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Salivary Lactate Dehydrogenase, C-Reactive Protein, and Cancer Antigen 125 Levels in Patients with Oral Lichen Planus and Oral Squamous Cell Carcinoma

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and oral lichen planus (OLP) is considered a premalignant disease.
Objectives: This study aims at comparing the salivary levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), and cancer antigen 125 (CA125) among cases with OSCC, OLP, and healthy persons.
Methods: In this case-control study, salivary markers were evaluated in 55 cases (15 patients with OSCC, 20 patients with OLP, and 20 healthy persons); non-stimulated saliva samples were collected from the patients and saliva markers were measured by the enzyme-linked immunosorbent assay (ELISA) method. The data were analyzed, using SPSS 21 software and ANOVA test and $P < 0.05$ was regarded as significant.
Results: Salivary LDH and CA125 levels were significantly higher in OSCC and OLP patients compared to the control group ($P < 0.05$). Salivary CRP levels were significantly higher in OSCC patients compared to OLP patients ($P < 0.05$). Besides, salivary CRP levels were higher in OLP subjects than in the control group, but the difference was not significant ($P = 0.56$).
Conclusions: The identification of the salivary LDH, CA125, and CRP may provide a suitable non-invasive predictive tool for malignant changes. However, its use in clinical practice needs further research.

Keywords: Squamous Cell Carcinoma, Oral Lichen Planus, Saliva, Biomarkers

1. Background

Approximately 90% of oral cancers are oral squamous cell carcinoma (OSCC) and it is the 8th cause of death due to cancers worldwide. Risk factors related to OSCC include age, gender, race, tobacco use, and alcohol (1). About 95% of OSCC is diagnosed among patients over 40 years of age with a mean age of about 60 years (2).

Lichen Planus is known as a common chronic inflammatory mucocutaneous condition with the potential for malignancy. The World Health Organization (WHO) has identified oral lichen planus (OLP) as a premalignant disease. The underlying molecular mechanisms are unclear in the development of oral cancer (3). The prevalence of Lichen Planus is 0.5 to 2.2% and it is more common in women than men with an average age of 55 years (2).

Tumor markers include several substances, such as cell surface antigens, cytoplasmic proteins, enzymes, and hormones. These substances are found in the blood, saliva, urine, stool, tumor tissue, and other tissues of patients with cancer and are either secreted from the tumor or are the result of host defense against the tumor (4, 5).

Saliva can be used as a non-invasive and inexpensive method to screen patients without the need for advanced techniques. Saliva collection is better than other non-invasive methods because of the lower risk of infection (needle stickiness during bleeding) (6).

Lactate dehydrogenase (LDH) is reported as an essential crucial enzyme catalyzing lactate production via pyruvate during anaerobic glycolysis. LDH is present in the cell cytoplasm under normal conditions and turns extracellular following cell death. Therefore, cell necrosis and tissue

breakdown are causes to observe its extracellular form (7).

Cancer Antigen 125 (CA125) is a high molecular weight glycoprotein also known as mucin 16. This glycoprotein is a surface antigen in epithelial cells. Serum CA125 levels are increased in ovarian, lung, breast, and colorectal cancers; therefore, it is often used to diagnose or track recurrences of cancers (8, 9).

A study by Shweta et al. found higher salivary levels of LDH and CA125 among cases with oral cancer compared to the normal cases (10).

C-reactive protein (CRP) is an inflammatory marker that is synthesized by hepatocytes. CRP synthesis is regulated by pro-inflammatory cytokines such as Interleukin1 (IL1), Interleukin6 (IL6), and tumor necrosis factor (TNF), and the effects of these cytokines have been reported in various types of malignancies (11). Vankadara et al. examined serum levels of CRP in patients with pre-malignant lesions and OSCC. They demonstrated that the prognostic concentration of CRP is associated with the subsequent development of oral cancer (12).

2. Objectives

Many studies have investigated salivary LDH, CRP, and CA125 levels in OSCC patients (10, 13-15). However, to our knowledge, limited studies have evaluated the salivary level of LDH, CRP, and CA125 in patients with OLP. Due to the development of some cases of OLP to OSCC, the early detection of this alteration is important; therefore, this study aimed at comparing these markers in patients with OSCC, OLP, and the control group.

3. Methods

3.1. The Study Population

This case-control study was performed on 15 cases with OSCC and 20 cases with OLP, who were referred to the Department of Oral Medicine, Faculty of Dentistry, Zahedan University of Medical Sciences from October 2017 to November 2018. The control group consisted of 20 normal individuals, who had no oral disease. They were selected, using the purposive non-probability sampling technique and 15 patients with new OSCC, confirmed by biopsy and pathologic examination (all patients were in stage III-IV at the time of diagnosis), had no other oral disease; 20 patients with OLP (presence of bilateral lesions, reticular lesions, and Wickham steria in the oral) also had no other oral disease and had histological confirmation, if necessary. The subjects with systemic diseases, history of malignancy, and previous treatment in the form of chemotherapy, radiotherapy, surgery, drug and tobacco consumption in the past 3 months, history of Sjogren's syndrome, and pregnancy or lactation were excluded. All groups were matched by age and sex.

3.2. Saliva Sampling

Non-stimulated whole saliva collection was done in a quiet room between 9 to 11 A.M. under resting conditions and patients were asked to avoid eating, drinking, and smoking 90 minutes before sampling; 2 mL saliva samples were collected by spitting method in a clean disposable glass. Then, the saliva was transferred to the immunology laboratory and centrifuged at 3500 rpm for 20 minutes. The supernatants were separated and frozen at -70 °C until sampling was completed.

3.3. Measurement of Salivary Markers

The salivary markers levels were calculated by the commercial enzyme-linked immunosorbent assay (ELISA) kits (CK-E11183, CK-E91651, CK-E10891, Eastbiopharm Company; China). The sensitivity of the LDH kit was 2.48 U/L with a normal range of 5 U/L to 1000 U/L. The sensitivity of the CA125 kit was 0.11 kU/L with a normal range of 0.2 kU/L to 60 kU/L. The sensitivity of the high sensitivity CRP kit was 0.01 mg/L with a normal range of 0.05 mg/L to 12 mg/L.

3.4. Ethical Considerations

All patients were enrolled after informed consent. The Ethics Committee of the Zahedan University of Medical Sciences confirmed the research protocol (code: IR.ZAUMS.REC.1395. 38).

3.5. Statistical Analysis

The data were analyzed, using SPSS 21. Salivary markers in 3 groups were compared with one-way ANOVA and Post Hoc tests. P values smaller than 0.05 were regarded as significant.

4. Results

The present research aimed at comparing the salivary levels of LDH, CRP, and CA125 among subjects with OSCC, OLP, and healthy persons.

Fifteen individuals with a mean age of 50.4 ± 8.37 years in the group with squamous cell carcinoma, 20 individuals with a mean age of 45.4 ± 10.08 years in the OLP group, and 20 individuals with a mean age of 45.6 ± 9.77 years in the healthy group were studied. Table 1 shows the salivary LDH, CA125, and CRP levels in the three study groups. Post Hoc tests revealed a significant difference in salivary LDH levels among the patient groups ($P = 0.025$). A significant difference was found among the OLP and control groups (P

Table 1. Comparison of Salivary LDH, CA125, and CRP in the Study Groups [a]

Groups	OSCC	OLP	Control	P-Value
LDH (U/L)	505.44 ± 126.79	382.7 ± 154.48	215.98 ± 114.1	< 0.0001
CRP (mg/L)	3.44 ± 2.18	2.1 ± 1.08	1.1 ± 0.49	< 0.0001
CA125 (kU/L)	18.96 ± 4.01	16 ± 1.87	6.9 ± 4.16	< 0.0001

Abbreviations: OSCC, oral squamous cell carcinoma; OLP, oral lichen planus; LDH, lactate dehydrogenase; CRP, C-reactive protein; CA125, cancer antigen 125.
[a] Values are expressed as mean ± SD unless otherwise expressed.

Table 2. Post Hoc Tests for Comparing the Groups in Pairs Considering the Salivary LDH, CRP, CA125

Dependent Variables/ Groups	P-Value
LDH	
OSCC - OLP	0.025
OLP - Control	0.001
Control - OSCC	< 0.001
CRP	
OSCC - OLP	0.014
OLP - Control	0.056
Control - OSCC	< 0.001
CA125	
OSCC - OLP	0.040
OLP - Control	< 0.001
Control - OSCC	< 0.001

Abbreviations: OSCC, oral squamous cell carcinoma; OLP, oral lichen planus; LDH, lactate dehydrogenase; CRP, C-reactive protein; CA125, cancer antigen 125.

= 0.001) and the OSCC and control groups showed a significant difference (P < 0.001,

Both patient groups indicated a significant difference regarding salivary CRP levels (P = 0.014). No significant difference was found among the two groups with OLP and control groups (P = 0.056). Also, the OSCC and control groups showed a significant difference (P < 0.001, Table 2).

Salivary CA125 levels were found to be significantly different in both patient groups (P = 0.04). Moreover, the OLP and healthy groups also had a significant difference (P < 0.001). Furthermore, there was a significant difference between the OSCC group and the control group (P < 0.001, Table 2).

5. Discussion

OSCC is a common human malignancy that accounts for about 50% mortality rate at 5 years that has not significantly changed over 50 years and has a high incidence of complications (16). OLP is considered a premalignant disorder. It is extensively established that individuals with OLP are predisposed to progress oral carcinomas (2). Some of the new diagnostic tools are molecular markers in body fluids that predict cancer progression in the first step or the precancerous stage (17).

The salivary test is a non-invasive method and also a suitable alternative to serum testing, which can be used as a useful method for the diagnosis, prognosis of oral cancer, and the monitoring of post-treatment status (16, 18). Salivary tests reduce the anxiety and inconvenience of the patients and are an easy method for obtaining repeated samples for long monitoring (19).

Nagler et al. concluded that the primary source for LDH is not from salivary glands and that the oral epithelium is the primary source (20). Thus, LDH saliva representing cellular necrosis can be used as a particular marker regarding oral lesions affecting oral mucosa integrity.

In this study, salivary LDH levels were significantly increased in cases with OSCC and OLP compared to the control group. Some studies have reported a significant increase in salivary LDH levels among those with OSCC compared to the control group (21-23).

Kallalli et al. reported that salivary LDH levels were increased in subjects with oral submucosal fibrosis and OSCC compared to the control group (24). Some studies have also reported significant increases in total salivary LDH in the OSCC and oral leukoplakia groups. Salivary LDH measurement may be a practical and simple approach for screening pre-malignancies (14, 19). However, we did not find a study comparing salivary LDH in patients with oral cancer and lichen planus. According to our search, only one study examined salivary LDH levels among cases with OLP. They compared the levels of 3 isoenzymes LDH 3, LDH 4, LDH 5 in the saliva of 10 subjects suffering from OLP with 25 healthy individuals, indicating a significant increase in these isoenzymes in OLP patients (25). Nalin et al. evaluated the serum levels of LDH in patients with OLP. The study showed no significant difference in serum levels of LDH among lichen planus and the control group. In Nalin et al.'s study, like ours, none of the lichen planus cases showed histological evidence of epithelial dysplasia. However, in the current study, a significant difference was observed in salivary LDH between OLP patients and

healthy individuals. Therefore, the saliva measurement of this marker may be more accurate than the serum (26).

Cancer antigen 125 (CA125, also known as mucin 16) is a cell surface protein. CA125 is the largest member of the mucin family of proteins. The hydrophilic nature of mucin proteins provides them with the ability to form protective and lubricating barriers to protect against foreign particles and infectious agents. Serum CA125 levels increase in ovarian, lung, breast, and colorectal cancers (8, 9, 27).

In the present study, salivary CA125 levels were higher in OSCC and OLP patients than in the control group. Some studies have reported significantly higher levels of salivary CA125 in OSCC patients compared to the control group. Also, in patients with OSCC, this marker increased as the tumor stage increased (13, 27). A study by Shweta et al. found higher salivary levels of LDH and CA125 among cases with oral cancer compared to the normal cases (10).

In a study by Geng et al., higher salivary CA125 was found for OSCC cases in comparison to the normal subjects and those with no neoplastic lesions. In this study, non-neoplastic patients had leukoplakia, lichen planus, and chronic ulcer. In this study, salivary CA125 was not significantly different in the no neoplastic group from the control group, which may be due to the presence of patients with chronic ulcers that are not classified for pre-malignant lesions (15). Except for Geng's study (15), we did not find a study examining salivary CA125 in patients with lichen planus.

CRP is an acute-phase protein with changeable levels on daily basis. CRP levels can increase by aging, high blood pressure, smoking, coffee and alcohol consumption, decreased physical activity, raised levels of triglycerides, insulin resistance, diabetes, and foods including high protein, chronic tiredness, and sleep disorders, and depression, which are also observed in different malignancies (28).

Some studies have reported an increase in CRP levels in patients with OSCC and have shown high CRP levels in OSCC patients linked to the advanced tumor stages (29-31).

Vankadara et al. examined serum levels of CRP in patients with pre-malignant lesions (leukoplakia, oral submucous fibrosis, and OLP). They demonstrated that the concentrations of CRP are associated with the subsequent development of oral cancer (12).

The results of this study indicated the increased salivary CRP levels among cases with OSCC compared to those with OLP and the control group. Besides, we found CRP levels higher in OLP subjects than in the control group, but the difference was not significant. Shahidi et al. showed significantly increased levels of salivary CRP, which was elevated in dysplastic OLP and OSCC (32). Tvarijonaviciute et al. found increased salivary CRP in OLP patients compared to burning mouth syndrome (BMS) patients and control subjects with statistically significant differences (33). Also, Shiva et al. reported that salivary and serum CRP levels in the OLP group were statistically significantly higher than the control group (34). Lack of dysplastic changes in our lichen planus patients, differences in sampling method, and differences in studied populations can be the reasons for the discrepancy between the results of the present study and other studies.

5.1. Conclusions

Salivary LDH and CA125 levels were significantly higher in OSCC and OLP patients compared to the control group. Salivary CRP levels were significantly higher in OSCC patients compared to OLP patients. Also, salivary CRP levels were higher in OLP subjects than in the control group, but the difference was not significant. The identification of the salivary LDH, CA125, and CRP may provide a suitable non-invasive predictive tool for malignant changes. However, its use in clinical practice needs further research.

Footnotes

Authors' Contribution: MH, RS, and LFM designed the research. MH, AE Collected data. RS performed laboratory tests. MH and AE analyzed data. MH, RS, LFM and AE wrote the paper. All authors approved the final version of the manuscript.

Conflict of Interests: The authors declare that they have no conflict of interest.

Ethical Approval: The Ethics Committee of the Zahedan University of Medical Sciences confirmed the research protocol (code: IR.ZAUMS.REC.1395. 38).

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Informed Consent: All patients were enrolled after informed consent.

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