Original Article

Evaluation of Serum and Salivary Lactate Dehydrogenase Levels in Patients with Oral Potentially Malignant Conditions/ Lesions: A Clinical and Biochemical Study

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Abstract

Background: Oral cancer encompasses all malignancies that originate in the oral tissues and remains a major public health problem throughout the world as an important case of poor health and illness. Head and neck cancer accounts for 9.8% of the estimated 6,44,600 incidental cancer cases in India. Oral Squamous Cell Carcinoma (SCC) is a serious and developing concern globally, accounting for more than 90% of malignant cancers of the oral cavity. Salivary diagnostics have been demonstrated to have potential in the detection and screening of oral pre-cancer and cancer in a variety of research settings. The continual and close contact between saliva and the mucosa, where cancer develops, is the foundation of this diagnostic capability. **Materials and Methods:** This research utilized spectrophotometry to quantify Lactate Dehydrogenase levels in serum and saliva of 30 healthy people which consisted the control group and 31 Oral Potentially Malignant people which constituted the study group. **Results:** On estimation and comparison, the mean Lactate Dehydrogenase levels in serum (397.4968+71.6392 IU/L) and saliva (675.4935+139.3352 IU/L) among patients with Oral Potentially malignant lesions/conditions were higher than the mean Lactate Dehydrogenase levels in serum (390.8667+71.0953 IU/L) and saliva (201.3700+89.1439 IU/L) among controls. **Conclusion:** Higher serum and salivary LDH levels in Oral Potentially malignant lesions/conditions than in control groups signifies the importance of assessing salivary LDH levels, in the prognosis of the same. Further prospective longitudinal studies are required to assess the salivary LDH levels among the patients with malignant transformation of Oral Potentially malignant lesions/conditions to oral cancers.

Keywords: Antioxidants, lactate dehydrogenase, oral cancer, oral potentially malignant disorders, saliva, serum

Introduction

Cancer is one of the most prevalent diseases and causes of deaths in today's world with more than 10 million new cases and more than 6 million fatalities each year. Oral cancer is a very lethal disease[1] that accounts for around 2% of all malignant tumors in Western Europe and North America, while up to half of all malignancies in India are found in the oral cavity.[2] Around 20% of deaths worldwide are caused by cancer and amount to 10% in low-income nations. Part of this increase in absolute numbers is due to the world's aging population. Substantial and growing levels of cancer risk factors are to be blamed for the cancer epidemic in both high-income and low- and middle-income nations.[3] Tobacco abuse, poor nutrition, alcohol use, unhealthy lifestyle, and disease are believed to be responsible for around 43% of cancer deaths.[4] The leading preventable cause of cancer in the world is tobacco usage. In addition to lung cancer, cancer of mouth, larynx, throat, stomach, esophagus, liver, pancreas, ureter, kidney, uterine cervix, urinary bladder, and bone marrow are other diseases brought on by tobacco use. When tobacco and alcohol usage are coupled, cancers of the oral cavity, larynx, pharynx, and esophagus develop.[5]

Creating a sensitive and precise method for identifying early oral malignant lesions and predicting regional recurrence and/

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or spreading metastases is vital. Tumor markers, which have recently been acknowledged as a useful tool for diagnosis, therapy monitoring, and prognosis, might be a simple and appealing way to accomplish this goal. The utility of several tumor markers in diagnosing premalignant diseases and malignancies of the oral cavity and/or head and neck has been investigated.[6]

Although the activity of lactate dehydrogenase (LDH) has been widely examined in numerous tissues and plasma, only a few analyses have been conducted in saliva, despite the fact that collection of saliva is significantly simpler, not invasive, and less expensive than serum collection.[6] When a cell membrane is destroyed, LDH is released. Therefore, by measuring LDH, one may determine the rate of tissue damage, necrosis, and cell death in various diseases.[7] A variety of diseases can damage the oral mucosa, causing epithelial changes and potentially the formation of oral squamous cell carcinoma. The quantity of LDH activity in saliva that has been studied thus far is minimal, and the results vary depending on the kind of sample, handling, and analytical processes used. The study and characterization of salivary LDH in order to see if it may be used as a diagnostic tool is of utmost interest. The findings suggest that LDH might be used as a potent salivary biomarker to detect and diagnose oral cancer and other potentially malignant illnesses of the mouth.

The goal of the current cross-sectional study was to compare the serum and salivary LDH levels of patients with potentially malignant diseases and lesions of the mouth to those of healthy people.

The current research was conducted with the hypothesis that patients with oral potentially malignant conditions or lesions would have altered serum and salivary LDH levels compared to healthy individuals.

Methodology

This study included healthy individuals as the control group and participants who had histopathologically verified oral potentially malignant/precancer diseases as cases. The participants and data were collected from out-patient department of oral medicine and radiology. Prior to performing the study, ethical approval was obtained from the Institutional Ethics Committee No.: ABSM/EC/153/2009. After being informed about the study's nature and objective, informed consent was obtained. The participants in the research ranged in age from 20 to 70 years old. A thorough oral examination was performed after a full case history.

The control group was composed of 30 healthy individuals who had no oral mucosal abnormalities and no history of drug or substance abuse. The research group consisted of 31 persons who had histopathologically verified oral potentially malignant/precancer diseases after considering for inclusion criteria and based on earlier research studies. Cases were selected based on clinical and histological finding of premalignant conditions. Participants having a history of pregnancy, persons on medications, systemic diseases, other known malignancies, or those individuals with any additional oral mucosal abnormalities were excluded from the study.

The patients were instructed not to eat or drink for 2 h before the saliva collection. Unstimulated saliva was allowed to collect in the mouth for a period of 5 min under resting conditions after a complete mouth rinse with distilled water. To collect pooled saliva, the spitting method was adopted. Two millimeters of saliva were collected and kept in plastic vials at −200°C for 24 h before being analyzed. The saliva of 60 people was taken in an unstimulated state (30 healthy people and 30 people with oral potentially malignant disorder). Saliva was collected and centrifuged for 10 min at 48°C at 800 rpm. Biochemical analysis was performed on the obtained supernatant. The serum was obtained from the blood collected from antecubital vein. It was stored at −20°C in polycarbonate glass vial with 3% citric acid for 24 h before being analyzed.

The sera were extracted from the antecubital vein using venous blood. It was stored at −20°C in polycarbonate vials containing 3% citric acid for 24 h before being analyzed. A standard kit was used to analyze serum and saliva samples (AGAPPE diagnostics). Spectrophotometry was then used to determine the amounts of LDH in the serum and saliva. Salivary LDH activities were evaluated for both cases and control group samples.

Statistical analysis

Each group was investigated for serum and salivary LDH activities and compared. SPSS 18, IBM, India, was used to analyze the statistical data. The Chi-square test was used to look at the association between age and gender and other characteristics, and the ANOVA test was performed to compare the groups. Pearson's correlation was used to calculate the correlations between the groups.

Results

The control group consists of 30 healthy individuals with no oral lesions and the study group with 31 subjects with histopathologically confirmed oral precancer/potentially malignant conditions/lesions.

The present study involves ages from 20 to 70 years with an average age of 34.9 years, while the males accounted for 53.3% (16/30) and the females accounted for 46.7% (14/30).

Table 1 indicates a comparison of mean values of serum and salivary LDH between controls and precancer/potentially malignant conditions/lesions groups. The mean value of serum LDH level in the control group was 390.8667 ± 71.0953 IU/L, while the mean value of serum LDH levels of the precancer group was 397.4968 ± 71.6392 IU/L [Table 1].

Table 2 indicates LDH levels in serum and saliva in relation to duration and frequency of tobacco usage in oral precancer/potentially malignant conditions/lesions. LDH level in serum was 399.3588 + 74.2401 IU/L in areca users who

Table 1: Mean Serum LDH Levels

Serum LDH (IU/L)	*n*	Mean	Std. deviation	Minimum	Maximum
Control	30	390.8667	71.0953	88.80	543.20
Pre cancer	31	397.4968	71.6392	238.30	510.60

ANOVA

Serum LDH	*F*	Sig.
Between groups	97.258	0.000

Table 2: Serum and salivary LDH levels based on duration and frequency of areca use in oral premalignant/precancerous conditions/lesions

	Serum LDH IU/L (85–300 IU/L)	Salivary LDH IU/L (360–430 IU/L)
Duration of areca usage (in years)		
1–10	399.3588±74.2401	704.9765±127.9746
10–20	390.6600±87.5245	658.7000±173.9125
20–30	399.5000±80.1859	721.3000±46.6691
>30	454.8000±78.9131	665.7500±298.0455
Frequency of areca usage (per day)		
<10 times	401.9615±74.2521	694.315385±139.3405
>10 times	428.3000±94.2334	582.800000±117.5365

chewed tobacco for 1–10 years, 399.5000 + 80.1859 IU/L in 20–30 years of tobacco usage, and 454.8000 + 78.9131 IU/L in those who chewed tobacco for above 30 years. The LDH levels in saliva areca users who chewed for 1–10 years were 704.9765 + 127.9746 IU/L; for 10–20 years, 20–30 years, and more than 30 years was 658.7000 + 173.9125 IU/L, 721.3000 + 46.6691 IU/L, and 665.7500 + 298.04551 IU/L, respectively [Table 2].

Table 2 indicates frequency and salivary LDH levels. Serum LDH levels were 401.9616 + 74.2521 IU/L in areca users who chewed fewer than 10 times per day and 428.3000 + 94.2334 IU/L in those who chewed well over 10 times per day [Table 2]. Salivary LDH levels were 694.3154 + 139.3405 IU/L in areca users who chewed fewer than 10 times per day, whereas those who chewed areca well over 10 times per day had 582.8000 + 117.5365 IU/L [Table 2].

The statistical difference between the LDH levels in saliva of the control group and that of the precancer group was very significant ($P < 0.001$) [Table 3]. But on correlation of salivary and serum LDH in the precancer group, results were not statistically significant ($r = -0.025$, $P = 0.894$) [Graph 1].

Among the oral potentially malignant/precancer group, increased mean serum LDH levels were seen in individuals with oral submucous fibrosis which was 434.81 + 32.01 IU/L, followed by oral leukoplakia which was 397.75 + 36.78 IU/L and erosive lichen planus which was 335.23 + 32.73 IU/L [Table 4]. Among the oral potentially malignant group/precancer group, increased mean salivary LDH levels were seen in individuals with oral leukoplakia which was 721.23 + 45.5 IU/L, followed by oral submucous fibrosis which was 716.74 + 37.31 IU/L and erosive lichen planus which was 675.36 + 49.89 IU/L [Table 4].

Discussion

LDH, also known as lactic acid dehydrogenase, is an enzyme found in virtually all physiological tissues. It is required for cellular respiration, the process through which sugar (glucose) from food is metabolized for our cells.

Despite the fact that LDH is prevalent in tissue cells, LDH levels in the blood are usually low. It is released into the extracellular space when tissues are injured during injury or illness. Although cellular enzymes in the extracellular environment have very little metabolic activity, they are nonetheless useful because they serve as markers of cellular integrity disruption generated by disease states. LDH is a cytoplasmic enzyme found in almost every organ system. LDH's extracellular presence is applied to identify cell damage and degradation.[8]

The purpose of this research was to determine the levels of salivary and serum LDH in healthy controls and oral precancer individuals. We have also compared the levels of salivary and serum LDH amongst the various oral precancer conditions/lesions in this study. The findings of a study by Javaraiah *et al*. have suggested similar to our study that when compared to healthy controls, LDH level showed a progressive rise from tobacco users without PMD to tobacco users with PMD. LDH level can be used as a prognostic biomarker in very early stages.[9]

The foremost study on estimation of increased salivary LDH levels was conducted in the year 2000 by Leyva Huerta *et al*.[10] in smokers. This was followed by a series of other salivary LDH studies by Nagler et al. following exposure of saliva and plasma to cigarette smoke (CS),[6] Rai *et al*. among smokers and nonsmokers,[11] Rai Balwant *et al*. in oral lichen planus,[12] Shpitzer *et al*. in tongue cancer patients,[13] Langavad *et al*. in submucous fibrosis, oral leucoplakia, and carcinoma of the oral mucosa.[14]

Method of determination of LDH values

Spectrophotometry was the method used in our study for standardization of serum and salivary LDH values. The various methods for evaluation of LDH levels over the years were determined by using Spectrophotometry in human serum by Dohjyo,[15] Bouafia *et al*.[16] using Spectrophotometry in human saliva by Rai et al.[11,12] using Kinetic Spectrophotometry in human serum by Shpitzer *et al*.[17] using Auto Analyzer in human saliva by De La Pen *et al*.[18] using UV Spectrophotometry in human saliva by Alagendran *et al*.[19] In our study, saliva has been studied as a possible adjunct or as an alternative to estimation of serum LDH levels.

Serum LDH levels

The total activity of LDH in serum was in the current study

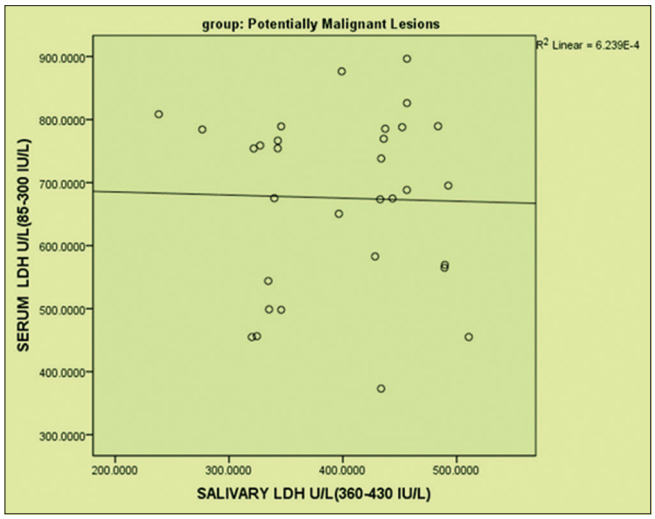
Table 3: Comparison of salivary LDH levels between controls and oral premalignant/precancerous conditions/lesions

	Group	*n*	Mean rank	Sum of ranks	Mann–Whitney *U*	*Z*	Asymp. sig. (two-tailed)
Salivary LDH IU/L (360–430 IU/L)	Healthy individuals	30	15.53	466	1.000	−6.694	**<0.001**
	Oral potentially malignant lesions	31	45.97	1425			

P<0.001: Significant, Bold: statistically significant

Table 4: Comparison of serum and salivary LDH levels in different oral premalignant/precancerous conditions/lesions

	Groups	*n*	Mean	Std. deviation
Leukoplakia	Serum LDH (300–500 IU/L)	16	397.75	36.78
	Salivary LDH (400–800 IU/L)	16	721.23	45.5
OSMF	Serum LDH (300–500 IU/L)	12	434.81	32.01
	Salivary LDH (400–800 IU/L)	12	716.74	37.31
Lichen planus	Serum LDH (300–500 IU/L)	3	335.23	32.73
	Salivary LDH (400–800 IU/L)	3	675.36	49.89



Graph 1: Correlation of salivary and serum LDH levels in premalignant/precancerous conditions/lesions

among healthy individuals was found to be in the range of 88.80–543.20 IU/L. This was consistent with study by Dohjyo[15] and in a study by Hafiz and Mannan[20] where the serum LDH level was 330 ± 30 IU/L and 362.32 ± 89.69 IU/L in the control group respectively. Comparatively lower range of serum LDH level was seen among the controls in a study carried out by Narang *et al*.,[21] where the level was 145.06 ± 59.09 IU/L.

In the extant research, the control group's mean serum LDH value was 390.8667 + 71.0953 IU/L. The higher LDH value in serum was seen in our study in the oral precancer group which was 397.4968 ± 71.6392 IU/L. Similar studies have been carried out by Dohjyo[15] with increased mean serum LDH values among the study groups which was 330 ± 30 IU/L in the normal patients, 357 ± 69 IU/L in cystic diseases, 394 ± 75 IU/L in other benign oral diseases and 426 ± 94 IU/L in oral cancer. In a study by Narang *et al*.[21] where the serum LDH levels were evaluated in head and neck malignancy, it was found to be 295.00 ± 197.67 IU/L when compared to 145.06 ± 59.09 IU/L in the control group. In a study done by Hafiz and Mannan,[20] mean serum LDH values were 2091.98 ± 1073.20 IU/L in childhood acute lymphoblastic leukemia patients when compared to controls with readings of 362.32 ± 89.69 IU/L. Similarly, increased readings in the levels of serum LDH were observed in the study groups by Muralidhar *et al*.,[22] Görögh *et al*.,[23] and Shpitzer *et al*.[17]

On comparison with the control group, the increase in LDH value in serum amongst oral precancer patients could be due to the reason stated by Drent *et al*.[8] and De La Pen *et al*.[18] where the presence of LDH in extracellular space serves as indicators suggestive of turbulences in cellular integrity induced by pathological conditions. They also indicated that cell damage or death causes the extracellular appearance of LDH in peripheral blood.

Salivary LDH levels

In this study, salivary LDH levels have been evaluated in healthy individuals and the oral precancer group. Very few studies of salivary LDH level analysis have been carried out in the Indian population by Rai *et al*.[11] and Rai *et al*.[12] where increased salivary LDH values were seen in their study groups.

In the current research, the total activity of LDH in saliva was estimated to be in the range of 69.40–378.50 IU/L in the control group, which is in conformity with the salivary LDH levels of 360–430 IU/L as observed in a study by Nagler *et al*.[6] However, lower level of the salivary LDH was seen in a study by Rai *et al*.[12] which was 146.07 ± 23.2 IU/L in the control group.

In this study, a higher mean salivary LDH level was seen in the oral precancer group which was 675.4935 ± 139.3352 IU/L when compared to controls with mean salivary LDH values of 201.3700 ± 89.1439 IU/L. The findings are consistent with research carried out by De La Pen VA *et al*.[18] and Rai *et al*.[12] where higher salivary LDH values were seen in their study groups. The higher values of salivary LDH levels in the precancer group when compared to the control group could be due to the reason stated by Nagler *et al*.[6] that the nonsalivary

secretory LDH in entire saliva comes mostly from the epithelial tissue. This information leads to the hypothesis that oral epithelial cell shedding and death cause LDH to be released, resulting in an increase in LDH levels in the total saliva. They also claimed that pathogenic mutations in the oral epithelium may result in pathological variations in LDH profiles, which would be anticipated to be paralleled in fluctuations in salivary LDH profiles.

The possible bias in this study could be observer bias and blinding was not performed to avoid participant selection bias. The test specificity and sensitivity could be ascertained.

In modern medicine, the evaluation of diagnostic tests is essential both for establishing the existence of a disease and for ruling it out in healthy people. For the evaluation of medical diagnostic tests, receiver operating characteristic (ROC) curve analysis may provide a more accurate assessment of accuracy. The area under the curve, which has been taken into consideration as an effective measure of accuracy with meaningful interpretations, is a plot of sensitivity versus specificity and is known as the ROC curve. This curve is crucial for comparing two different diagnostic tasks when they are carried out on the same subject, determining the best threshold values, and assessing a test's capacity to diagnose an individual's actual state.[24]

Comparison of mean LDH values in serum and saliva of study groups

In the current research, the rise in salivary LDH value was greater than the serum LDH value when the mean serum and saliva of each group were compared. This was in agreement with a study by Nagler *et al*.[6] in which a higher mean salivary LDH value of 252 IU/L was seen in the saliva when exposed to CS for 3 h in comparison to a lower rate of increase as suggested by the value of 136.1 IU/L when plasma was exposed to CS for 3 h. The increased salivary LDH activity which was significantly greater than the LDH activity in serum renders the easy detection and facilitates the possible relevance of salivary LDH in clinical surveillance and utilization.

The limitation of this study was the smaller sample size and inclusion in a particular geographic area. Further studies are needed on the larger sample size with salivary diagnostic criteria to validate the results.

Conclusion

The goal of this research was to assess LDH levels in saliva as a potential biomarker in the initial propagation of oral precancer may aid to preclude diagnosis of oral cancer diagnosis. In spite of the ease of direct inspection of oral cavity, oral cancers are frequently not discovered or diagnosed until advanced stages. As a result, the therapy of head and neck cancer and potentially malignant disorders are delayed. Therefore, saliva has received more attention recently, particularly for diagnostic purposes. The findings of this study show that salivary LDH levels can be employed as a biomarker in the initial detection of oral precancer/cancer and are superior to serum estimation. The use of saliva as an additional diagnostic tool and efficient probe when compared to serum analysis is also highlighted in this study.

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Conflicts of interest

There are no conflicts of interest.

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