

Salivary Lactate Dehydrogenase and Salivary Alkaline Phosphatase as Salivary Biomarkers in Oral Potentially Malignant Disorders and Oral Squamous Cell Carcinoma - A Narrative Review

Bhakta Ipsita¹, Banerjee Abhishek¹, Abhinandan¹, Barua Akash Narayan Dutta², Singh Subhasini¹

ABSTRACT

Background: Salivary lactate dehydrogenase (LDH) is categorized in altered protein markers present in saliva which shows significantly increased level in oral carcinoma. On the other hand salivary alkaline phosphatase (ALP) is one of the sensitive markers for early detection of oral malignancy. As saliva sample collection is simpler, non-invasive and patient friendly, the use of salivary biomarkers for early detection of oral cancer has been increased remarkably in last decade.

Aims & Objectives: To analyze the potential diagnostic role of major two biomarkers i.e, salivary LDH & salivary ALP in oral potentially malignant disorders & oral squamous cell carcinoma.

Materials & Methods: In depth search of topic on major search engines like pubmed, google scholar, EBSCO, Wiley online pertaining to the enzymes like salivary LDH, salivary ALP with keywords like salivary LDH, salivary ALP, oral potentially malignant disorders, oral squamous cell carcinoma, salivary biomarkers were done. The literature review was done from 2010-2019. The available data is tabulated & presented under various topics of discussion regarding their regulation & functionality in the body harbouring those disorders & conditions.

Conclusion: The salivary LDH is found to be more promising salivary biomarker for detection of oral cancer as per this study. Quite a number of studies have been done during the last decade on the same. Whereas, there is paucity of studies on the role of salivary ALP as a biomarker for oral cancer, instead we can say the role of salivary ALP is rather more in periodontitis in comparison to carcinoma.

Keywords: salivary LDH, salivary ALP, oral potentially malignant disorders, oral squamous cell carcinoma, salivary biomarkers.

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INTRODUCTION

WHO subdivided the term 'precancer' into 'lesion' and 'condition'. But now as per their recommendation the term 'oral potentially malignant disorder' (OPMD) is used to indicate both. The term OPMD denotes the risk of malignancy being present in a lesion or condition either during the time of initial diagnosis or at a future date as per definition.

Among all carcinoma OSCC occupies 3% in western population and 30% in indian population. It is 6th most common human cancer. Almost 90% of all oral malignancies are found to be OSCC. OSCC is recognized to have 50% five year survival rate but with early diagnosis almost 80% five year survival rate is observed. Almost 300000 of new cases are emerging every year all over the world which leads to an average of 280000 deaths annually.

An early detection is really important in case of oral cancer as this way we can avoid mutilating surgeries and we can improve quality of life of the patient.^{1,2,3}

To combat this problem, we can take the help of biomarkers. We will be discussing about two biomarkers that are salivary lactate dehydrogenase and salivary alkaline phosphatase.

¹Department of Oral and Maxillofacial Pathology, Awadh Dental College and Hospital, Jamsheedpur; ²Department of Conservative Dentistry and Endodontics, Govt Dental College and Hospital, Silchar, Assam.

Corresponding Author: Bhakta Ipsita, Department of Oral and Maxillofacial Pathology, Awadh Dental College and Hospital. email id: ibhakt2016@gmail.com

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Conflict of Interest: None

Our main concern will be studies done on these two salivary enzymes in last 10 years and whether these are reliable enough as biomarkers after investigating all the findings.

MATERIALS AND METHODS

All the studies selected here have used saliva as a sample because obtaining saliva is easy, inexpensive, non invasive, patient friendly and risk of cross infection or contamination is absent. There are quite a few methods of saliva collections used in various studies and specific reagents are used to obtain the salivary enzymes.

Type of the articles included here are mostly original studies, reviews, systematic analysis on the same.

In depth search of topic on major search engines like PUBMED, GOOGLE SCHOLAR, EBSCO, Wiley online pertaining to the enzymes like salivary LDH, salivary ALP with keywords like salivary LDH, salivary ALP, oral potentially malignant disorders, oral squamous cell carcinoma, salivary biomarkers were done.

The literature review was done from 2010-2019. Study can be described as retrospective analysis type. The available data is tabulated & presented under various topics of discussion regarding their regulation & functionality in the body harbouring those disorders & conditions. (Table 1, 2); (Figure 1, 2)

DISCUSSION

SALIVARY LDH:

The enzyme Lactate Dehydrogenase (LDH) is found in the cells of almost all body tissues. LDH is believed to vary according to the metabolic requirement of each tissue and alternation in LDH levels have been observed during development, under changing biological conditions, and in response to pathological processes. The profile of salivary LDH is similar to that found in oral epithelium, indicating the major source of salivary LDH is probably the oral epithelium-shedding cells⁴.

SALIVARY ALP:

ALP belongs to hydrolase group of enzymes. ALP functions by catalyzing the hydrolysis of monoesters of phosphoric acid and also transphosphorylation reaction in the presence of large concentrations of phosphate acceptors⁹. The source of this enzyme in the oral cavity includes neutrophils, bacteria and oral epithelial cells.

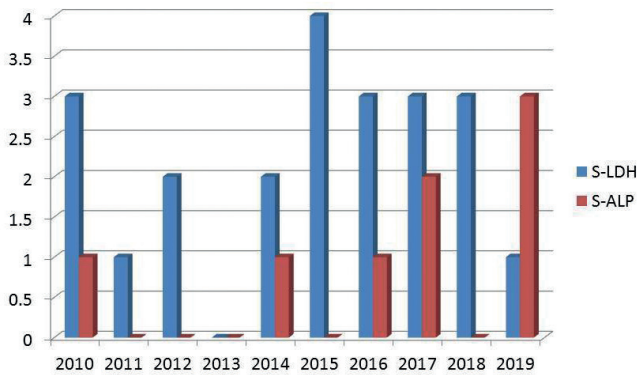


Fig. 1: SAMPLING: Studies done on s-LDH & s-ALP (2010 to 2019)

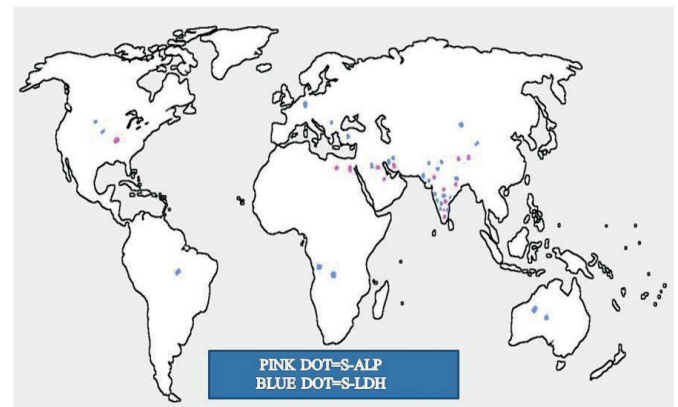
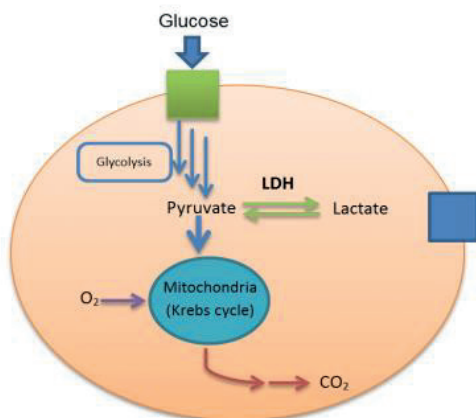


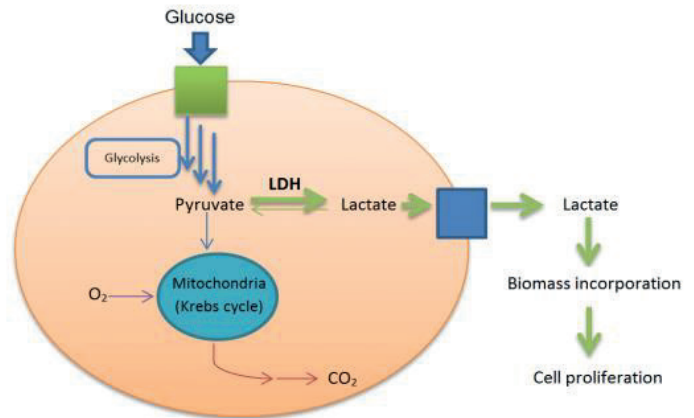
Fig. 2: Mapping of the studies across the world (2010-2019)

Normal Cell



Oxidative phosphorylation- high ATP: glucose ratio, low LDH activity in both directions results in high energy production.

Cancer Cell



Aerobic glycolysis (Warburg effect) - low ATP: glucose ratio, high LDH activity in one direction. Results in biomass incorporation and cell proliferation.

Fig. 3: Warburg effect: it is a modified cellular metabolism seen in cancer cell where anaerobic glycolysis is more preferred than oxidative phosphorylation.

Table 1: Studies done on Salivary LDH and brief findings Decade Review 2010-2019

SL NO	YEAR	JOURNAL	ARTICLE & AUTHOR	SAMPLE	DISEASE	INFERENCE
1	2010	<i>Iraqi Journal of Science.</i>	“COMPARATIVE STUDY ON LACTATE DEHYDROGENASE, ALKALINE PHOSPHATASE AND INNUNO-GLOBULINS IN SERUM AND SALIVA OF ACUTE LEUKEMIA AND ORAL SQUAMOUS CELL CARCINOMA PATIENTS” <i>Merza et al.</i>	CONTROL:20 AL:70 OSCC:20 PERIODONTITIS:12	OSCC, AL	SALIVARY LDH VALUE(IU/L) CONTROL:211.6+-97.7 OSCC:325.4+-156.5 SALIVARY ALP VALUE CONTROL:1.03+-1.74 OSCC:2.24+-2.94
2	2010	<i>The Open Dentistry Journal.</i>	“SALIVARY MARKERS FOR ORAL CANCER DETECTION” <i>Marcopoulos et al.</i>		PERIODONTITIS OSCC	LISTED LDH IN ALTERED PROTEIN MARKERS ALSO DESCRIBED LDH AS AN ALTERED SALIVARY BIOMARKER.
3	2011	<i>Indian Journal of Clinical Biochemistry</i>	“A REVIEW ON SALIVARY GENOMICS AND PROTEOMICS BIOMARKERS IN ORAL CANCER” <i>Shah et al.</i>		OSCC	MENTIONED ABOUT INCREASED SALIVARY LDH IN ORAL CANCER PATIENTS.
4	2012	<i>International Journal of Oral & Maxillofacial Pathology.</i>	COMPARISON BETWEEN SALIVARY AND SERUM LACTATE DEHYDROGENASE LEVELS IN PATIENTS WITH ORAL LEUKOPLAKIA AND OSCC-A PILOT STUDY” <i>Joshi et al.</i>	CONTROL-7 OL-7 OSCC-7	OL OSCC	SALIVRY LDH LEVEL CONTROL<OL<OSCC IN ALL THE CASES.
5	2012	<i>Journal of Cancer Research Therapeutics</i>	“SALIVARY LACTATE DEHYDROGENASE LEVELS IN ORAL LEUKOPLAKIA AND OSCC: A BIOCHEMICAL AND CLINICOPATHOLOGICAL STUDY” <i>Shetty et al.</i>	CONTROL:25 OL:25 OSCC:25	OL & OSCC	MEAN SALIVARY LDH (IU/L) CONTROL:79.50+-4.67 OL:136.46+-3.36 OSCC:148.77+-4.83 i.e, CONTROL<OL<OSCC & ALSO FOUND IN ALL THREE GROUPS SALIVARY LDH LEVEL MALE>FEMALE.
6	2014	<i>Journal of Oral & Maxillofacial Pathology.</i>	A STUDY OF SALIVARY LACTATE DEHYDROGENASE ISOENZYME LEVELS IN PATIENTS WITH ORAL LEUKOPLAKIA AND SQUAMOUS CELL CARCINOMA BY GEL ELECTROPHORESIS METHOD” <i>PRIYA JOSHI, SOMESHWAR GOLGIRE.</i>	CONTROL:30 OL:30 OSCC:30	OL & OSCC	TOTAL SALIVARY LDH(IU/L) CONTROL:267.2 OL:519.37 OSCC:788.7 CONTROL<OL<OSCC ISOENZYME LEVELS: CONTROL: LDH1 IS LOW, LDH5 IS HIGH AND REST ARE INTERMEDIATE. OL:STATISTICALLY SIGNIFICANT INCREASE OF LDH2, LDH3, LDH4, LDH5. OSCC:STATISTICALLY SIGNIFICANT LDH3, LDH4, LDH5.



7	2014	Journal of Oral Pathology & Medicine	“EVALUATION OF LACTATE DEHYDROGENASE ENZYME ACTIVITY IN SALIVA AND SERUM OF ORAL SUBMUCOUS FIBROSIS PATIENTS”. Sivaramkrishnan et al.	CONTROL:30 OSMF:30	OSMF	AVERAGE SALIVARY LDH VALUE(IU/L) CONTROL:80.73+-20.06 OSMF:606.83+-60.09
8	2015	Journal of Cancer Research & Therapeutics	“ESTIMATION OF SALIVARY LACTATE DEHYDROGENASE IN OL AND OSCC:A BIOCHEMICAL STUDY” SHRIKANT PATEL RASHMI METGUD	CONTROL:25 OL:25 OSCC:25	OL OSCC	MEAN & SD OF SALIVARY LDH(IU/L) CONTROL:261.16+-75.851 OL:497+-100.404 OSCC:686.40+-81.752 i.e, CONTROL<OL<OSCC.
9	2015	South Asian Journal of Cancer	HISTOPATHOLOGICAL DIFFERENTIATION OF OSCC AND SALIVARY LACTATE DEHYDROGENASE-A BIOCHEMICAL STUDY” Audrey M D'cruz, Varsha Pathiyil.	CONTROL:30 OSCC:30	OSCC	SALIVARY LDH LEVEL(IU/L) CONTROL:117.33+-19.37 WD OSCC:355.83+-16.73 MD OSCC:484.18+-25.84 PD OSCC:620.35+-18.69
10	2015	Journal of Pharmaceutical Sciences & Research.	“A STUDY OF SALIVARY LACTATE DEHYDROGENASE LEVELS IN ORAL CANCER AND OSMF PATIENTS AMONG THE NORMAL INDIVIDUALS” SRI VASAVI KADIYALA.	CONTROL:20 OSMF:20 OSCC:20	OSMF OSCC	MEAN SALIVARY LDH LEVEL(IU/L) CONTROL:126.7+-58.2 OSMF:328.9+-00 OSCC:515.7+-257.8 i.e, CONTROL<OSMF<OSCC
11	2016	Journal of Clinical Diagnostic & Research.	“SALIVARY LACTATE DEHYDROGENASE- A NOVEL TECHNIQUE IN ORAL CANCER DETECTION & DIAGNOSIS”. Lokesh et al.	CONTROL:20 OSCC:30	OSCC	MEAN SALIVARY LACTATE DEHYDROGENASE(IU/L) CONTROL:497+-51.57 OSCC:1225.40+-221.79
	2016	Journal of Dental & Oral Health.	“SALIVARY LACTATE DEHYDROGENASE ENZYME ACTIVITY IN OSMF” Bhambal et al.	CONTROL:80 OSMF:80	OSMF	MEAN SALIVARY LDH CONTROL:8.97+-0.84 MALE:78.46+-7.76(GR I) 511.37+-46.25(GR II) 628.09+-99.18(GR III) FEMALE:72.05+-5.69(GR I) 528.77+-68.92(GR II) 618.39+-95.67(GR III).
12	2016	Journal of Oral Pathology & Medicine.	“LACTATE DEHYDROGENASE AS A BIOMARKER IN ORAL CANCER & ORAL SUBMUCOUS FIBROSIS”. Kallalli et al.	CONTROL:10 OSMF:25 OSCC:25	OSMF & OSCC	MEAN SALIVARY LDH VALUE(IU/L) CONTROL:182.21+-34.85 OSMF:608.28+-30.22 OSCC:630.96+-39.80
13	2017	Journal of Medical Science & Clinical Research.	“A STUDY OF SALIVARY AND SERUM LACTATE DEHYDROGENASE LEVELS IN TOBACCO USERS AND POTENTIALLY MALIGNANT DISORDERS”. Mohan et al.	CONTROL+ NO TOBACCO: 10 SUBJECT+ TOBACCO: 10 SUBJECT+ TOBACCO+ PMD:10	PMD	MEAN SALIVARY LDH & SD VALUE (IU/L) CONTROL:426.70+216.51 TOBACCO:677.90+235.87 PMD:2470.60+938.20

It's very evident from the selected studies that in almost every cases salivary LDH level is CONTROL<PMD<OSCC⁵. But while going through various studies we have found that level of this enzyme might be higher in OSMF than OSCC in few cases⁶. This can happen as OSMF takes quite a good time to progress into an well defined lesion from initial stage. So the cases chosen in OSMF can show variation in the level of the enzyme. Another finding is salivary LDH level sequence well differentiated carcinoma<moderately

differentiated carcinoma<poorly differentiated carcinoma⁷. Here also it is evident that in every cases salivary ALP level is CONTROL<PMD<OSCC². Salivary ALP change is more in local malignancies like OSCC. In contrast serum ALP change is more in disseminated malignancies like leukaemia⁸. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to breakdown of glycoprotein. LDH activity is mainly due to genomic changes during malignant transformation⁴.

14	2017	Journal of Health Sciences.	“SALIVARY LACTATE DEHYDROGENASE AS A BIOMARKER FOR SQUAMOUS CELL CARCINOMA” GEETA SHARMA MOHD. FAHAD..		OSCC	INCREASED SALIVARY LDH IN CANCER
15	2017	International Journal of Dental Research.	ESTIMATION OF SALIVARY AND SERUM LACTATE DEHYDROGENASE LEVELS AMONG HEALTHY INDIVIDUALS AND ORAL CANCER PATIENTS” Rao et al.	CONTROL:30 STUDY:30	OSCC	MEAN SALIVARY LDH(IU/L) CONTROL:201.370+89.144 STUDY:906.418+239.465
16	2018	International Journal of Scientific Research.	“SALIVARY LDH-A SUBSTITUTE FOR SERUM LDH AS A BIOMARKER IN POTENTIALLY MALIGNANT DISORDERS AND ORAL MALIGNANCY:A BIOCHEMICAL STUDY” Gantala et al.	CONTROL:10 OSMF:10 OL:10 OSCC:10	OSMF, OL, OSCC.	MEAN SALIVARY LDH(IU/L) CONTROL:200.3+-13.74 OSMF:490.5+-76.18 OL:354.0+-56.43 OSCC:1023+-161.4
17	2018	Acta Scientific Cancer Biology.	“PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE SALIVARY AND SERUM LACTATE DEHYDROGENASE IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS”. Acharya et al.	CONTROL:30 OSCC:60	OSCC	MEAN SALIVARY LDH (IU/L) CONTROL:268.23+-67.84 OSCC:1143.70+-749.53
18	2018	Journal of International Society of Preventive & Community Dentistry.	ESTIMATION OF SALIVARY AND SERUM LACTATE DEHYDROGENASE IN OSMF”. Mishra et al.	CONTROL:20 OSMF:20	OSMF PML	MEAN SALIVARY LDH(IU/L) CONTROL:668.25+-498.45 OSMF:1057.30+-640.12
19	2018	International Journal of Pathology & Microbiology	“ROLE OF SALIVARY BIOMARKERS IN EARLY DETECTION OF ORAL SQUAMOUS CELL CARCINOMA”. NIDHI AWASTHI.	CONTROL:25 PML:9 OSCC:30	OSCC	SALIVARY LDH(MEAN+2SD & MEDIAN VALUE) CONTROL:109.8+-67.4,98.4 PML:274.2+-60,274.4 OSCC:425.4+-158.2+-386.5
20	2019	Reports of Biochemistry & Molecular Biology	“OVEREXPRESSION OF LACTATE DEHYDROGENASE IN THE SALIVA AND TISSUES OF PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA”. Mohajertehranfet et al.	CONTROL:44 HNSCC:44	OSCC	THE MEAN PERCENTAGE OF CELLS SHOWING LDH EXPRESSION IN THE TUMOR TISSUES WAS 72%±17, AND THE PERCENTAGE OF LDH EXPRESSION IN THE HEALTHY MARGIN AROUND A TUMOR WAS 43%±21 (P<0.001).



Table 2: Studies done on Salivary LDH and brief findings Decade Review 2010-2019

SL NO	YEAR	JOURNAL	ARTICLE & AUTHOR	SAMPLE	DISEASE	INFERENCE
1	2010	<i>Iraqi Journal of Science.</i>	“COMPARATIVE STUDY ON LACTATE DEHYDROGENASE, ALKALINE PHOSPHATASE AND INNUNOGLOBULINS IN SERUM AND SALIVA OF ACUTE LEUKEMIA AND ORAL SQUAMOUS CELL CARCINOMA PATIENTS” <i>Merza et al.</i>	CONTROL:20 AL:70 OSCC:20 PERIODONTITIS: 12	OSCC, AL PERIODONTITIS	SALIVARY ALP VALUE CONTROL:1.03+-1.74 OSCC:2.24+-2.94
2	2014	INTERNATIONAL JOURNAL OF CHEMTECH RESEARCH	“EXPRESSION OF SALIVARY BIOMARKERS- ALKALINE PHOSPHATASE AND LACTATE DEHYDROGEASE IN ORAL LEUKOPLAKIA” <i>DHIVYALAKHSMI M. UMAMAHESWARI T.N.</i>	CONTROL-14 LEUKOPLAKIA-14 OSCC-14	OL OSCC	MEAN SALIVARY ALP CONTROL-11.88IU/L OL-23.04IU/L OSCC-35.43IU/L
3	2016	JOURNAL OF ORAL AND MAXILLOFACIAL PATHOLOGY	SALIVARY ALKALINE PHOSPHATASE LEVEL SPEAK ABOUT ASSOCIATION OF SMOKING, DIABETES AND POTENTIALLY MALIGNANT DISEASES???” <i>Prakash et al.</i>	Group A 10 smokers who are diabetic. Group B 10 smokers who are nondiabetic. Group C 10 nonsmokers who are diabetic. Group D 10 nonsmokers and nondiabetic as control.	PMD	SALIVARY ALP IS ONE OF THE SENSITIVE MARKER FOR EARLY DETECTION OF ORAL MALIGNANCY.
4	2017	JOURNAL OF MEDICAL SCIENCE AND CLINICAL RESEARCH	“ROLE OF SALIVARY ALKALINE PHOSPHATASE IN DETECTING ORAL DISEASES-A REVIEW” <i>Manimegalal et al.</i>		OSCC, PERIODONTITIS, BONE DISEASES, GROWTH.	AGREED TO FACTS LIKE-CELLULAR ALP INDICATES INDUCTION OF TUMOR CELL DIFFERENTIATION. BETWEEN ALP AND LDH, LDH IS MORE RELIABLE IN OSCC DIAGNOSIS. SALIVARY ALP CHANGES IS MORE IN LOCAL MALIGNANCY.
5	2017	ITALIAN JOURNAL OF DENTAL MEDICINE	SALIVARY ALKALINE PHOSPHATASE AND ORAL HEALTH:A REVIEW” <i>Shetty et al.</i>		PERIODONTITIS, CARIES, GROWTH, PMD.	AGREED TO FACTS THAT SCREENING OF PMD AND OSCC CAN BE MADE BY INCREASED SALIVARY ALP. LDH IS MORE RELIABLE THAN ALP. INCREASED SERUM ALP IN DISSEMINATED MALIGNANCY LIKE LEUKAEMIA. INCREASED SALIVARY ALP MORE IN LOCAL MALIGNANCY LIKE OSCC.

6	2019	INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH.	“COMPARATIVE ANALYSIS ON ALKALINE PHOSPHATASE, LACTATE DEHYDROGENASE AND IMMUNOGLOBULINS IN SALIVA OF PATIENTS SUFFERING FROM ORAL MALIGNANCY AND ORAL SQUAMOUS CELL CARCINOMA”. NITA SAHI NEHA SAXENA.	CONTROL-30 OSCC-30	OSCC	SALIVARY ALP VALUE CONTROL-89.53+-22.91 OSCC-220.17+-36.91.
7	2019	JOURNAL OF ORAL AND MAXILLOFACIAL PATHOLOGY.	EVALUATION OF SALIVARY ALKALINE PHOSPHATASE LEVELS IN TOBACCO USERS TO DETERMINE ITS ROLE AS A BIOMARKER IN ORAL POTENTIALLY MALIGNANT DISORDERS”. Menaka et al.	CONTROL GROUP, GROUP WITH HABIT OF CHEWING TOBACCO, GROUP WITH HABIT OF SMOKING, GROUP WITH PMD ALONG WITH TOBACCO HABIT.	PMD	CONTROL-18.00 IU/L PMD-64.00 IU/L.
9	2019	INTERNATIONAL JOURNAL OF RESEARCH IN HEALTH AND ALLIED SCIENCES	“CORRELATION AND COMPARISON OF SALIVARY ALKALINE PHOSPHATASE AND LACTATE DEHYDROGENASE IN PATIENTS WITH POTENTIALLY MALIGNANT DISORDERS AND ORAL SQUAMOUS CELL CARCINOMA” GEETA SHARMA RANDHIR KUMAR	CONTROL-15 OSCC-15 PMD-15	PMD OSCC	SALIVARY ALP VALUE CONTROL-24.4+-4.07 PMD-41.33+-4.79 OSCC-72.13+-13.28

Warburg effect got it's immense role in carcinoma (Figure 3). There are probable reasons for increased level of salivary ALP. Firstly, the increased S-ALP levels observed in OPMD cases could be secondary to the increase in the oxidative stress associated with the lesion. The rise in reactive oxygen species induces cellular damage which leads to increased release of ALP in saliva. Secondly, the increased rate of cellular turnover in OPMD as a compensatory mechanism or due to genetic mutation, can also lead to increase in ALP production by epithelial cells. Thirdly increased inflammatory reaction seen in association with OPMD could also be another contributing factor for the high levels of S-ALP observed. Hence rise in salivary ALP (S-ALP) levels reflects inflammation and destruction of healthy epithelial tissues suggesting it as clinical biomarker¹⁰. A sampling has been done on the basis of the studies done on these two particular enzymes during the last decade (Figure 2). The amount of studies done on salivary LDH seemed to be quite higher than salivary ALP. Salivary LDH and salivary ALP both found to be equally sensitive biomarkers in early detection of oral cancer according to majority of these studies. But according to M. Dhivyalakshmi, T.N. Uma Maheswari s-LDH could be more reliable marker than s-ALP in the detection of oral carcinoma¹¹. On the contrary Geeta Sharma and Randhir Kumar found that s-ALP levels are consistently higher in oral pre-cancer and cancer hence it could be future marker for potential significance in clinical diagnosis and prognosis of cancer²

But, the roles of S-LDH have to be further evaluated with a larger sample size.

A world mapping done where we have put pink and blue dots in various places where recent studies are in progress on these enzymes (Figure 3). Pink dots indicate salivary ALP, blue dots indicate salivary LDH.

CONCLUSION

Thus by looking at all the studies and observations throughout the decade we can conclude that s-LDH & s-ALP are definitely reliable salivary biomarkers for early detection of oral cancer. Though in majority of the cases the level of s-LDH and s-ALP are found to be CONTROL<PMD<OSCC; a few conflicts are there so studies with a larger size of population is still in need.

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- suffering from oral malignancy like oral squamous cell carcinoma” *Int J Scin Res.*2019;8(4):1-3.
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