ORIGINAL RESEARCH PAPER

Biochemistry

STUDY BIOCHEMICAL PARAMETER LDH IN OVARIAN TUMORS BEFORE AND AFTER CHEMOTHERAPY

KEY WORDS:

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ABSTRACT

Serum LDH elevations occur in a variety of clinical conditions including of MI, hemolysis and disorders of the liver, kidneys, lung and muscle. A systematic review of Literature concluded that serum LDH is relevant in the diagnosis of MI, hemolytic anemia, ovarian dysgerminoma and testicular germ cell tumor. Although not that relavent for epithelial ovarian cancer, LDH is considered important in the follow up of dysgerminoma for assessing response to therapy and prognostification of disease. The current study designied with an aim To explore the changes in LDH levels of malignant and benign ovarian tumours pre therapy and post therapy.To explore the differences in the LDH levels between healthy individuals and patients with ovarian tumours.To study the Correlation between CA125 and LDH. To study the Correlation between CA125 LDH.

A study was conducted on 40 patients suffering from ovarian tumors (Benign and Malignant) who had reported to Rangaraya Medical College hospital, Kakinada. The mean duration of symptoms was 12.6 ± 20.89 weeks (range 0.4- 104 weeks) and the median was 6.5 weeks in our cohort of patients. The mean duration of symptoms for benign (n=11) tumors was 23.1 ± 33.1 weeks whereas for malignant (n=29) tumors the duration of symptoms was 8.62 ± 12.50 weeks. all patients with ovarian tumours (both malignant & benign) had a pretreatment mean ± SD value of CA125 was 767 ±1069 U/ml which reduced to a mean± SD value of 46.28 ± 41.28 U/ml post treatment ($p < 0.0004$).

A significant change was found in the levels of LDH (Pretreatment value of 479±320.6 U/L and post treatment levels of 182.8±107U/L) ($P<0.0001$). When compared to healthy controls (mean CA-125:15.48 (range:5.7-22) & mean LDH:182.8 (range:140-300) [table-7], ovarian tumour patients had a higher CA-125 & LDH levels(mean CA-125: 767 & mean LDH:479.36). We also tried to see the correlation between CA-125 and LDH both in benign and malignant ovarian tumours. A positive correlation was found between CA125 levels and LDH in malignant ovarian tumours. In benign tumours, a positive correlation was found between CA125 and LDH. a negative correlation was observed between CA-125 and cholesterol levels.

INTRODUCTION

Ovarian cancer is the malignant proliferation of ovarian cells arising from the ovary. It represents a spectrum of disease entities which arise from various cells such as epithelial, germ cell or sex cord stromal cells. Epithelial ovarian cancer arises from epithelial cells and typically occurs in postmenopausal women. In contrast, most germ cell tumours present at a younger age while sex cord stromal tumours may occur at any age. Approximately 90% of ovarian tumours are epithelial in origin. Managing these cancers poses significant therapeutic challenges as they present at an advance stage and tend to recur in majority of the cases. In contrast other malignant ovarian tumours like germ cell and sex cord stromal tumours are often localized in distribution, and amenable to complete surgical resection thus having a favorable prognosis.

Although majority of the ovarian cancers arise from the surface epithelium of the ovaries. However, a minority of these tumours also arise from the epithelial lining of the fallopian tube. Since ovaries and tubes are closely related to each other, it is thought that these fallopian cancer cells can mimic ovarian cancer.

Early ovarian cancer is diagnosed by surgical evaluation of an adnexal mass. The decision to subject a patient to surgical exploration is difficult to make, however. Ultrasonography evaluation of adnexal masses has improved the ability to distinguish patients who should have surgical exploration from patients who can be further evaluated through observation, but it also has resulted in an increasing number of patients who are found to have an asymptomatic ovarian cyst. This result is of particular concern in postmenopausal women.

Serum LDH elevations occur in a variety of clinical conditions including of MI, hemolysis and disorders of the liver, kidneys, lung and muscle. A systematic review of Literature concluded that serum LDH is relevant in the diagnosis of MI, hemolytic anemia, ovarian dysgerminoma and testicular germ cell tumor. Although not that relavent for epithelial ovarian cancer, LDH is considered important in the follow up of dysgerminoma for assessing response to therapy and prognostification of disease.

Patients with malignant disease show increased LDH activity in serum, upto 70% a patients with liver metastasis and 20% to 60% of patients with other non-hepatic metastases have elevated total LDH activity. No subtly elevated LD1 is observed in germ cell tumours (61% of cases) such as teratomas, seminoma and dysgerminoma of the ovary. The percent of patients with increased LD-1 depend on the stage of the disease, LD-1 appear to be a useful predictor of outcome in patients of ovarian dysgerminoma

REVIEW OF LITERATURE

Schneider, MD, et al has estimated Peritoneal Fluid Lactate Dehydrogenase in ovarian cancer. LDH has been demonstrated to be increased in ovarian cancer.

In order to differentiate between ovarian cancer patients and those with benign ovarian tumour cut off levels were determined, peritoneal fluid LDH above 410U/L, serum LDH above 340 U/L and serum (CA – 125 > 100 U/ml). In the present study, the feasibility of peritoneal fluid LDH was examined and compared to serum LDH to differentiate ovarian cancer from benign tumor.

Both peritoneal fluid & serum LDH levels were significantly higher in patients with ovarian cancer than in benign ovarian tumour. (P<0.001) or other gynecological malignancies.(P<0.001 and P <0.03) this significant difference in peritoneal fluid LDH level, as expressed between ovarian cancer and other gynecological malignancies, is not so remarkable considering serum LDH levels. Serum LDH levels are higher in ovarian endometrioid carcinoma than is serous, cyst adenocarcinoma. Positive serum LDH activity was found more frequently in patients with advanced ovarian cancer than in those with early stage disease.

Kikuchi Y et al. estimated Total lactate dehydrogenase and its isozymes in serum from patients with primary carcinoma of the ovary.

The positive result of ovarian carcinoma was highest at LDH-4 activity (43.6%), followed by LDH activity (42.1%), HBD activity (34.6%), LDH-5 activity (32.7%), percent fractions of LDH-4 and LDH-5 (20.0%). On the other hand, the false-positive rate in patients with benign ovarian tumor was highest at LDH activity (12.7%), followed by HBD activity (10.0%), LDH-5 activity (8.6%), percent fraction of LDH-5 (8.2%), LDH-4 activity (6.8%) and percent fraction LDH-4 (3.6%).The detection rate for early ovarian carcinoma (stages I and II) was elevated from 4.5% by HBD activity alone to 50.0% by a combination assay of LDH, LDH-4, LDH-5 and HBD, while that for advanced ovarian carcinoma (stages III and IV) was elevated from 50.0% by HBD alone to 79.4% by the combination assay.

AIMS AND OBJECTIVES

- To explore the changes in LDH levels of malignant and benign ovarian tumours pre therapy and post therapy.
- To explore the differences in the LDH levels between healthy individuals and patients with ovarian tumours.
- To study the Correlation between CA125 and LDH
- To study the Correlation between CA125 LDH

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry, Rangaraya Medical College, Kakinada, Andhra Pradesh. The present study was undertaken to study the various changes in the biochemical parameters in the serum of patients with ovarian tumors before and after therapy (Surgery and/or chemotherapy). The serum of 40 patients of ovarian tumors was taken out of which 11 were benign tumors and 29 were malignant tumours. The values were compared with the values of 40 healthy women taken as Control groups. All the subjects were accrued from the department of Gynaecology, Govt. General Hospital who were admitted for treatment. Demographic and clinical data were collected at routine Gynaecology visits. Blood samples were obtained by venous puncture from the antecubital vein of each woman before and after therapy (Surgery and/or Chemotherapy). The control group denied any history of chronic disease and of same age group and test group. Consent was obtained from both the cases and control groups. Serum was separated and analyzed by using standard methods. The observed values were compared with control group for statistical analysis.

All data were expressed as Mean ± Standard deviation and standard error of mean. Differences with a P-value of less than 0.05 were considered to be stastically significant.

Lactate dehydrogenase levels were estimated by lactate dehydrogenase method (Siemens auto analyzer method) is a modification of the enzymatic lactate to pyruvate procedure first reported by Wacker and later modified by Gray et al.

OBSERVATION AND RESULTS

The study was approved by the institutional scientific and review committee. We present our observations on the demographic, treatment and biochemical profile ovarian tumours (benign and malignant) pretreatment and post treatment and compared them with matched healthy individuals. We accrued 40 healthy female individuals and 40 patients with ovarian tumours of which 29 patients had malignant ovarian cancers (epithelial and non epithelial) and 11 patients had benign ovarian cysts) over a period of 1.5 years

DEMOGRAPHIC PROFILE OF PATIENTS WITH TUMOURS AND TREATMENT PARAMETERS

Patient and tumour profile		Frequency	%
Age (N =40)	Mean age :44.77 years Median Age: 48 years Mean ± SD: 44.77± 11.76 Mean± SEM:44.77 ± 1.86		
	Range:13- 65yrs		
Duration of symptoms For all patients (N =40)	Mean duration 12. 6 weeks Median duration: 6.5 weeks Mean ± SD:12.61± 20.89 Mean± SEM: 12.61± 3.30		
	Range :0.4 -104 weeks		
Duration of symptoms for patients with malignant tumours (N = 29)	Mean duration: 8.62 weeks Median Duration: 6 weeks Mean ± SD:8.62 ± 12.50 Mean± SEM:8.62 ± 2.32		
	Range: 0.6 -52 weeks		
Duration of symptoms for patients with benign tumours (N = 11)	Mean Duration: 23.1 weeks Median duration: 8 weeks Mean ± SD:23.1 ± 33.1 weeks Mean ± SEM:23.1 ± 9.98 weeks		
	Range: 0.4 - 104 weeks		
Histology of tumour (N =40	Benign Cyst Serous Cystadenocarcinoma Mucinous Cystadenocarcinoma Granulosa cell tumour Yolk sac tumour Cyst adenoma	10 12 15 1 1 1	25 30 37.5 2.5 2.5 2.5
Type of tumour (N = 40)	Benign	11	27.5
	Malignant	29	72.5
Age of pts with malignant tumours (N = 29)	Mean Age: 47.72 years Median Age: 49 years Mean ± SD: 47.72 ± 9.26 years Mean± SEM:47.72 ± 1.72 years		
	Range:15- 65 years		
Age of pts with Benign Tumours (N = 11)	Mean Age: 37 years Median Age: 40 years Mean ± SD: 37 ± 14.4 years Mean ± SEM : 37 ± 4.34 years		

Biochemical profile of healthy female individuals (N = 40)

Parameters	Mean	Median	Mean ± SEM	Mean ± SD	Range
Age (years)	44.02	44	44.02±1.47	44.02±9.36	27-70
LDH(U/L)	182.87	178.5	182.87±4.96	182.87±31.39	140.300

BIOCHEMICAL PROFILE OF PATIENTS FOR ALL OVARIAN TUMOURS (PRE-TREATMENT AND POST TREATMENT) [N= 40]

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range
LDH (U/L)	Pre	479.36	386.65	50.69	320.61	152-1499
	Post	182.82	148.00	17.02	107.66	100-551
	Post	164.57	154.00	6.09	38.52	111-300
	Post	7.27	5.95	0.61	3.88	3.30-20.0

TABLE-9 CHANGES IN PRETREATMENT AND POST TREATMENT BIOCHEMICAL PARAMETERS IN BENIGN OVARIAN TUMOURS

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
LDH (U/L)	Pre	269.9	195	39.26	130.2	152-552	**0.003**
	Post	137.5	149	8.67	28.77	102-179	
	Post	164.5	146	15.97	52.96	111-300	

CHANGES IN PRETREATMENT AND POST TREATMENT BIOCHEMICAL PARAMETERS IN MALIGNANT OVARIAN TUMOURS

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P-Value
LDH (U/L)	Pre				558.8	500	62.52
	Post	200	147	22.54	121.4	100-551	
	Post	164.6	156	6.06	32.64	120-227	
	Post	7.03	5.90	0.74	4.02	3.3-20.0	
	Post	2.96	2.50	0.29	1.56	1.5-9.80	

Changes in Pretreatment and post treatment biochemical parameters in ovarian tumours (benign & Malignant)

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P-Value
LDH (U/L)	Pre	479.4	386.7	50.69	320.6	152-1499	**<0.0001**
	Post	182.8	148	17.02	107.7	100-551	
	Post	163.3	152	6.10	38.10	111-300	
	Post	7.29	5.9	0.63	3.93	3.3-20.0	
	Post	2.88	2.6	0.22	1.41	1-9.8	

Biochemical profile of healthy female individuals (controls) vs. females with ovarian tumours. (N = 40)

Parameters	Controls/ Tumours	Mean	Median	± SEM	± SD	Range	P-Value
LDH (U/L)	Controls	182.87	178.5	4.96	31.39	140.300	<0.0001
	Ovarian tumours	479.36	386.65	50.69	320.61	152-1499	
	Ovarian tumours	182.55	178.50	10.14	64.17	101-471	
	Ovarian tumours	10.56	8.20	1.14	7.24	6.00-38.00	

Correlation Between Ca125 And Other Biochemical Parameters In Benign Ovarian Tumours

Parameter 1	Parameter 2	R value	Correlati
CA125	LDH	0.76	Positive

DISCUSSION

A study was conducted on 40 patients suffering from ovarian tumors (Benign and Malignant) who had reported to Rangaraya Medical College hospital, Kakinada. The demographic and treatment profile of patients with ovarian tumours are illustrated in tables 6 &7. The mean age of the patients were found to be 44.77 ± 11.66. Mean age of the patients with malignant tumors (n=29) was 47.7 to ± 9.26 years whereas for benign tumors (n=11) it was only 37± 4.34 years. A similar finding of mean age of 49.9 ± 17.5 years was found in a study conducted in ovarian cancer patients by Umran Kucukgoz Gulec, et al (76)

The mean duration of symptoms was 12.6 ± 20.89 weeks (range 0.4- 104 weeks) and the median was 6.5 weeks in our cohort of patients. The mean duration of symptoms for benign (n=11) tumors was 23.1 ± 33.1 weeks whereas for malignant (n=29) tumors the duration of symptoms was 8.62 ± 12.50 weeks. As expected the symptomatology in malignant tumours was more aggressive than benign tumours.

Platinum based chemotherapy using cisplatin or carboplatin in combination with paclitaxel is the standard adjuvant therapy in ovarian cancers. (77,78) In our study, the number of chemotherapy cycles in patients with malignant ovarian tumours was 5.4 ± 1.27 cycles with a compliance rate of 79.3%. (Table-6) In a study of 218 ovarian cancer patients reported from india, the compliance to chemotherapy was extremely poor at 45%. (79). In our study, 87.5% had complete surgery for their condition. 89.6% of patients required surgery + adjuvant chemotherapy and 6.9% took only chemotherapy as a palliative treatment due to advance stage of the disease. (Table -6)

The main objective of the study was to explore the changes in the biochemical parameters in pre and post therapy in both benign and malignant ovarian tumours. Moreover, we sought to study the differences in these parameters between the afflicted patients and the healthy controls. We also did a subset analysis to study the correlation of other biochemical parameters with the main tumour marker CA-125 in patients with both benign and malignant ovarian tumours.

In our study, all patients with ovarian tumours (both malignant & benign) had a pretreatment mean ± SD value of CA125 was 767 ±1069 U/ml which reduced to a mean± SD value of 46.28 ± 41.28 U/ml post treatment ($p < 0.0004$). A significant change was found in the levels of LDH (Pretreatment value of 479±320.6 U/L and post treatment levels of 182.8±107U/L) ($P<0.0001$). When compared to healthy controls (mean CA-125:15.48 (range:5.7-22) & mean LDH:182.8 (range:140-300) [table-7], ovarian tumour patients had a higher CA-125 & LDH levels(mean CA-125: 767 & mean LDH:479.36)[table-8]. On comparing the CA-125 & LDH levels in benign vs. malignant ovarian tumours, as expected these markers were highly elevated in the pretreatment serum samples of malignant ovarian tumours except in germ cell and sex chord ovarian cancers. The mean CA-125 and LDH levels levels in benign ovarian tumours were (mean CA-125: 97.93; range: 3.4-361

&mean LDH: 137; range: 102-179) while in malignant ovarian cancers (mean CA-125:940.3; range: 14-4784 & mean LDH: 558.8; range: 192-1499). In benign ovarian tumour patients the CA-125 levels were 2-3 times above the normal while LDH levels were within the normal range. However, in ovarian cancers both CA-125 and LDH were grossly elevated. Thus both CA-125 and LDH can be considered as biomarkers for diagnosis and prognostification of ovarian cancers as both the serum levels of both these markers reduced significantly following surgery and adjuvant chemotherapy in epithelial ovarian cancers. However, the same cannot be said in case of benign tumours as both these markers did not show any significant changes pre and post treatment. The pre treatment and post treatment serum levels of CA125 & LDH are summarized in tables 8-10 and figure 9-12 in the results section. The reduction in the serum CA125 and serum LDH indicates post therapy (surgery and /or chemotherapy) indicates reduction in tumour burden which is an indirect reflection of response to therapy. We are unable to comment on the duration of response and survival of patients as the data was not collected for these patients since it would entail both clinical and biochemical follow-up at each and every visit. The findings in our study can be well corroborated with multiple other studies which have shown that both serum CA-125 and LDH can be used as a prognostic marker with high accuracy (low false positive and negative). (93-98) Hence all the clinical trials incorporating newer strategies in the management of ovarian tumours use CA-125 and LDH as surrogate marker for response and prognostication.

We also tried to see the correlation between CA-125 and LDH both in benign and malignant ovarian tumours. A positive correlation was found between CA125 levels and LDH in malignant ovarian tumours. In benign tumours, a positive correlation was found between CA125 and LDH. a negative correlation was observed between CA-125 and cholesterol levels. However none of them were statistically significant to draw any tangible conclusions (r-value did not straddle unity) either in benign or in malignant tumour

CONCLUSION

The study of biochemical parameters of ovarian tumors carried out in Rangaraya Medical College with the objective of exploring the changes in the biochemical profile of malignant and benign ovarian tumors pre and post therapy.

- The changes in LDH levels were also significant in both malignant and benign tumors.
- A positive correlation was found between CA125 levels and LDH in both malignant and benign tumors.

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