Diagnostic and prognostic value of serum and peritoneal fluid lactate dehydrogenase in epithelial ovarian cancer

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Summary

Objective: The aim of this study was to investigate the peritoneal fluid and serum lactate dehydrogenase (LDH) levels in patients with ovarian masses.

Materials & Methods: Peritoneal fluid and serum lactate dehydrogenase (LDH) levels were measured in 27 patients with epithelial ovarian carcinoma and 38 with benign ovarian tumors. Serum and peritoneal fluid LDH levels were also compared with the levels of CA-125.

Results: Both of the marker levels in ovarian cancer patients were significantly higher than those in patients with benign ovarian tumors. Serous and undifferantiated carcinomas presented higher marker levels than endometrioid and mucinous carcinomas. High grade, advanced stage and positive cytology were associated with higher serum and peritoneal fluid LDH levels; there was an inefficient correlation between them but, when these two markers were used together with CA-125, sensitivity of CA-125 increased to 70%.

Conclusions: In conclusion, serum LDH can be used to discriminate adnexal mass origin and peritoneal fluid LDH may have prognostic value because of the strict relationship with advanced stage, poor histologic type, higher grade and positive abdominal cytology. Peritoneal LDH is found to be a reliable biochemical marker related to prognosis in ovarian carcinoma patients.

Key words: Lactate dehydrogenase; Ovarian carcinoma; Prognosis.

Introduction

Ovarian carcinoma has the worst prognosis among the female genital cancers and the mortality rate is fourth among women's cancers [1]. Although new treatment modalities have been developing, no improvement has been seen in the prognosis of ovarian cancer in the last 30 years [2, 3]. A major factor for this poor prognosis is the high rate of intraperitoneal spread of tumor at the time of diagnosis [4]. Therefore early diagnosis is very important and progress in the treatment of carcinoma of the ovary will only emerge from an improvement in early diagnosis and from the development of reliable markers to monitor subsequent therapeutic modalities. These markers and screening methods will be used in early diagnosis of the disease, selecting high risk patients, preventing unnecessary re-operations, early diagnosis of recurrences, determining the success of chemotherapeutics, and discriminating benign and borderline tumors.

Too many studies are going on worldwide to determine the value of different markers which are extracted from human tissue and fluids. Thousands of markers are studied as tumor markers in ovarian carcinomas [5, 6]. The most popular marker, CA-125, was first reported by Bast *et al.* in 1981 and used for the diagnosis and follow-up of ovarian carcinomas [7]. But still there is need for new markers because CA-125 can be found elevated in benign tumors, and its sensitivity is low in early stage carcinomas and mucinous tumors.

As one of the major enzymes of glycolysis, lactate dehydrogenase (LDH) is an important enzyme in tumor tissues. The glycolytic pathway is known to become more active in malignant tissue [8], and in these tissues LDH passes to the circulation in great amounts because of the necrosis [9, 10]. The aim of this study was to determine the value of serum and peritoneal fluid LDH levels as a tumor marker in epithelial ovarian cancer.

Materials and Methods

In this study 65 patients with ovarian masses were included and followed-up at a single institution between December 1998 and June 1999, prospectively. All of the patients were operated on; in 27 patients malignant ovarian tumors were detected whereas in 38 patients the ovarian masses were found to be benign. In the patients with malignant neoplasms, a complete surgical staging procedure was carried out, whereas in the

Table 1. — *Patient histopathologic characteristics.*

Histopathologic Type	No
Malignant Group	
Serous Cystadenocarcinoma	16
Mucinous Cystadenocarcinoma	3
Endometrioid Ca	3
Undifferentiated Ca	3
Clear Cell Ca	1
Mixed Ca	1
Benign Group	
Simple	12
Endometrioma	9
Serous Cystadenoma	8
Mucinous Cystadenoma	3
Thecofibroma	2
Dermoid Cyst	4

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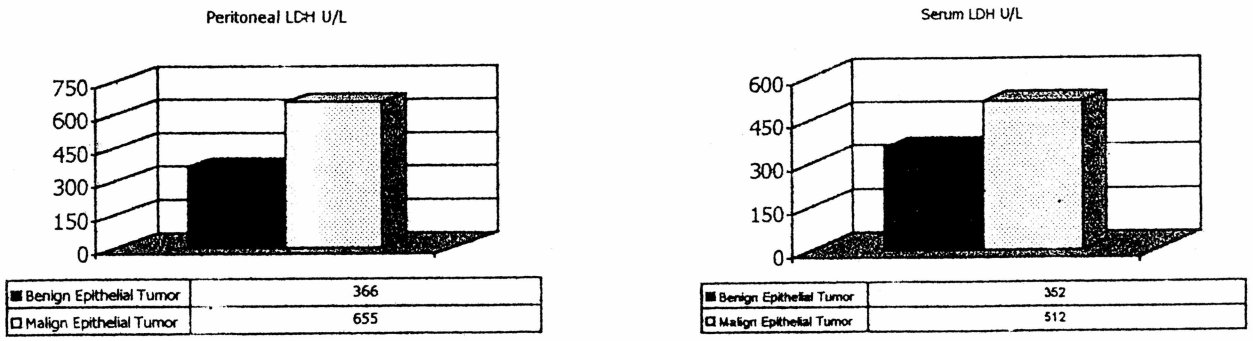

Figure 1. — Comparison of serum and peritoneal fluid LDH levels in benign and malignant cases.

benign group different surgeries were performed according to the age of the patient and status of the mass. Subtypes of these epithelial tumors and benign masses are given in Table 1.

The mean age in the benign group was 45.3 (range 22-77) and 55.3% of these patients were postmenopausal whereas in the malignant group the mean age was 58.6 (range 20-78) and 55.6% were postmenopausal. The median age was not significantly different between groups ($p > 0.05$). No liver disease was present in either study group and there were three patients with congestive heart failure and six with hypertension in the benign group and two and four in the malignant group, respectively.

Prognostic factors were described as solid-cystic mass, peritoneal thickening, ascites, cystic mass, cystic mass with heterogenous echoes, solid mass and septated cystic mass.

All of the patients were evaluated by ultrasonography (USG) before the operation. Venous blood samples were taken from all of the patients one week before the operation, and a peritoneal fluid sample – ascites if present, or washing fluid when there was no ascites – was collected during the operation. LDH activity was studied with a LDH OPTIMISE IC 1.1.1.27 Test UV Kit. In the same specimens CA-125 levels were also measured by IMMULITE® OM-MA 5 for comparison.

Statistical analysis

For statistical analysis, the Student' t-test, Mann Whitney U test, Wilcoxon Rank Sum W test, Kruskal-Wallis 1-Way Anova and Spearman correlation test were used where appropriate. P-values of < 0.05 were considered statistically significant. Calculations were done using the SPSS for Windows version 9.0.

Results

Serum mean LDH activity was 352.5±120.15 U/L with a median of 332 U/L (204-863) in benign masses whereas the mean was 512.5±454 U/L with a median of 390 U/L (166-2304) in the malignant group. The statistical difference was significant ($p < 0.05$). Peritoneal fluid mean LDH value was 366.76±336.47 U/L with a median of 300 U/L (73-1989) in benign and 655±700.63 U/L with a median of 655 U/L (63-3357) in the malignant group. The statistical difference was significant ($p < 0.001$) (Figure 1).

When the serum LDH values are interpreted according to the subtypes of epithelial ovarian carcinomas, the highest figure was in serous cystadenocarcinoma; this was also true for peritoneal fluid LDH values (Table 2).

Table 2. — *Serum and peritoneal fluid LDH levels according to histological subtypes*

		Peritoneal LDH (U/L)			Serum LDH (U/L)		
Subtypes	No	Mean	Range	Median	Mean	Range	Median
Serous	16	860	63-3357	713	609.2	248-2304	384
Endometrioid	3	651	430-838	685	346.3	309-400	330
Mucinous	3	395	222-655	308	268	166-443	195
Undifferentiated	3	875	384-1576	665	493.3	391-621	468
Clear cell	1	175	–	–	486	–	–
Mixed	1	299	–	–	405	–	–

When serum and peritoneal LDH levels were compared with FIGO stages of tumors it was found that the median value of peritoneal LDH increased as the stage of tumor advanced, but the serum median LDH value did not change. In stage IA the median peritoneal LDH was 303 U/L, and it was 837 U/L in stage II-IV. Statistical analyses were made between early stage (IA-IB-IC) and advanced stage tumors (Stage II-IV) because there were not enough case numbers (Table 3).

Table 3. — *Serum and peritoneal LDH values according to FIGO staging ($p < 0.05$)*

			Serum LDH U/L		Peritoneal LDH U/L	
Stage	No	%	Median	Range	Median	Range
IA	8	29.6	319	166-405	303	63-685
IB	2	7.4	313	248-379	380	291-470
IC	2	7.4	394	284-504	448	407-490
II-IV	15	55.6	431	300-2304	837	170-3357
Benign cases	38		332	204-863	300	73-1989

When serum and peritoneal LDH levels were compared with grade of epithelial tumors it was found that serum and peritoneal LDH values were increasing as the grade of the tumor increased. This relationship is shown in Table 4.

Table 4. — *Serum and peritoneal LDH values according to grade*

			Serum LDH U/L		Peritoneal LDH U/L	
Grade	No	%	Median	Range	Median	Range
1	12	44.4	340	166-405	303	63-859
2	6	22.2	533	300-2304	741	319-3357
3	9	33.4	431	330-819	837	304-1576
Benign cases	38		332	204-863	300	73-1989

Sonographic findings of the masses were evaluated and compared with serum and peritoneal LDH levels. Serum LDH values showed no difference according to the sonographic findings. Peritoneal LDH values were found to be the highest in the presence of omental thickening and ascites (Table 5).

Table 5. — *Comparison of USG findings and serum and peritoneal LDH values*

			Serum LDH U/L		Peritoneal LDH U/L	
USG	No	%	Median	Range	Median	Range
Omental thickening and ascites	11	40	391	712	837	1035
Solid-cystic mass	13	48	366	372	308	529
Cystic mass	3	12	400	382	655	572

In the malignant group serum LDH showed no significant difference between solid cystic masses and the group that had omental thickening and ascites ($p > 0.05$). However, peritoneal LDH showed a statistically significant difference between the two groups ($p < 0.008$) (Figure 2).

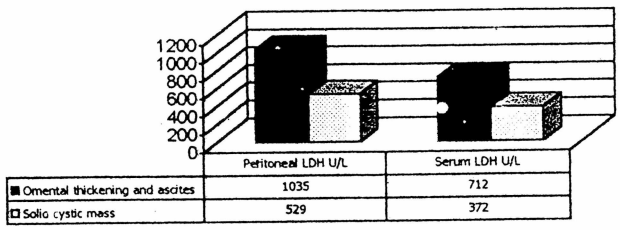

Figure 2. — Comparison of sonographic omental thickening and ascites, with solid cystic masses according to mean serum LDH ($p > 0.05$) and mean peritoneal LDH ($p < 0.008$).

Malignant epithelial carcinomas were classified according to abdominal cytology results; 14 were cytologically positive and 13 were negative. There was a significant correlation between cytologic findings and mean serum LDH ($p < 0.018$). However, the highest correlation was found between cytologic findings and mean peritoneal LDH ($p < 0.0001$). Of the four markers (serum and peritoneal CA-125 and LDH) peritoneal LDH was found to be the most powerful indicator of cytologic positivity.

As CA-125 is the most accepted tumor marker in epithelial ovarian carcinoma, correlations between serum and peritoneal LDH and serum and peritoneal CA-125 levels were evaluated. For this evaluation, previously calculated cut-off levels were used (Table 6). The Spearman correlation analysis was performed between serum Ca-125 and LDH values, and a poor correlation was found (0.47). Also there was a poor correlation between peritoneal Ca-125 and LDH values (0.28).

Table 6. — *Cut-off levels for every marker measured were determined statistically as shown*

Marker	Cut-off level
Serum CA125	129.09 U/ml
Serum LDH	512.28 U/ml
Peritoneal CA125	291.07 U/ml
Peritoneal LDH	650 U/ml

Moreover with these calculated cut-off levels, sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated for both CA-125 and LDH and also for combinations (Table 7).

Table 7. — *Diagnostic accuracy of the tumor markers*

Marker	Threshold value U/ml	Sensitivity %	Specifity %	(+) P value %	(–) P value %	Diagnostic Accuracy %
Serum CA125	129	62.9	94.7	89.5	78.2	81.54
Serum LDH	512	18.5	94.7	71.4	62.1	63.1
Peritoneal CA125	291	55.6	89.4	78.9	73.9	75.38
Peritoneal LDH	650	48.1	92.1	81.2	71.4	73.85
Serum CA125 and LDH	129-512	70.4	89.4	79.2	80.9	81.5
Serum CA125 and Peritoneal LDH	129-650	74.1	89.9	83.3	82.9	83.1

Among these markers, serum CA-125 was found to be the most important one with 62.9% sensitivity and 81.54% diagnostic accuracy. Peritoneal fluid CA-125 was in second place with 55.6% sensitivity and 75.3% diagnostic accuracy. Figures for peritoneal LDH were nearly the same. Serum LDH was the worst marker with 18.5% sensitivity and 63.1% diagnostic accuracy. Specificity of all markers was nearly the same (89-94%). When serum CA-125 and LDH were used together in the differential diagnosis of adnexal masses, a 7% increase was determined (70.4%) in sensitivity, but it was not statistically significant ($p=0.18$). While specificity decreased 5%, diagnostic accuracy did not change (81.5%). When the serum CA-125 level was used with the peritoneal LDH level, sensitivity increased to 12%, but it was not statistically significant ($p > 0.08$), specificity decreased to 5%, but the diagnostic accuracy was found to be the same (83.1%). The success of these four tumor markers to determine early stage tumors was made by comparing mean values in benign and malignant tumors (stage I). Of the four markers only Ca-125 was able to discriminate these two groups ($p < 0.05$).

Discussion

In the literature there are conflicting reports about serum LDH levels in ovarian carcinomas. Some reports support that serum LDH levels are altered in ovarian carcinomas, but some others support the opposite [6, 11-13]. Serum LDH activity in ovarian carcinomas was first studied by Asada and Galambos [11]. Increased serum LDH activity was found in five patients with ovarian carcinoma in their trial. After that time many reports determined that serum LDH levels increase in ovarian carcinomas. Kikuchi *et al.* evaluated 12 different tumor markers other than CA-125 in 54 ovarian cancers and 66 benign cases and found that LDH was the most reliable

among these markers [6]. Moreover, in another study by the same authors they found that serum LDH levels and also some LDH isoenzymes (LDH-4 and 5) can be used in the differential diagnosis of adnexal masses [12]. Younis *et al.* determined high levels of serum LDH in ovarian cancer cases, and they stated that serum LDH was helpful in the differential diagnosis of adnexal masses, but because they could not find any correlation between LDH levels and second-look operation findings, they concluded it was not useful in the management of the disease [13].

In our study, serum LDH activity was significantly higher in the patients with ovarian cancer than the ones with benign ovarian masses. Using the calculated cut-off level, sensitivity of serum LDH was low, specificity was high and the diagnostic accuracy was 63.1%. With these results we conclude that increased serum LDH activity may be helpful in discriminating malignant masses from benign conditions although its sensitivity is low.

In this series, peritoneal LDH levels were significantly higher in ovarian carcinomas compared to the levels in benign masses. LDH activity in the peritoneal fluid was first studied by McGowan *et al.* [14] and they found that peritoneal fluid LDH activity in 22 patients with epithelial ovarian cancer was significantly higher when compared to the levels of ten healthy patients and ten patients with benign adnexal masses. In a study in 1997, Schneider *et al.* found the sensitivity of peritoneal LDH to be 87%, specificity 93% and diagnostic accuracy 90% [15]. In our study diagnostic accuracy was found to be 73% and the reason for this lower figure may be the higher calculated cut-off level of our study due to a larger range than their level (410 U/L) and a higher incidence of Stage I cases in our series (44.4%). In the study reported by Schneider *et al.* 80% of the cases were in Stage II-IV and the most significant difference was found in peritoneal LDH levels between Stage I and Stage II-IV cases. In our study, LDH levels were found to increase as the stage increased. This can be explained with the increased tumor volume and necrosis in advanced stage tumors. Among the evaluated tumor markers, the most statistically significant difference between the Stage I and II-IV cases was found in peritoneal LDH activity.

Mean LDH value was the highest in serous and undifferentiated carcinomas, and the lowest in mucinous carcinomas. This result is in accordance with the literature [11, 14]. Among the four tumor markers, the highest difference between grade 1 and grade 2-3 tumors was found in peritoneal LDH levels. It was also significant in the group that had positive cytology. We conclude that these results may be helpful to pathologists and cytologists in the differential diagnosis of tumoral grade. Occurrence of omental thickening and ascites in USG was correlated with the malignancy in surgery and high levels of peritoneal LDH when compared with solid-cystic masses. This means omental thickening and ascites were the most reliable diagnostic ultrasonographic findings of malignancy together with high levels of serum and peritoneal fluid LDH.

There was a weak correlation between peritoneal CA-125 and LDH. However, when peritoneal LDH levels were put together with serum CA-125, sensitivity of CA-125 increased by 12%, but diagnostic accuracy did not change. As a result, in the differential diagnosis of adnexal masses using CA-125 and serum and peritoneal fluid LDH together will increase the sensitivity of CA-125 without decreasing specificity, but no increase in diagnostic accuracy should not be expected.

In our study we found serum LDH alterations to be statistically significant in epithelial ovarian cancers, thus they can, be used as a marker also for this subtype of ovarian cancers. We also found high levels of serum LDH in poor histologic subtypes and this can be related to invasiveness. Degree of LDH production seems to differ according to the histologic subtype of tumor. A comparison was made between early and advanced stage tumors and between benign tumors and early stage malignant tumors. Our findings showed that there is a significant difference between early and advanced stage malignant tumors and that serum LDH level is correlated with stage as it was altered in advanced stages. There was no difference between early stage malignant tumors and benign tumors, so serum LDH levels should not be used for early diagnosis or differentiation of benign cases in ovarian masses. Serum LDH levels have a good correlation with advanced stage and are more useful in differentiation of adnexial masses. McGowan, Kikuchi, and Younis reported that they found an alteration of LDH as the tumor advances, the same as our finding [12-14]. Grade of the tumor was also found to be correlated with LDH levels and grade 2-3 tumors showed higher LDH levels than grade 1 tumors and this finding can be a helpful tool for objective pathologic grading systems. Patients who had positive cytology showed higher LDH levels than ones who had negative cytology, thus altered LDH levels can be a predictor of positive cytology.

In the second leg of this study we looked for a correlation between serum CA 125 levels and serum LDH levels but found a weak correlation and we also found that these two markers have different places in the diagnosis and treatment of ovarian cancers.

Peritoneal LDH measurement can be a guide for oncologists because it is correlated with poor histologic type (serous and undifferentiated), advanced stage, high grade, and positive cytology. Thus, peritoneal LDH can be easily accepted as a prognostic factor for ovarian carcinomas. Evaluating preoperative or intraoperative peritoneal fluid LDH values can be helpful in making an exact decision about the nature of the ovarian mass and moreover to predict the prognosis. Also it will be helpful to use peritoneal LDH values before second-look laparatomies to determine if there is any residuel tumor or if there is ascites.

We conclude that serum LDH can be used to differentiate benign ovarian masses from malignant ones and this will help clinicians make better surgical plans preoperatively. Peritoneal LDH seems to be a reliable marker which is correlated with known clinicopathologic prognostic parameters in ovarian carcinomas, and evaluation

of this marker will give the clinician and pathologist a chance to predict disease progression.

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