Serum Lactic Dehydrogenase (LDH) Activity in Lymphomas: Prognostic Significance and Relationship to Presentation, Stage and Histologic Type

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ABSTRACT

Background and Objective: Studying the relation of LDH level to presentation, stage and histological subtype of lymphoma and to evaluate its prognostic significance.

Patients and Methods: Hospital records of 13 Hodgkin's and 37 non-Hodgkin's lymphoma patients were reviewed. Patients were followed up; their serum LDH levels were measured after completing therapy. A group of 25 apparently healthy persons matched for age and gender served as controls and their serum LDH levels were measured.

Results: Serum LDH activity was significantly higher in lymphoma patients compared to control group (P <0.001); although none of the Hodgkin's lymphoma patients had serum LDH level above the normal range. Serum LDH activity was not of value in relation to grade and histological subtype of lymphoma, and ESR; but significantly associated with stage of the disease. There was no significant difference in the mean enzyme level among patients who responded and those who not responded to chemotherapy.

Conclusions: Serum LDH level was of no clinical or prognostic significance in Hodgkin's lymphoma. The stage of the disease rather than serum LDH value was the main prognostic marker in non-Hodgkin's lymphoma.

Key words: Hodgkin's Lymphoma, Non-Hodgkin's lymphoma, LDH.

INTRODUCTION:

Lactic dehydrogenase (LDH), a pyridine-linked enzyme found in virtually all animal and human tissues, functions primarily in the metabolism of glucose, catalyzing the reduction of free pyruvate to lactate during the last step of glycolysis, as well as the conversion of lactate to pyruvate in gluconeogenesis. Five LDH isoenzymes have been described (LDH-1,2,3,4&5), its concentration is highest in liver followed in descending order in skeletal muscle, heart and kidney[1]. Escape of LDH due to damage of cells in any of these tissues will tend to produce elevated serum levels which are often transient[2]. Since long time, it has been observed that high level of serum LDH are seen in patients with different malignancies[3]. Increased LDH levels has been reported in solid tumors, leukemia and diffuse lymphoma, particularly Burkett's lymphoma, although correlation has been established with any specific neoplastic disease or with any clinical or histologic parameter[4,5]. The metabolism in malignant cells is rather distinct, there is poor integration between the glycolytic sequence and tricarboxylic acid cycle, hence the cells tends to utilize from five to ten times as much glucose as do normal tissues, converting most of it into lactate[1]. Whether the increased serum levels of LDH commonly found in cancer patients reflect greater production and release of the enzyme by malignant cells, is not clear[6]. LDH is one of the components of lymphoma International Prognostic Index; it represent a valuable biochemical parameter in patients with lymphomas and its serum level has been considered as very important in the evaluation of disease extension in both Hodgkin's and non-Hodgkin's lymphomas[7,8]. Considering that elevation of serum LDH level correlates with

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represents an important independent prognostic factor for patients with lymphomas[11,12].In this study, serum LDH level was measured and its relation with presentation, stage of the disease, histological type and response to therapy was investigated in patients with Hodgkin's and non-Hodgkin's lymphoma.

PATIENTS METHODS:

Follow up of 13 patients with Hodgkin's lymphoma (HL) and 37 patients with non-Hodgkin's lymphoma (NHL) was done from April to October 2009. Hospital records of the registered lymphoma patients in Nanakaly hospital (40 cases) and Rizgary teaching hospitals (10 cases) in Erbil City were reviewed. Patients were registered between November 2008 and May 2009; they were referred from different areas of Iraqi Kurdistan and neighboring governorates. Patients had already a confirmed histologic diagnosis of lymphoma according to the working formulation. Personal and clinical data of age, gender, address, and presenting features, together with results of full physical examination, stage of disease and histologic subtype were recorded into a data collection sheet. Likewise, reports of radio-imaging investigations and results of all laboratory investigations including CBC, tissue biopsy, bone marrow aspirate and biopsy and biochemical tests including pretreatment serum LDH level were recorded. Patients were contacted and reassessed following completion of chemotherapy. Response to therapy, and remission status for each patient was recorded as decided by the specialist physician and as stated in patient's file. Serum LDH level was re-measured using similar procedure as for the initial pretreatment sample (ILab Chemistry System) at Nanakaly hospital's biochemistry laboratory. LDH level of > 460 U/L is considered high according to *ILab Test ^{TM} LDH-P (Normal range is 230-460U/ L)*. Twenty five, apparently healthy persons matched for age and gender served as controls. Statistical analysis was performed using Stata statistical software. Results are expressed as mean±SD. Differences between lymphoma and control groups were assessed using the Student's t test. Differences between variables in the different groups were assessed using one-way analysis of variance (ANOVA). Regression and correlation analyses between variables were performed by calculating Pearson's correlation coefficients (r). P values of > 0.05 were considered not significant[13].

RESULTS:

Age and gender distribution of all lymphoma patients, HL and NHL, and control groups are summarized in (Table 1). Serum LDH levels in the lymphoma and control groups are presented in (Table 2). The mean serum LDH level was significantly higher in lymphoma patients compared to control group (P <0.001). When HL and NHL patients were separately studied against the control group the difference was significantly high, more remarkably in NHL patients. On the other hand, the mean serum LDH level in NHL patients was significantly higher than that of HL (P <0.001) (Table 2).

Table 1: Age and sex distribution of patients and controls

Age	Cases				Controls	
	HL		NHL			
	Male	Female	Male	Female	Male	Female
1-15	2	0	5	2	4	2
16-30	3	4	6	0	3	2
31-50	3	0	6	1	4	3
>50	0	1	9	8	4	3
Totals	**8**	**5**	**26**	**11**	**15**	**10**
	13		**37**		**25**	

Table 2: Mean level of serum LDH in patients and controls.

	No. of patients	Serum LDH activity (U/L)		Serum LDH range (U/L)	P value
		Mean	SD		
HL	13	306.3	54.1	235-432	***0.004***
NHL	37	777.9	334.5	300-1817	***< 0.001***
Controls	25	247.6	54.02	175-350	

P value < 0.001* (*difference between mean serum LDH level of NHL and HL cases)

There was no relationship between mean LDH level and histological subtype among HL patients. While in NHL, the mean LDH level among high-grade NHL patients was somewhat higher than that of patients with intermediate grade NHL though this difference did not reach a statistically significant level (P = 0.082). Table 3 shows the relation of histologic sub-type of NHL to the mean LDH level.

Table 3: Relation of histologic sub-type of NHL to the mean serum LDH (IU/L) level

	Sub-type	No.	Serum LDH (Mean-SD)	P value
NHL	**Intermediate Grade**	**20**	**683.5 ± 191.1**	***0.082***
	High Grade	**17**	**888.9 ± 429.2**	

Pearson correlation analysis of serum LDH among HL and NHL patient groups showed no correlation between serum LDH levels and ESR (r=0.36 for HL and r=0.15 for NHL) (Figure 1). The association between serum LDH level and ESR in HL and NHL patient groups was weak and statistically non-significant; β =0.73, p=0.22 for HL and β=-0.14, p=0.96 for NHL. Correlation between the enzyme level and bone marrow involvement was statistically not feasible because only two patients with NHL had bone marrow involvement at presentation.

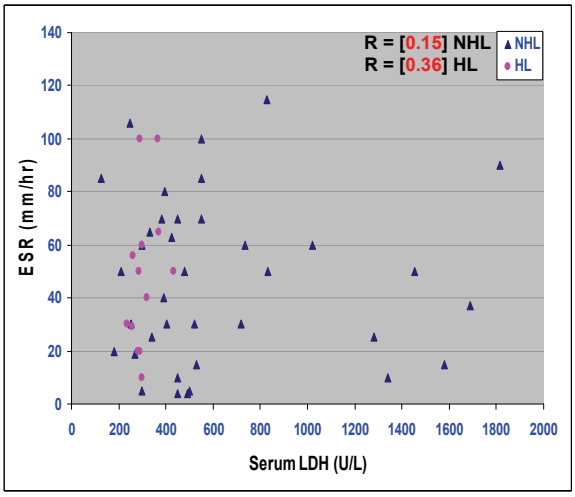

Figure 1: Correlation between serum LDH level and ESR in HL and NHL

(Table 4) shows relation of extent of the disease represented by stage of lymphoma to the mean serum LDH level. It was observed that the higher is the stage of the disease, the more serum LDH level will be. This difference was notably high among NHL groups.

Table 4: The stage of lymphoma in relation to mean serum LDH (IU/L) level.

	Stage	No.	Serum LDH (Mean±SD)	P value
HL	I & II	8	283.5 ± 26.4	***0.048***
	III & IV	5	342.8 ± 69.6	
	Total	13	306.3 ± 54.1	
NHL	I & II	14	619.7 ± 324.3	***0.025***
	III & IV	23	874.2 ± 308.8	
	Total	37	631.5 ± 447.4	

(Table 5) shows the effect of chemotherapeutic treatment on serum LDH level in HL and NHL patients. As illustrated, there was a significant fall in serum LDH activity by completion of the chemotherapeutic courses in both HL and NHL groups of patients.

Table 5: Mean serum LDH level before and after treatment in Hodgkin and non-Hodgkin Lymphoma

	No.	Mean LDH activity (U/L)		P value
		Before therapy	After therapy	
HL	13	306.3 ± 54.1	211.5 ± 31.1	*< 0.001*
NHL	37	777.9 ± 334.5	304.7 ± 74.9	*< 0.001*

Majority of HL patients (77%) reached remission, while only 40.5% of NHL patients got remission after completing chemotherapy as shown in (Table 6). There was no significant difference in the mean LDH level among patients who responded to chemotherapy and those who partially responded or resisted therapy.

Table 6: Mean serum LDH level in responded and resisted lymphoma patients

		Mean LDH activity (U/L)		P value
		Responded to therapy	Partially responded or resisted therapy	
HL (13 patients)	No. (%)	10 (77%)	3 (13%)	*0.789*
	Mean/ SD	213 ± 32.1	206.6 ± 33.3	
NHL (37 patients)	No. (%)	15 (40.5%)	22 (49.5%)	*0.437*
	Mean/ SD	293.3 ± 67	312.5 ± 80.5	

DISCUSSION:

In the past, a marked increase in serum LDH activity in lymphomas was reported by several authors[2,14,15]. Many others have studied the prognostic significance of this enzyme and its relation to the clinical stage and subtype of lymphoma[2,5,16-18]. In this study, the relation between serum LDH level and clinical presentation, stage, histological type and response to treatment was investigated in 13 patients with HL and 37 patients with NHL. The mean LDH level was considerably elevated in lymphoma patients compared to the mean LDH level in controls. At diagnosis, none of HL patients has had an LDH level above the normal cutoff point (460 U/L), indicating that LDH level is of limited clinical and prognostic value in HL. This finding disagrees with results of Garcia et al[8] who reported elevated enzyme level but agrees with results of Flanagan et al[2], and Martinow et al[16]. On the other hand, majority of NHL patients (29 cases – 78.4%) had elevated serum LDH level at diagnosis. The difference in the mean LDH level between HL and NHL groups was highly significant ($p < 0.001$). It was found that serum LDH activity was independent on the grade or histological subtype of lymphoma. This is quite consistent with results of Cowan et al[17]; Fasola et al[18]; and Dumontet et al[19]. There was also no correlation between serum LDH activity and ESR. Only 2 cases of NHL group had bone marrow involvement at diagnosis, therefore statistical correlation between serum LDH level and marrow involvement could not be estimated. Similar to results of many previous studies, there was a significant correlation between serum LDH activity and the extent of the lymphoma represented by stage of the disease[5,20]. In addition, another study[21] reported that serum LDH levels, which may reflect the mass of tumor present, were lowest in patients with localized disease. This could explain the markedly elevated levels of serum LDH in untreated patients with extensive and spread tumors. With regards to the effect of chemotherapy on serum LDH level, and comparable to the results reported by Fasola et al[18], it was observed that serum LDH levels in all NHL patients dropped to <460U/L after completing chemotherapy courses regardless whether clinical remission was attained or not. In our report, only 15 patients with NHL (40.5%) reached clinical remission by the end of treatment courses. The remaining 22 patients (59.5%) either partially

responded or resisted therapy; however, their serum LDH levels decreased to within normal ranges. These results suggest that measuring enzyme activity is of limited usefulness for detecting and monitoring minimal residual disease. For that purpose, LDH isoenzyme studies would be more appropriate. In our report, 65% of NHL patients who responded well to therapy and attained clinical remission were in stage I or stage II disease; while 60% of partial responders or resistant patients had stage III or stage IV disease at diagnosis. Our results suggest that the extent of the disease represented by the stage of lymphoma is the principal predictor for the outcome and best responsiveness to therapy represented by attaining clinical remission rather than serum LDH value. This is comparable to results reported by a previous study[17], but not with results of another study[5] which reported significant relation between serum LDH level and remission status.

CONCLUSIONS:

Serum LDH activity remained within normal range among HL patients therefore was of no prognostic value; whereas it was significantly high among NHL patients where its level associated mainly with the stage of the disease. Short term prognosis in NHL represented by reaching clinical remission after therapy was best deliberated with the stage of lymphoma.

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