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Salivary LDH-Diagnostic and Prognostic Marker in Oral Squamous Cell Carcinoma

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Abstract

The enzyme lactate dehydrogenase (LDH) found in the cells is believed to vary according to the metabolic requirement of each tissue. Increased levels of serum LDH is seen due to cellular necrosis and acts as a biochemical marker in diagnosis of various cancers. Similarly increased salivary LDH levels may be due to oral epithelium-shedding cells.

We measured and compared the LDH levels in serum and saliva in patients with oral leukoplakia and oral squamous cell carcinoma and we correlated the levels of salivary LDH with the histological differentiation of the tumor and compared there levels before and after surgery.

LDH levels in serum are increased to greater extent compared to salivary LDH in oral leukoplakia. However, serum and salivary LDH levels are almost same in oral squamous cell carcinoma. The salivary LDH levels are greatly increased in poorly differentiated OSCC than well differentiated OSCC. These values were seen to revert back to almost normal levels after surgical excision of the tumor.

Salivary LDH estimation which is simple and non invasive can be used as a biochemical marker, over serum LDH in diagnosis and prognosis of SCC.

Keywords: Lactate dehydrogenase; Oral leukoplakia; Saliva; Serum; Squamous cell carcinoma

Introduction

Oral Squamous Cell Carcinoma (OSCC) is the sixth most common human cancer that encompasses at least 90% of all oral malignancies. OSCC is recognized to have a 50%, five-year survival rate. Oral mucosal epithelium exposed to exogenous and endogenous factors or carcinogens produces precancerous changes. The most common precancerous lesions are oral leukoplakia (OL) and oral erythroplakia [1].

Prevention and early diagnosis of oral cancer remain the best method. The enzyme lactate dehydrogenase (LDH) catalyzes the reaction of lactate production via pyruvate reduction during anaerobic glycolysis. LDH is found in the cells of almost all body tissues and is especially concentrated in the heart, liver, red blood cells, kidneys, muscles, brain and lungs [2]. Increased serum LDH is due to increase proliferation of tumor cells and is considered as a marker of cellular necrosis. Dysplastic changes also increase LDH in oral leukoplakia and OSCC [3-5].

Saliva-based diagnostics are more accessible, accurate, less expensive and present less risk of infection to the patient than current methodologies. Salivary LDH can be used as a non-invasive alternative to serum LDH for diagnosis and for the

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prognosis of oral diseases including cancer. Follow-up of patients who have undergone surgery for oral cancer (oral squamous cell carcinoma (OSCC) can be done with the detection of salivary LDH [2,6].

Aim

To compare LDH levels in serum and saliva of patients with leukoplakia and OSCC. To measure salivary LDH levels in OSCC with different differentiation. To measure salivary LDH levels before and after surgery. To evaluate whether salivary LDH analysis can substitute serum LDH analysis.

Materials and Methods

A case-control study was conducted at Kasturba Medical College, Manipal. Institutional ethical clearance was taken.10 newly diagnosed cases of OL and 10 newly diagnosed operable cases of OSCC were included in the study along with 10 controls. Written informed consent of the patient was obtained and case history was recorded. Unstimulated whole saliva was collected in a wide mouth container by spitting method for 5 min. The sample was centrifuged and the supernatant was processed for LDH estimation using enzymatic kits with biochemistry autoanalyzer (ERBA XL640). Blood was collected using standard aseptic precautions and processed for LDH. The same kit was used to process both the samples for LDH levels. Incisional biopsy of the cases was performed and clinical diagnosis of the cases was confirmed and graded by histopathological examination.

Subjects suffering from any systemic conditions that could affect the salivary LDH level in the body and patients undergoing treatment for systemic conditions known to alter LDH enzyme levels were excluded from the study.

Statistical Analysis

Levels of the enzyme activity in both control and study groups were tabulated and compared statistically using student t-test; Similarly, the levels of enzyme activity in the subgroups of the study group were also compared using student t-test thus correlating tumor differentiation to levels of enzyme activity in saliva. A p-value of <0.005 was considered significant and <0.001 was considered highly significant.

Results

The present study showed that the mean salivary LDH levels in OL (1433) and OSCC (3109)are higher than the control group with a p-value of <0.001. Poorer the differentiation higher increase in salivary LDH levels. Salivary LDH levels decreased one month after surgical therapy, the difference of which was statistically significant (p<0.001) **(TABLE 1 and FIG. 1- 3)**.

TABLE 1. **Comparison of mean salivary and serum LDH levels in controls, OL and OSCC.**

S. No.	**Control Group (10 controls)**		**OL Group (10 Cases)**		**OSCC Group (10 cases)**	
	Serum Total LDH IU/L	Salivary Total LDH IU/L	Serum Total LDH IU/L	Salivary Total LDH IU/L	Serum Total LDH IU/L	Salivary Total LDH IU/L
1	317	269	2153	1423	3559	3095

2	308	262	2298	1432	3561	3129
3	305	283	2109	1440	3593	3109
4	316	247	2151	1427	3453	3090
5	287	250	2269	1431	3487	3107
6	329	252	2113	1430	3551	3152
7	320	265	2237	1433	3436	3099
8	302	279	2213	1443	3580	3091
9	309	253	2269	1441	3495	3106
10	285	241	2219	1432	3517	3119

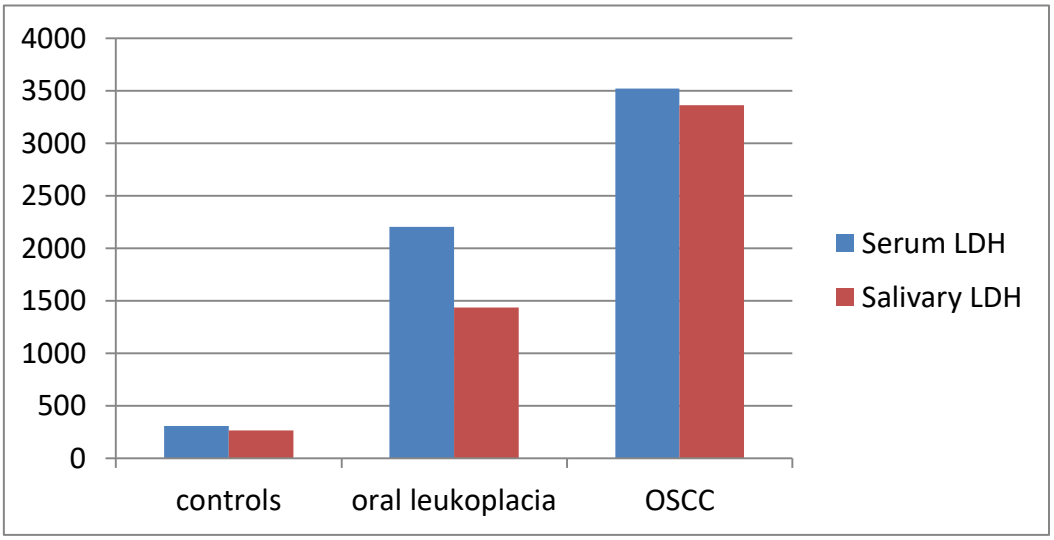

FIG. 1. **Comparison of mean serum and mean salivary LDH levels.**

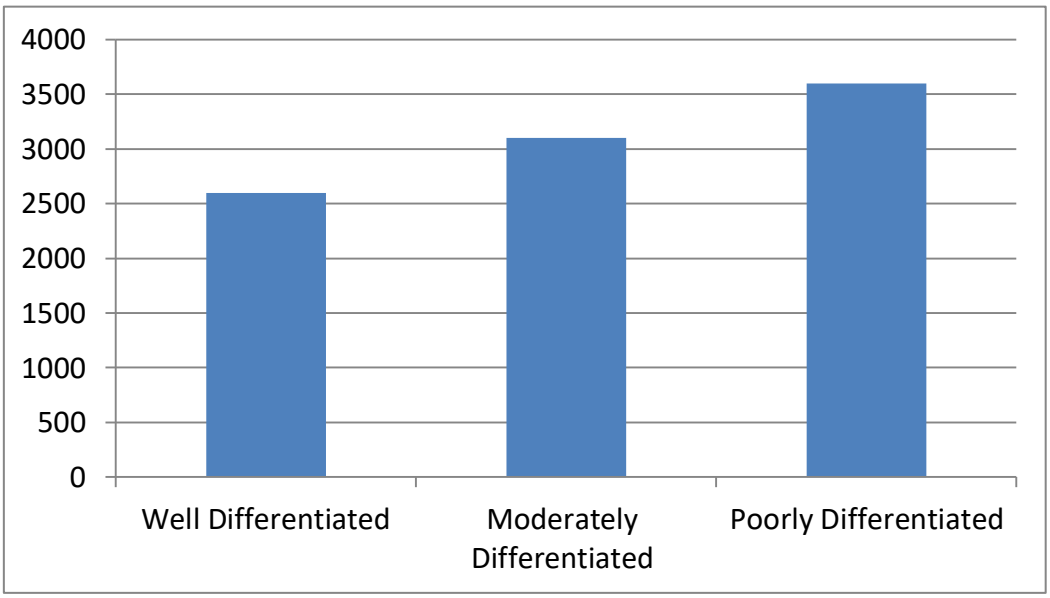

FIG. 2. **Salivary LDH levels in OSCC with different differentiation.**

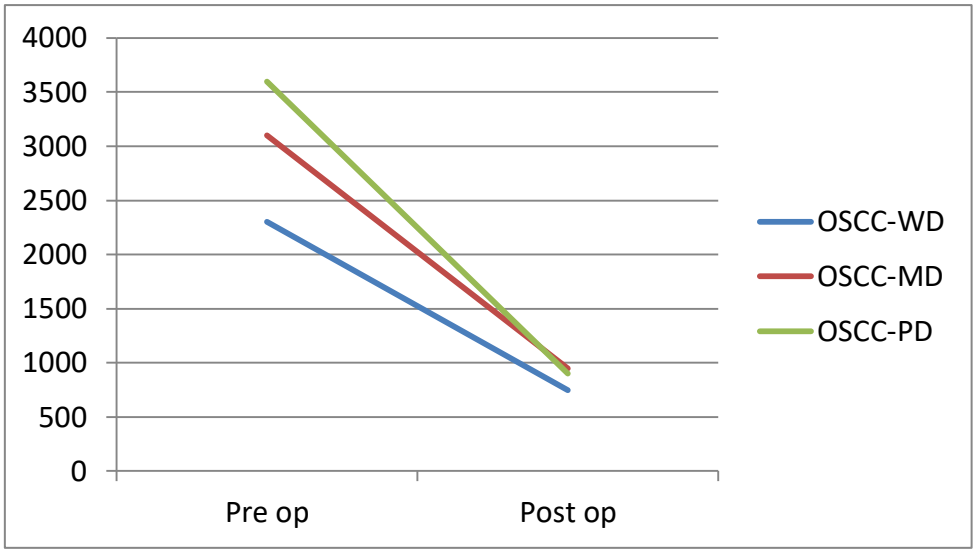

FIG. 3. **Levels of salivary LDH in pre and post-operative (one month) patients.**

Discussion

Oral cancer is highly prevalent in India due to tobacco chewing. Due to its poor prognosis, it is important for early diagnosis and follows up to increase the cure rate. Early detection followed by appropriate treatment, can increase cure rates to 80% or 90% [7]. The present study showed that the mean salivary LDH levels in OL (1433) and OSCC (3109) are higher than the control group with a p-value of <0.001. Similar findings were observed by Joshi et al. [2], Shpitzer et al. [3], Lokesh et al. [4], Shetty et al. [5], Pujari et al. [6], Patel et al. [7], Ahenthem et al. [8], and Khan et al. [9].

The LDH in the saliva originates from various sources mainly oral epithelium, gingival, cellular and other debris. Pathological alternations of oral epithelium like dysplasia or cancer may result in increased salivary LDH levels. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to the breakdown of glycoprotein [1].

The major compositional difference between serum and saliva is that saliva is not a passive ultra-filtrate of serum and that salivary constituents may play a distinct physiological role. The major source of salivary LDH is oral epithelium shedding cells and pathological alterations of oral epithelium like dysplasia or cancer may result in alteration of LDH profile in saliva. Therefore, salivary LDH may be evaluated for possible oral mucosal pathologies in a manner similar to that used for evaluating other tissue pathologies–such as those in the heart, muscle, or liver for LDH detection in plasma [7].

Poorer the differentiation higher increase in salivary LDH levels. Similar findings were observed by Lokesh et al. [4], Patel et al. [7] and D'Cruz et al. [10]. There is a progressive increase in the salivary LDH levels from well-differentiated to the poorly differentiated OSCC. This is a result of the amount of the enzyme forming tissue, rate of synthesis of enzymes and alteration in the permeability of the cell member. As the mitotic differentiation is higher in poorly differentiated OSCC than the well-differentiated and moderately differentiated carcinoma hence the salivary enzyme levels are higher in poorly differentiated OSCC [10].

Salivary LDH levels decreased one month after surgical therapy the difference of which was statistically significant ($p<0.001$). The salivary levels in poorly differentiated and moderately differentiated OSCC decreased at a higher rate compared to well-differentiated OSCC, suggesting that more aggressive tumors were producing more salivary LDH due to the volume of tumor cells which when surgically removed salivary LDH levels came down drastically.

Conclusion

Salivary LDH is a feasible, simple, efficient, non-invasive and convenient approach for screening, monitoring and for the prognosis of the disease activity in patients with OSCC. Hence salivary LDH can be used not only as a diagnostic marker in OSCC but also as a prognostic biomarker in patients treated surgically for OSCC.

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