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Research Article

Salivary Lactate Dehydrogenase and Matrix Metalloproteinase-9 as Potential Diagnostic Markers for Oral Squamous Cell Carcinoma

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Abstract

Background: Saliva is probably the most promising sample for the finding of biomarkers for oral squamous cell carcinoma **(**OSCC), as its collection is easy, non-invasive, fast, and cost-effective. ***Objective***: The aim of this study was to examine increased salivary levels of lactate dehydrogenase (LDH) and matrix metalloproteinase-9 (MMP-9) that have been assessed as possible biomarkers for the diagnosis of OSCC. ***Methods***: In this case-control study, participants were divided into 30 healthy controls (15 male and 15 female), and 65 patients (45 male and 20 female) were diagnosed with OSCC. Saliva samples were obtained to measure levels of both LDH and MMP-9 spectrophotometrically using standard LDH and MMP-9 kits. One-way ANOVA, the chi-square test, and Pearson's correlation test were applied to analyze the data. ***Results***: The salivary levels of LDH and MMP-9 in OSCC patients were significantly higher than those in the control groups. Significant associations were noted between LDH and MMP-9 salivary levels. ***Conclusions***: Patients with OSCC had higher saliva levels of both LDH and MMP-9 than the healthy subjects in the control group. Assessment of salivary LDH and MMP-9 can be beneficial for diagnosing OSCC.

Keywords: Lactate dehydrogenase, Matrix metalloproteinase-9, Oral squamous cell carcinoma, Saliva.

نازعة هيدروجين اللاكتات اللعابية ومصفوفة البروتيناز المعدني -9 كعلامات تشخيصية محتملة لسرطان الخلايا الحرشفية الفموية

الخلاصة

الخلفية: من المحتمل أن يكون اللعاب هو الإفراز الأكثر جاذبية للعثور على المؤشرات الحيوية ل OSCC ، حيث أن جمعه سهل وغير جراحي وسريع وفعال، وبكلفة منخفضة. **الهدف**: كان الهدف من هذه الدراسة هو فحص المستويات اللعابية المتزايدة من نازعة هيدروجين اللاكتات (LDH) ومصفوفة البروتيناز المعدني -9 (MMP-9) التي تم تقييمها كمؤشرات حيوية محتملة لتشخيص سرطان الخلايا الحرشفية الفموية (OSCC). **الطرائق**: تم تقسيم المشاركين إلى المجموعة الظابطة وشملت اشخاص اصحاء وعددهم ٣٠ (15 ذكرا و 15 أنثى)، وتم تشخيص 65 مريضا (45 ذكرا و 20 أنثى) ب OSCC. تم قياس مستويات اللعاب لكل من LDH و MMP-9 طيفيا باستخدام مجموعات LDH و MMP-9 القياسية. تم تطبيق ANOVA أحادي الاتجاه ، واختبار مربع كاي، واختبار ارتباط بيرسون لتحليل البيانات. **النتائج**: كان مستوى LDH و MMP-9 في اللعاب لدى مرضى سرطان الفم أعلى بشكل معنوي مقارنةً بالمجموعة الضابطة. لوحظت ارتباطات كبيرة بين مستويات اللعاب LDH و MMP-9. **الاستنتاجات**: كان لدى المرضى الذين يعانون من OSCC مستويات لعاب أعلى من كل من LDH و MMP-9 من المجموعات الضابطة.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common form of head and neck cancer [1]. In spite of the oral cavity being of "easy access," OSCC is still being diagnosed mostly in stages III and IV of the disease. That means there is real difficulty in OSCC diagnosis, which translates to significant morbidity and an estimated overall survival of about 50% during the first 5 years [2]. Saliva is probably the most attractive secretion for the finding of biomarkers for OSCC, as its collection is easy, non-invasive, fast, and cost-effective. Consequently, different studies have explored the possibility of using salivary factors as biomarkers for the expansion and development of OSCC [3]. Lactate dehydrogenase, which is found in almost all cell types, is a biomarker for cancer detection [4]. Actually, serum (not salivary) level of LDH is the usual target for cancer diagnosis in different cancer types such as lung, cervical, nasopharyngeal, hematopoietic, and stomach cancers [5-7]. Furthermore, increased levels of this serum tumor marker have been reported in malignant and premalignant oral lesions, such as leukoplakia and submucosal fibrosis, compared with normal tissue [8, 9]. Though the salivary LDH alone or in combination with its serum level has been less commonly studied [9-10]. On the other hand, matrix metalloproteinase-9 (MMP-9) is an important protease that plays vital roles in numerous biological processes since it can

cleave many extracellular matrix (ECM) proteins for regulating ECM remodeling. It can also cleave many plasma surface proteins to release them from the cell surface. Thus, it is widely found to relate to the pathology of cancers. Some recent research evaluated the value of serum (not salivary) levels of MMP-9 as biomarkers for various specific cancers [11-14]. Since saliva, as a non-invasive medium, is not yet routinely used for diagnostic purposes, further studies are required to determine the normal range and correlation of different biomarkers present not only in the routinely diagnostic items like serum and blood but also in saliva. Thus, the present study was designed not only to evaluate the level of LDH and MMP-9 in the saliva of patients with OSCC as well as healthy controls but also to explore if there is a correlation between their levels in OSCC as a step to assess the efficacy of saliva sampling as a valuable tool for diagnosing OSCC. The roles of MMPs in cancer growth and metastasis are various, and they include degradation of extracellular matrices, cancer cell adhesion, migration, and secretion of growth factors, cytokines, and factors of angiogenesis. The process of extracellular matrix remodeling is an integral part of normal tissue growth and differentiation, but unregulated proteolysis may lead to an advantage during carcinogenesis. This study aims to evaluate the changes in salivary levels of LDH and MMP-9 as possible biomarkers for the diagnosis of OSCC.

METHODS

Study design and setting

In this case-control study, we evaluated 95 participants presenting to the Oral and Maxillofacial Medicine Center in Baghdad, Iraq, during August to November 2024, who were divided into two groups: 30 participants were healthy controls, and 65 participants were OSCC patients.

Inclusion criteria

Patients diagnosed as cases of ODCC based on histological evidence and histopathological evidence, clinically and histopathologically confirmed according to the modified WHO criteria [15].

Exclusion criteria

Patients with systemic conditions such as cardiac, hepatic, or renal disease; diabetes mellitus; other malignancies; substance abusers; children under 15 years; pregnant women; those taking medications; patients with OSCC under treatment; and patients with periodontitis or other mucosal lesions that could affect the LDH and MMP-9 levels were excluded.

Sampling and outcome measurements

Saliva samples were collected between 10 a.m. and 12 p.m. for both unstimulated and stimulated saliva analysis. Participants were instructed to refrain from eating or drinking for 60–90 minutes before the sampling process. For unstimulated saliva collection, they were asked to sit in a resting position, swallow their saliva, tilt their head forward, and expel their saliva into sterile, graded plastic vials. For stimulated saliva collection, participants were provided with equal-sized pieces of mastic gum to chew for one minute before spitting out the gum, swallowing any residual saliva, and depositing the saliva into a Falcon tube. Then, saliva samples were centrifuged, and pure saliva without sputum was transferred into microtubes. Following collection, saliva was immediately centrifuged at 2000 rpm for 10 min to remove squamous cells and cell debris. The supernatants were stored at −20 °C until further analysis. Salivary levels of LDH and MMP-9 were spectrophotometrically measured within 24 h using standard LDH and MMP-9 kits.

Ethical considerations

The study protocol was approved by the Ethics Committee Iraqi Centre of Cancer and Medical Genetic Research, Baghdad, Iraq (no. 317, 2024). We informed the participants about the nature of the study and obtained their verbal consent.

Statistical analysis

Data were analyzed using GraphPad Prism version 23. One-way ANOVA and t-tests were used to compare the raw data between the groups. The chi-square test was applied to assess the correlation of parameters such as age and gender. The correlations between the groups were analyzed using the Pearson's correlation test.

RESULTS

This case-control study evaluated 95 participants, including 65 males and 30 females. The two groups were matched in terms of gender with no significant difference. The mean age of participants was 39.53±1.17 years in the control group and 47.83±4.79 years in the OSCC group. The mean age of OSCC patients was higher than that of the control group (Table 1).

Table 1: Age and gender of participants in the study groups

Participants	No.	Age (year)	Male\Female
OSCC	65	47.83±4.79	35\20
Control	30	39.53±1.17	15\15
p-value		0.005	>0.05

Values were expressed as ratio and mean±SD. OSSC: oral squamous cell carcinoma.

Table 2 shows the mean stimulated and unstimulated salivary LDH in both OSCC and control groups, which were significantly higher in the patient group as compared to the control group in both stimulated and unstimulated salivary samples (p= 0.0001). Also, Table 3 shows the average levels of MMP-9 in saliva

when it was stimulated and when it wasn't stimulated in both the OSCC and control groups.

Table 2: Stimulated and Unstimulated salivary levels of LDH in the study groups

Participants	No.	LDH (IU\ml)	
		Stimulated saliva	Unstimulated saliva
OSCC	65	66.33± 12.7	65.2±1.2
Control	30	20.43±1.1	14.1± 3.3
p-value		0.0001	0.001

Values were expressed as mean±SD. OSSC: oral squamous carcinoma cell.

The patient group had significantly higher levels than the control group in both types of saliva (p= 0.001).

Table 3: Stimulated and Unstimulated salivary levels of MMP-9 in the study groups

Participants	No.	MMP-9 (ng\ml)	
		Stimulated saliva	Unstimulated saliva
OSCC	65	36.33± 2.8	35.2±5.5
Control	30	19.51±5.2	19.9±2.9
p-value		0.001	0.001

Values were expressed as mean±SD. OSSC: oral squamous cell carcinoma.

Moreover, the Pearson's correlation test revealed a significant association between the stimulated salivary level of LDH and MMP-9 level in both patients and controls, which showed that with an increase in the salivary level of LDH, the level of MMP-9 in stimulated and unstimulated saliva also increased (Table 4).

Table 4: Correlation between stimulated salivary levels of LDH and MMP-9

	S.S LDH	U.S LDH	S.S MMP-9	U.S MMP-9
S.S LDH		0.04	0.7	0.08
U.S LDH	0.04		0.1	0.1
S.S MMP-9	+ 0.7	0.1		0.003
U.S MMP-9	0.08	0.1	0.003	
R	0.88	0.86	0.89	0.88
p-value	0.05	0.05	0.05	0.05

Data was analyzed using Pearson correlation. S.S LDH: Stimulated salivary LDH, U.S LDH: unstimulated salivary LDH, S.S MMP-9: stimulated MMP-9, U.S MMP-9: unstimulated MMP-9.

DISCUSSION

Few studies evaluated various tumor markers in the saliva of OSCC subjects [16]. There is a need to identify specific and sensitive molecular biomarkers, which can be used to screen OSCC. According to the current results, the salivary levels of LDH in OSCC patients were significantly higher than the corresponding values in control groups. Typically, LDH catalyzes the conversion of pyruvate into lactate and vice versa, in addition to the conversion of reduced nicotinamide adenine dinucleotide (NADH) to oxidized form (NAD^+) and vice versa [17]. The LDH level of each tissue may vary depending on its metabolic requirements. The LDH levels may change during the process of growth and development due to biological changes as well as in response to pathological conditions [18]. As it is commonly known, LDH releases upon the destruction of cell membranes; for this reason, measurement of LDH can estimate the rate of cell death, necrosis, and tissue injury in different diseases [19]. Malignant tumor tissue or the contiguous tissue damaged by the tumor often releases LDH into the body; in this regard, the majority of recent studies highlight the increased level of LDH in serum samples of oral cancer [20-22]. The increase in dysplastic changes from a normal tissue to a malignant tissue triggers a shift to the anaerobic glycolytic pathway [23]. However, the salivary LDH profile can almost reflect the condition of oral mucosal epithelium (but not salivary glands), which indicates that the main source of salivary LDH is probably the oral mucosal epithelial cell shedding. LDH activity is mainly due to an increase in mitotic index and further production of lactic acid by cancer cells due to glycoprotein breakdown in the process of malignant changes. Greater dysplastic or malignant changes would further elevate the level of LDH [21]. For this reason, assessment of salivary LDH can serve as an efficient tool for evaluation of oral conditions such as oral dysplasia and cancer that compromise the integrity of oral mucosa [20]. Shpitzer *et al*., in studies conducted in 2007 and 2009, showed a complete change in the composition of saliva in oral cancer patients. They reported alterations in parameters such as matrix metalloproteinases 2 and 9, insulin-like growth factor-1 (IGF-1), and sigma in the saliva and demonstrated a significant increase in salivary LDH level of oral cancer patients, which agreed with the current results [24]. Samlin *et al*. (2020) showed that salivary levels of LDH significantly increased in oral premalignant and malignant lesions [25]. Shetty *et al*. reported a significant increase in LDH level in males compared with females and in leukoplakia and oral cancer compared with the control group [26]. Similar results were reported by another study conducted in 2014 on unstimulated saliva samples of leukoplakia and oral cancer patients for estimation of LDH levels using gel electrophoresis [27,28]. In 2015, Patel *et al*. reported a significant increase in LDH level of oral cancer and leukoplakia patients compared with the control group using a semi-automatic analyzer [7]. Sivaramakrishnan *et al*. reported increased salivary levels of LDH using a specific kit in OSMF patients as compared to controls [27]. Furthermore, Ghallab and Shaker (2017) reported a significant increase in salivary levels of LDH in leukoplakia and OSCC patients [28]. In the same regard, Rao *et al*. used spectrophotometry and showed that the salivary levels of LDH in OSCC patients were significantly higher than the corresponding values in the control group. They also found a significant correlation between the salivary and serum levels of LDH in the two groups. Moreover, they showed that the salivary level fold was correlated with the frequency and duration of tobacco use in OSCC patients, while no such correlation with serum level of LDH was noted [29]. So, measuring the total level of LDH and its isoenzymes is important in the detection of cancerous and potentially malignant lesions and can also serve as an important prognostic marker [30]. On the other hand, according to the current results, the salivary levels of MMP-9 in OSCC patients were significantly higher than the

corresponding values in control groups. MMPs can degrade the extracellular matrix. It is secreted by neutrophils, macrophages, and fibroblasts on the stimulus provided by transforming growth factor-β and interleukin-8. The MMP sustains the bioavailability of growth factors, thus aiding in the proliferation of cancerous cells [31]. MMPs are proteolytic enzymes involved especially in the dissolution of the extracellular matrix (ECM) components. Lately, they have been acknowledged as biomarkers for a variety of diseases, mostly cancerous pathologies. Physiologically, MMPs participate in processes like cellular differentiation and mobility, angiogenesis, apoptosis, and tissue remodeling. Though the deregulation of their function promotes the development of several pathologies associated with tissue destruction, ECM loosening, and fibrosis [32]. The most important step in the development of OSCC is the breakdown of the extracellular matrix (ECM). This leads to a major change in the phenotype of cells. This causes the epithelial–mesenchymal transition, which is marked by cells losing their polarity and sticking together with other cells. This makes it easier for tumor cells to spread. Moreover, by degrading collagen, MMPs reveal normally hidden sites in the ECM, allowing integrins to interact with its components. MMP-2 helps the release of tumor growth factor-beta when ECM is broken down. This factor plays a role in the growth and invasion of tumors. The most prominent characteristic of the tumor microenvironment in OSCC was the stimulation of ECM degradation via MMP activity, which is associated with the release of local growth factors and angiogenesis, further promoting lymph node metastasis [33-35]. Moreover, evaluation of genetic expression levels of various markers as predisposing factors in many cancers are recommended to improve diagnosis [36,37]. To the best of the authors' knowledge, this study is the first to show a higher level of salivary MMP-9 and LDH in patients with OSSC compared with the control. Thus, accurate diagnostic clinical and histological criteria, appropriate treatment planning, and regular follow-ups are strongly recommended for such patients to prevent malignant transformation.

Conclusion

Patients with OSCC had higher salivary levels of LDH and MMP-9 compared with the control group. Assessment of salivary LDH and MMP-9 can be beneficial for diagnosing OSCC. We recommend further prospective longitudinal studies especially for assessment of the tissue levels of LDH and MMP-9.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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