bulky disease, intraabdominal lymphadenopathy and disease relapse (table 2).

## DISCUSSION:

In this study, increased S.LDH levels were seen more frequently in mixed cellularity and lymphocyte-depleted than in lymphocyte-predominant and nodular sclerosis histological types, but the association was statistically insignificant (P value<0.092). These results are comparable to those found by Chim CS. et al, Gobbi PG. et al and Schilling RF. et al who all found no significant correlation between S.LDH levels and various histological subtypes of HD [4-6]. On the contrary, Boyd and Feinstein and Keller AR. et al reported that elevated S.LDH levels were significantly related to mixed cellularity and lymphocyte-depleted subtypes [7,8], but in these studies the proportions of cases of mixed cellularity and lymphocyte-depleted subtypes were more than in our study. Additionally, most of the patients were in stage III and IV disease. Regarding the stage of disease, we found that increased S.LDH values were seen more frequently in stages III and IV than in stages I and II and the association was statistically significant (P value < 0.014). When considering the association between S.LDH levels and bulky disease, although increased S.LDH levels were seen more frequently in bulky than in non-bulky tumors, the association was statistically insignificant (P value<0.1047). The results of this study regarding the association between S.LDH levels and stage of disease were comparable to those found in other studies although in our study staging was not optimal. Significant association between increased S.LDH levels and advanced stages of disease was shown by Chim CS. et al, Gobbi PG. et al, Robert F. Schilling et al and Boyd and Feinstein [4-7]. Chim CS. et al and Gobbi PG et al have found that there was no significant association between high S.LDH levels and the presence of bulky disease, while Schilling RF. et al and Boyd and Feinstein reported that there was a significant association between high S.LDH levels and bulky tumor masses. The explanation of this difference is probably related to the difference in the numbers of cases of bulky disease in different studies and because the definition of bulky disease is liable to subjective variation. In this study increased S.LDH levels were found more frequently in the presence of B-symptoms than in their absence, but this association was insignificant (P value < 0.058). Gobbi PG. et al and Schilling RF. et al reported that there was no significant association between S.LDH level and B-symptoms, similar to our result [5,6]. On the other hand, Chim CS. et al and Boyd and Feinstein reported that there was a significant correlation between S.LDH level and B-symptoms [4,7]. This difference might be due to the fact that in the last two studies, most of patients with B-symptoms were in stage III and IV disease, while in our study and in the first two studies [5,6]

the distribution of patients with B-symptoms according to the clinical stages was nearly equal in stages I, II and stages III, IV and since advanced clinical stages were significantly associated with high S.LDH values, this could result the significant association in the last two studies [4,7]. In this study, increased S.LDH level was significantly associated with the presence of splenomegaly (P value < 0.024). Similar association was present between high S.LDH level and the presence of liver involvement (P value < 0.013). Gobbi PG. et al found that high S.LDH levels significantly correlated with splenomegaly and liver involvement [5]. Schilling RF. et al and Ascari E. [6,9] also reported similar findings. In this study, increased S.LDH levels were significantly associated with bone marrow (B.M) involvement (P value < 0.038). Gobbi PG. et al have found that increased S.LDH levels were significantly associated with B.M involvement by lymphoma [5]. Similar finding was also reported by Ascari E. [9]. It was also found that cases of lymphocyte-depleted HD, which presented with disease restricted to the B.M and/or retroperitoneal lymph nodes were also associated with very high S.LDH levels [10]. B.M involvement usually occurs in advanced disease and the majority of patients have B-symptoms [11,12]. In this study, high S.LDH was significantly associated with the presence of mediastinal and/or hilar tumors (P value < 0.049). Schilling RF. et al indicated that there was a significant association between high S.LDH values and the presence of mediastinal and/or hilar tumors [6]. Smolewski P. et al reported the same finding and indicated that this association was more significant in nodular sclerosis and mixed cellularity histological subtypes [13]. Chim CS. et al and Jurisic V. et al showed that high S.LDH levels were associated with mediastinal and hilar tumors even in localized intrathoracic HD [4,14]. In this study, intraabdominal lymphadenopathy was not significantly related to increased S.LDH levels (P value < 0.104). Schilling RF. et al indicated that patients in stage III disease having involvement of lower abdominal lymph nodes had higher S.LDH levels compared to those in whom abdominal involvement was limited to spleen and/or upper abdominal nodes i.e. splenic, celiac, or hepatic portal nodes [6]. Gobbi PG. et al reported that in HD, high S.LDH levels correlated with intraabdominal lymphadenopathy [5]. On the contrary, Chim CS. et al and Jurisic V. et al showed that there was no significant association between high S.LDH levels and intraabdominal lymph node involvement [4,14]. In HD, lymphangiography is the best way to evaluate the retroperitoneum because it can detect nodes involved by the disease yet not enlarged and thus cannot be detected by CT scan. Staging laparotomy is the most accurate means of determining the extent of abdominal involvement by HD [15]. In this study, lymphangiography was not done in any patient, abdominal CT scan was not a routine study in all patients, and laparotomy was done only in the presence of detectable intraabdominal lesions by imaging studies and in the absence of peripherally accessible lesions. Therefore, we might have missed some of HD patients with intraabdominal lymphadenopathy. In this study, high S.LDH levels were not significantly associated with relapsed cases (P value < 0.119). Ascari E. and Gobbi PG. found that relapsed cases of malignant lymphomas (Hodgkin and non-Hodgkin) were significantly associated with high S.LDH levels regardless of the histological type or the stage of disease [9]. Jurisic V. et al showed the same association in HD [14]. On the other hand, Child JA. et al and Schneider RJ. et al showed that elevated S.LDH levels were not significantly associated with relapsed cases of HD [16,17]. This difference might be due to the difference in number of relapsed cases of HD in the different studies. In our study, the relapsed cases constituted only about 13% of patients with HD, so they might not be representative of the significance of clinical relapse in relation to S.LDH level.

## CONCLUSION:

The serum LDH concentration, at the time of diagnosis of Hodgkin's disease, is associated with several features, many of them are well known poor prognostic features in Hodgkin's disease.

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**ble (1): Characteristics of the Sample Populations and Serum LDH Levels in Patients with Hodgkin's Disease and Control Subjects.**

| Sample Description | Hodgkin's Disease | Control |
|---|---|---|
| Number | 54 | 55 |
| Sex Distribution | ♂= 33 ♀=21 | ♂= 30 ♀=25 |
| Mean Age ± SD (year) | Total =28.7 ± 14.4<br>♂ = 30.9±14.7<br>♀ =25.3±13.5 | Total=31.8 ± 12.5<br>♂=32.6 ±13.0<br>♀=30.5±11.7 |
| Mean Duration of Disease (Months) | Total=5.7<br>♂ =5.9<br>♀=4.8 | |
| S.LDH Level (Range)(U/L) | 110 – 520 | 80 – 185 |
| Mean S.LDH Level ± SD(U/L) | 284 ± 105.5 | 127 ± 21.3 |
| No. of Patients with Increased S.LDH Level (%) | 21 (38.8) | |

**LDH: Lactate dehydrogenase**
**SD: Standard deviation**
**♂: Males**
**♀: Females**

Table (2): Serum LDH Levels in Relation to Histological Types, Clinical Stage, B-Symptoms, Bulky Di
Mediastinal and/or Hilar Tumors, Splenomegaly, Liver Involvement, Bone Marrow Involvement,
Intraabdominal Lymphadenopathy and Relapsed Disease in Patients with Hodgkin's Disease.

| Disease Category | | No. of Patients with Increased S.LDH | % | P. Value |
|---|---|---|---|---|
| Histological Types | Lymphocyte- predominant | 1 | 14.2 | 0.092 NS |
| | Nodular sclerosis | 6 | 28.5 | |
| | Mixed cellularity | 9 | 47.3 | |
| | Lymphocyte-depleted | 5 | 71.4 | |
| Stage of Disease | I | 1 | 14.28 | 0.014 |
| | II | 7 | 31.81 | |
| | III | 10 | 50 | |
| | IV | 5 | 100 | |
| B-Symptoms | Present | 14 | 53.8 | 0.058 NS |
| | Absent | 8 | 28.57 | |
| Bulky disease | Present | 11 | 52.38 | 0.1047 NS |
| | Absent | 10 | 30.3 | |
| Splenomegaly | Present | 7 | 77.77 | 0.024 |
| | Absent | 14 | 31.11 | |
| Liver Involvement | Present | 5 | 100 | 0.013 |
| | Absent | 16 | 32.65 | |
| Bone Marrow | Present | 4 | 100 | 0.38 |
| | Absent | 17 | 34 | |
| Mediastinal and/or | Present | 12 | 54.54 | 0.049 |
| | Absent | 9 | 28.12 | |
| Intraabdominal | Present | 11 | 52.38 | 0.104 N.S. |
| | Absent | 10 | 30.3 | |
| Relapsed Disease | Present | 5 | 71.42 | 0.139 NS |
| | Absent | 16 | 34.04 | |

LDH: Lactate dehydrogenase
NS: not significant