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RESEARCH ARTICLE

SALIVARY LACTATE DEHYDROGENASE A DIAGNOSTIC MARKERS FOR ORAL LEUKOPLAKIA- A SHORT STUDY

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ABSTRACT

Introduction: Leukoplakia has evolved as a clinic-pathologic concept over many years, with the current clinical term being established worldwide. Insightful of the biology of leukoplakia is the concept of cellular atypia and epithelial dysplasia. It is the most common potential premaliganant lesion and has high incidence of conversion into malignant lesion. Various noninvasive methods were studied to demonstrate metabolic changes in oral pathological condition. Lactate dehydrogenase (LDH) enzyme is found in various cells in our body. Salivary LDH is similar to that found in oral epithelium & serum. Conversion of a normal tissue into a premalignant lesion result in an alteration in glycolytic pathway causes variation in LDH level. Therefore this study was carried out to determine changes in salivary LDH level of individual with normal and to compare it with patient of different grades oral dysplasia.

Method: Sixty patients reported to Department of Oral Medicine & Radiology at Vyas Dental College & Hospital were enrolled into study of which 15 patients with for each grade of dysplasia and 15 healthy controls were taken. Unstimulated saliva measuring 1ml was collected from each of the patient by spit method. The collected sample was centrifuged & evaluated for LDH level using Vitros 250 autoanalyzer. The data obtained were subjected to statistical analysis.

Result: Salivary LDH level was higher in different grades of dysplasia patients when compared to healthy control group.

Conclusion: Salivary LDH estimation can prove to be a valuable substitute as a biochemical marker as it is simple noninvasive and easily accepted by the patient.

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INTRODUCTION

Non invasive methods are gaining popularity in the diagnosis of oral mucosal pathology nowadays. The reliability of these methods is not well studied for oral premalignant and malignant lesions. Identification of various tumor markers in saliva also showing a promising role in diagnosis of these lesions. The term Oral leukoplakia (OLP) is the most common precancerouslesion of the oral cavity accounting 85%of such lesions. (Neville *et al*., 2002) and worldwide estimated prevalence of OLP is approximately 2%. (Petti, 2003) Although OLP is used as a clinical term only and when tissue is taken for histopathological diagnosis term leukoplakia is replaced with atrophy, hyperplasia and varying degree of epithelial dysplasia. (Adriana *et al*., 2010) histopathologically epithelial dysplasia can be an important predictive factor of malignant transformation. The annual transformation rate of leukoplakia into OSCC is approximately 1%. (Van der Waal, 2009) It has been a challenge to the scientific community for several decades to find out the cause of OLP. Some evidence of Genetic alterations in keratinocytes in epithelium is involved. (Mithani *et al*., 2007) Early diagnosis and treatment of precancerous lesions can avert the probability of developing cancer which can help in improving patient quality of life and can decrease chances of converting dysplasia into OSCC. The role of tumor markers in detection of oral cancers is increasing nowadays. Various tumor markers in serum, tissue and other body fluids during neoplastic changes are of clinical value in the diagnosis of patients with various body cancers. Blood investigation is an invasive process and has high potential risk of disease transmission through needle stick injuries. A

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growing number of researchers are finding that saliva provides non-invasive diagnostic medium for rapidly widening range of disease and clinical situations. (Denny and Ho, 2005) Serumlactate dehydrogenase (LDH) is an enzyme found in blood cells and heart muscle and has been used as a biochemical marker for detection of various diseases and tissue injury. LDH plays an important role in the final step of the "Warburg effect" by converting pyruvate to lactate. 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. In various types of human cancers, the expression of LDH was up-regulated (Lewis *et al*., 1997; Shim *et al*., 1997). The use of saliva to monitor a patient's health and disease state is a highly desirable goal for health promotion and health care research. The salivary LDH isoenzymes profile is entirely different from that found in plasma, similar to that found in oral epithelium. Major source of salivary LDH is probably the oral epithelium shedding cells. (Kaufman and Lamster, 2002) Salivary LDH level has not been studied regularly in oral lesions. Hence this study is conducted to measure and compare Salivary LDH levels in patients with different grades of dysplasia and normal healthy individuals.

MATERIALS AND METHODS

The present study comprised of sixty subjects in age range of 20 to 65 years reporting to the Department of Oral Medicine and Radiology at Vyas Dental College and Hospital. In group I fifteen healthy individual were included. Forty five clinically diagnosed and histopathologically confirmed cases of dysplasia fifteen cases for each grade (mild, Moderate and severe) were included as group II, III and IV. The patients suffering from systemic conditions like cardiovascular disease, anemia, liver, kidney and pancreatic diseases, muscular dystrophy and other mucosal lesions were excluded. Patients with history of previous malignancy were also excluded from the study. There is probability of altering glycolytic activity of body which may alter LDH level. Unstimulated saliva samples were collected from each of the patient by spit method (Figure 1) in the calibrated test tube. Care was taken to see that volunteers did not consume food, smoke or chew gum at least one hour before the saliva collection procedure the samples were diluted 1:1 ratio with saline and assayed using the Vitros 250 autoanalyzer. The LDH concentrations were expressed in terms of IU/L. The data were analyzed by using Student's 't' test and the difference were considered to be statistically significant if '*P*' values were 0.05 or less. Institutional Ethical Clearance was obtained prior to begin the study. Written informed consent of the patient was obtained and case history was recorded. Unstimulated whole saliva was aseptically collected in wide mouth container by spitting method.

RESULTS

Mean salivary LDH level in Mild Oral Epithelial Dysplasia was 839.20 ± 119.04 followed by Moderate Oral Epithelial Dysplasia 1468.86 ± 206.06 and Severe Oral Epithelial Dysplasia 2545.60 ± 449.70. The mean value of the entire dysplastic group was significantly high when compared with healthy control group 447.26 ± 87.06 IU/L (Table 1 and II and Graph I). Intra group comparison of mean salivary LDH Levels in Different grades of Dysplasia showed increased mean value with increasing grades of Oral Epithelial Dysplasia. (Table III and Graph II).

Table I. Mean salivary LDH levels in control and dysplasia groups

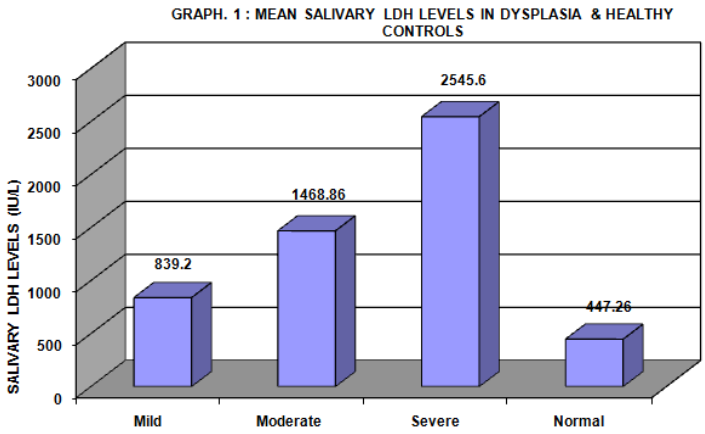
Case no.	Control group	Mild dysplasia	Moderate dysplasia	Severe dysplasia
	Salivary ldh levels (IU/L)	Salivary ldh levels (IU/L)	Salivary ldh levels (IU/L)	Salivary ldh levels (IU/L)
1	474	648	1350	3526
2	338	690	1210	2550
3	332	834	1025	1820
4	464	795	1510	1925
5	408	840	1635	3020
6	632	950	1602	2910
7	526	992	1520	2826
8	430	968	1335	2870
9	335	849	1680	2509
10	560	768	1725	2310
11	460	772	1778	2345
12	530	982	1552	2418
13	390	969	1420	2770
14	410	883	1305	2235
15	420	648	1386	2150
MEAN VALUE	447.2667±87.06IU/L	839.20 ±119.046IU/L	1468.866±206.064IU/L	2545.6±449.701IU/L

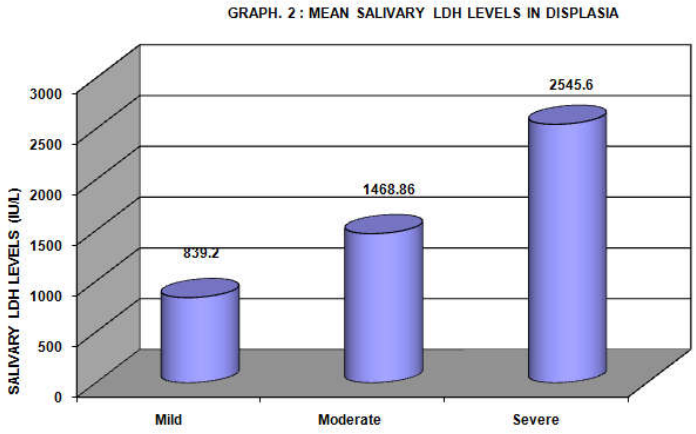
Table II. Intergroup statistical analysis (Comparison done using 't' test)

Inter group comparison	't' value	'P' value
Healthy control Vs Mild dysplasia	10.29	<0.001
Healthy control Vs Moderate dysplasia	17.68	<0.001
Healthy control Vs Severe dysplasia	17.74	<0.001

Table III: Interagroup statistical analysis (Comparison done using 't' test)

Intra group comparison	't' value	'p' value
Mild Vs Moderate	10.24	<0.001
Mild Vs Severe	14.20	<0.001
Moderate Vs Severe	8.43	<0.001





DISCUSSION

In 1920s, Warburg demonstrated the effect that most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria as in most normal cells. Malignant, rapidly growing tumor cells typically have glycolytic rates up to 200 times higher than those of their normal tissues of origin; this occurs even if oxygen is plentiful (Gatenby and Gillies, 2004; Gillies *et al*., 2008). The enzyme which is responsible for conversion of pyruvate into lactate, is LDH-A. It plays an important role in glycolysis. In various researches it have stated that the expression of LDH-A could be induced by a number of oncogenes (Dang and Semenza, 1999). Salivary LDH within the oral cavity may originate from various sources. Combination of salivary secretions from both major and minor salivary glands contains fluids diffused through the oral epithelium and gingiva, cellular component and other debris. Rafael *et al* have concluded that salivary LDH is nonglandular in origin and the major source for this is probably oral epithelium cells (Denny and Ho, 2005). As stated above the pathological alternations of oral epithelium like hyperplasia, dysplasia or cancer may result in alternation of LDH levels in saliva because of high glycolytic activity. Therefore, salivary LDH has been evaluated in this study for possible oral mucosal pathologies in a manner similar to that used for evaluating tissue pathologies in heart, muscle, or liver by LDH detection in plasma. (Nagler *et al*., 2001) In our study salivary LDH levels is significantly high with increasing grades of dysplasia when compared with healthy individual which is in correlation with previous studies done by Shetty *et al*. have evaluatedsalivary LDH levels in OSCC, OLP and healthy individual which shows significantly higher level of LDH in OSCC then in leukoplakia. (Shetty *et al*., *2015*) Tekcham *et al*. evaluated serum LDH in gallbladder cancer which was higher than normal counterparts. (Tekcham *et al*., 2015) Hariharan *et al* estimated serum LDH in buccal mucosa cancer. They made apparent that LDH are higher in cancer patients as compared to normal controls (Hariharan *et al*., 1977). Muralidhar *et al* in 1988 also reported a definite rise of serum LDH levels from normal in premalignant and malignant cases. (Muralidhar *et al*., 1998) It has been observed in various researches that saliva can be used as a diagnostic marker for oral cancer and precancerous lesions and it is indicated that this capacity is based on close relationship of saliva and oral mucosa where the cancer evolves.

Conclusion

Salivary LDH levels increases in oral mucosal pathologies like OLP and OSCC. It can be a valuable substitute in recent diagnostics methods as it is convenient to patient and observer because of noninvasive nature of the procedure.

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