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Research Article

COMPARATIVE EVALUATION OF LEVEL OF SERUM & SALIVARY LACTATE DEHYDROGENASE ENZYME AS A BIOMARKER IN ORAL POTENTIALLY MALIGNANT DISORDERS AND ORAL SQUAMOUS CELL CARCINOMA

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A B S T R A C T

Aim: Lactate dehydrogenase (LDH) is an ubiquitously present enzyme which acts as a catalyst in production of lactate via pyruvate reduction during anaerobic glycolysis. An increase in serum LDH enzymatic activity is used as a biomarker for diagnosis of various types of cancers.This study aims to compare levels of serum and salivary Lactate Dehydrogenase (LDH) enzyme as a biomarker in oral potentially malignant disorders (OPMDs) and Oral Squamous Cell carcinoma (OSCC).

Materials & Methods: A total of 150 subjects of 20 to 70 years were selected from Jharkhand province, divided in five groups, 30 patients each who were clinically and histopathologically diagnosed with Oral Leukoplakia, Oral Lichen planus, Oral Sub mucous Fibrosis (OSMF), Oral squamous cell carcinoma (OSCC) and the control group. Both their salivary& serum samples were collected. Both types of samples were subjected for biochemical analytical tests. The data obtained was analyzed using the statistical software- SPSS version 22.0. Analysis of Variance (ANOVA) and Tukey's Post Hoc analysis was for inter-group comparison. Pearson's correlation analysis was used for correlating salivary and serum LDH levels. A statistical difference of P value of 0.05 or less was considered as statistically significant.

Results: Pearson's correlation test showed statistical significance in various studied groups for both salivary and serum LDH levels. In OSMF subjects, both the salivary and serum LDH levels were exhibiting statistical significance of 0.02 and 0.03, respectively. Similarly in leukoplakia patients, extremely significant P values of 0.01 and 0.02 were observed in both salivary and serum LDH values, respectively. However, in oral lichen planus, no statistical significance was observed in both the salivary and serum LDH levels.

Conclusion: The salivary and serum Lactate Dehydrogenase levels was highest in the patients with Oral Squamous Cell Carcinoma, followed by Oral Leukoplakia, Oral Submucous Fibrosis and oral lichen planus, However, oral lichen planus demonstrated lowest value of both salivary and serum lactate dehydrogenase levels thus, indicating lowest potential towards malignancy.

Clinical Significance: saliva samples can be equally effective in analysis of biochemical markers such as lactate dehydrogenase. Its non-invasive nature is an advantage over serum use for analytical purposes.

INTRODUCTION

Age-standardized incidence rates of oral squamous cell carcinoma (OSCC) in India is 12.6 cases per 1,00,000 of entire population whereas, potentially malignant disorders constitute approximately 2.5% of general population.[1] Most common oral potentially malignant disorders which are diagnosed include- oral leukoplakia which constitutes 85% of entire spectrum of these diseases. The malignant transformation rates from oral potentially malignant disorders to oral squamous cell carcinoma may vary from 0.6% to 20%.[1]In case, where these management i.e elimination of main etiological as well as risk factors, conservative methods such as- prescribing anti-oxidants, vitamin therapy fail, biopsy is performed. However, since this is an invasive procedure sometimes, patient might not agree hence, non-invasive techniques such as diagnostics of saliva is more preferred. Apart from using salivary samples, other bodily fluids such as- serum and urinary samples may be used as biomarkers to analyze their malignant transformation potential.[1]

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Tumor markers play a significant role in managing these diseases. Tumor markers are basically biologically active substances that play a major role in studying the metabolic processes occurring within tumor cells.[2] Warburg was the first person to report higher degree of glycolysis to in cancerous tissues when compared to normal tissues.[3]

Lactate dehydrogenase (LDH) is an ubiquitously present enzyme which acts as a catalyst in production of lactate via pyruvate reduction during anaerobic glycolysis. Different tissues produce different levels of this enzyme due to variations in metabolic demands. [3,4]

An increase in Lactate Dehydrogenase (LDH) levels in tissues or other bodily fluids is due to an increase in mitotic rates which produces higher quantities of lactic acid by the timorous cells due to glyco proteincaeous breakdown. An increase in serum levels of LDH represents an increase in necrosis within the tumor cells. An increase in serum LDH enzymatic activity is used as a biomarker for diagnosis of various types of cancers, namely, the oral laryngeal and breast carcinoma. Numerous studies have demonstrated that the LDH levels may increase in subjects diagnosed with leukoplakia, oral submucous fibrosis and oral squamous cell carcinoma. Thus, the levels of these markers may be beneficial in predicting its prognosis. [5,6,7,8]

The study aims to compare levels of serum and salivary Lactate Dehydrogenase (LDH) enzyme as a biomarker in oral potentially malignant disorders (OPMDs) and Oral Squamous Cell carcinoma (OSCC).

MATERIALS AND METHODS

A total of 150 subjects with an age-range of 20 to 70 years were selected from Jharkhand province. The study subject were divided in five groups, 30 patients each who were clinically and histopathologically diagnosed with Oral Leukoplakia, Oral Lichen planus, Oral Sub mucous Fibrosis (OSMF), Oral squamous cell carcinoma (OSCC) and the control group.

Patients undergoing chemotherapy, radiotherapy, or any surgical procedure for oral cancer, or with a history of heart failure (myocardial infarction) within past 2 weeks, patients using procainamides and other drugs used to treat arrhythmia, pulmonary infarction, and stroke, Patients suffering from hepatitis, hypothyroidism, anemia (haemolytic or pernicious anemia), pulmonary diseases, hepatic diseases, renal disease, pancreatitis, muscle trauma, and muscular dystrophy and

Patients with history of consumption of aspirin, narcotics or alcohol were excluded from the study.

Written informed consent was obtained from each patient and Incisional biopsy was performed at clinically most representative areas for Oral Leukoplakia, Oral Lichen planus, OSMF and OSCC and stained with H & E. Further only those cases concurring histopathologically with the features of Oral Leukoplakia, Lichen planus, OSMF and OSCC were included in the study.

Collection of Salivary samples: Patients were instructed to be seated in a comfortable position with their head held in an upright position. They were asked to rinse their oral cavities with 30 millilitres of normal tap water. Following this, they were told to accumulate saliva (unstimulated whole saliva) for a duration of 5 minutes. They were then asked to spit accumulated saliva into a sterile and disposable container for a minimum quantity of 2 mL was collected.

Collection of Serum samples: Collection of serum samples was performed by venepuncture and obtaining 2 mL blood from median cubital vein. It was then transferred to sterile test tube. Both types of samples were subjected for biochemical analytical tests. LDH estimation was performed by employing Toshiba Semiautomatic Analyzer. Commercially available LDH detection kit (Agappe Pvt. Ltd, Kerala, India) was used for analysis.

Collected data was subjected to descriptive statistics and mean along with statistical deviation. The data obtained was analyzed using the statistical software- SPSS version 22.0. Analysis of Variance (ANOVA) and Tukey's Post Hoc analysis was for inter-group comparison. Pearson's correlation analysis was used for correlating salivary and serum LDH levels. A statistical difference of P value of 0.05 or less was considered as statistically significant.

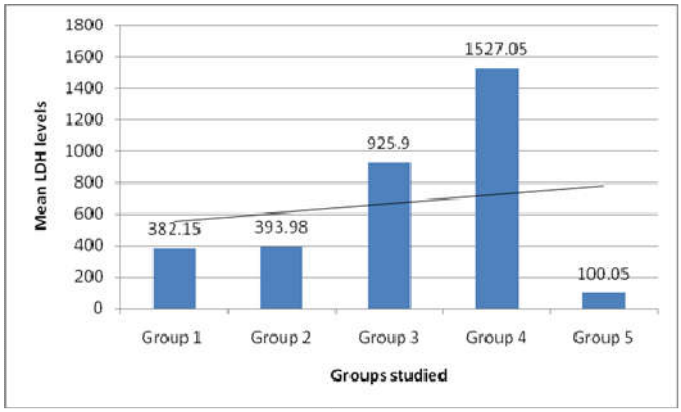
RESULTS

The healthy control group has a mean value of 100.05 ± 141.52 IU. The mean LDH value of group 1 is 382.15 ± 130.15 IU. The mean LDH of the subjects diagnosed with oral lichen planus was 393.98 ± 134.68 IU, whereas, group 3 was demonstrating mean LDH levels as 925.90 ± 205.56; the mean LDH of the subjects with oral squamous cell carcinoma was 1527.05 ± 321.65 IU. ANOVA test was performed for comparing the mean values. It showed highly significant difference as the P value was <0.001. (Table 1) (Graph 1)

Table 1 Mean Salivary LDH Levels In Study Groups

Study groups	Mean LDH (IU/L)	SD	p Value
Group 1	382.15	130.15	< 0.001**
Group 2	393.98	134.68	
Group 3	925.90	205.56	
Group 4	1527.05	321.65	
Group 5	100.05	141.52	

** Highly Significant



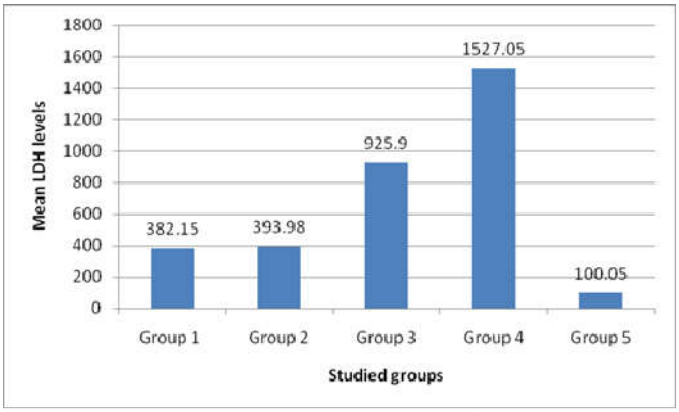
Graph 1 Graph is showing mean LDH salivary levels in various studied groups

The mean values of LDH in the leukoplakia group was 912.68 ± 176.59 IU/L; group 2 demonstrated 456.89 ± 56.24 IU/L; group 3 showed LDH levels was 868.78 ± 98.57; group 4 showed 987.89 ± 180.56 and group 5 showed 1323.05 ± 150.24. intra-group comparison showed P value of 0.002. (Table 2), (Graph 2)

Table 2 Intra-group comparisons of mean Serum LDH levels in OPMDs and Oral Squamous Cell Carcinoma

Study group	N	Mean	SD	P
Group 1	30	912.68	176.59	
Group 2	30	456.89	56.24	
Group 3	30	868.78	98.57	0.002
Group 4	30	987.89	180.56	
Group 5	30	123.05	150.24	

Pearson's correlation test showed statistical significance in various studied groups for both salivary and serum LDH levels. In OSMF subjects, both the salivary and serum LDH levels are exhibiting statistical significance of 0.02 and 0.03, respectively. Similarly in leukoplakia patients, extremely significant P values of 0.01 and 0.02 were observed in both salivary and serum LDH values, respectively. However, in oral lichen planus, no statistical significance was observed in both the salivary and serum LDH levels (0.13 and 0.11, respectively). (Table 3)



Graph 2 Graph is showing mean LDH serum levels in various studied groups

Table 3 Table showing Pearson's correlation test values between various subjects groups and control

Groups studied	Values	Salivary LDH	Serum LDH
OSMF	R	0.89	0.23
	P value	0.02	0.03
Leukoplakia	R	0.57	0.43
	P value	0.01	0.02
Oral lichen planus	R	0.42	0.21
	P value	0.13	0.11
Oral squamous cell carcinoma	R	0.92	0.76
	P value	0.005	0.002
Controls	r	0.1	0.2
	P value	0.45	0.13

DISCUSSION

Now-a-days, molecular biology techniques are being developed and are used to diagnose oral potentially malignant and malignant lesions and conditions. This may result in significant improvement in early detection of any malignant changes which may not be evident clinically or may not be microscopically evident. These tools may aid in identification of individuals who are at higher risk of development of oral squamous cell carcinoma.

Our study showed that the Mean salivary LDH levels were consistently higher in oral cancer (1527.05 ± 321.65); followed by OSMF (393.98 ± 134.68), oral leukoplakia (382.15 ± 130.15), oral lichen planus (393.98 ± 134.68) and control group (100.05 ± 141.52), respectively. Extremely significant difference (P<0.001) was obtained the mean LDH levels among all the groups using Post-hoc comparison tests between the study groups and controls (table 1 and graph 1). The Mean serum LDH levels in oral cancer, Oral Submucous Fibrosis, Oral leukoplakia, Oral lichen planus and control group were 987.89 ± 180.56; 868.78 ± 98.57; 912.68 ± 176.59 and 123.05 ± 150.24, respectively. Extremely significant P value (P = 0.02) was obtained on post-hoc comparisons (table 2 and graph 2).Similar findings have been reported by Mantri *et al*. They observed mean LDH salivary levels of 125.19 ± 13.42 IU/l, 592.09 ± 28.57 IH/l; 350.43 ± 5.90 IU/l and 86.12 ± 7.05 IU/l in tobacco pouch keratosis, oral cancer, habitual tobacco chewing subjects and normal controls, respectively.[9]

Mohan N *et al* in their study have shown statistical significant association of LDH levels in potentially malignant disorders and oral squamous cell carcinoma.[10]Samlin *et al* also reported a higher mean salivary LDH levels in OPMDs and oral squamous cell carcinoma when compared to normal control subjects. They reported mean LDH levels of 107.63, 1172.5 and 747.1 in leukoplakia, oral SCC and OSMF, respectively.[11] Nandita *et al* performed salivary and serum LDH levels among three lesional groups- a) Group I: Oral Submucous Fibrosis; b) Group II: Oral leukoplakia and c) Group III: Oral squamous cell carcinoma (OSCC) while d) Group IV were normal control subjects. LDH levels were found to be highly elevated in both serum and salivary samples of OSCC patients which was followed by OSMF and leukoplakia patients (P<0.001.[12] Sharma *et al* also reported an increase in serum LDH levels in oral potentially malignant disorders and OSCC.[13] Among the potentially malignant disorders, Rathore *et al* reported a high mean LDH level in patients with leukoplakia than in OSMF (p<0.01).[8]

Gantala *et al* in 2011 compared serum and salivary LDH levels in patients with OSMF, leukoplakia and OSCC and reported elevated levels of both serum and salivary LDH levels when compared with normal controls.[14]

Shipitzner *et al* also reported 88% increase in salivary LDH levels in OSCC on comparison with normal subjects and demonstrated highly significant difference (P=0.002).[15]

Joshi PS, Golgire S. performed a salivary analysis for LDH isoenzyme which revealed an overall increased salivary LDH isoenzyme level in oral leukoplakia and OSCC cases and a significant correlation between levels of salivary LDH isoenzymes and histopathologic grades of dysplasia in OL and OSCC.[16]

All the above studies have demonstrated a progressive rise in mean Lactate dehydrogenase values from Oral Leukoplakia to Oral Squamous Cell Carcinoma. These findings are similar to those of the current study. However, the mean LDH values obtained in the current study are considerably higher in the present study subjects. However, considerably lower LDH levels were observed in oral lichen planus in our study demonstrating its lesser potential towards malignant transformation.

In our present study we evaluated salivary and serum biomarker- lactate dehydrogenase enzyme in subjects with oral squamous cell carcinoma, potentially malignant disorders such as- leukoplakia, oral submucous fibrosis and lichen planus. It was concluded from the study analysis LDH levels in both saliva and serum may serve as reliable biomarker for prediction of development of malignancy. Thus, an evaluation of salivary LDH as a biomarker for detection of early

malignant transformation may be an equally effective tool as serum samples.

CONCLUSION

The salivary Lactate Dehydrogenase level and serum Lactate Dehydrogenase levels was highest in the patients with Oral Squamous Cell Carcinoma, followed by Oral Leukoplakia, Oral Submucous Fibrosis and oral lichen planus, However, oral lichen planus demonstrated lowest value of both salivary and serum lactate dehydrogenase levels thus, indicating lowest potential towards converting into malignancy

Hence, it can be concluded that saliva samples can be equally effective in analysis of biochemical markers such as lactate dehydrogenase. Its non-invasive nature is an advantage over serum use for analytical purposes.

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