Review Article

Evaluation of changes in Salivary Lactate Dehydrogenase Level for detection of Head and Neck Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis Study

Abstract

Background: Research has examined the relationship between salivary lactate dehydrogenase (LDH) levels and head and neck squamous cell carcinoma (HNSCC) screening and prognosis. Due to biochemical changes in cancer cells and increased production of lactate products in the body. The present systematic review aims to evaluate the changes in salivary LDH levels in HNSCC patients. **Methods:** The present study is a systematic review and meta-analysis. The data were collected by searching PubMed, Science Direct, Scopus, Web of Science, and Google Scholar from 2000 to 2021. The heterogeneity of the articles was analyzed using I^2 and TAU^2. **Results:** After searching the databases, of 988 articles, 665 duplicated articles were excluded by adopting the inclusion and exclusion criteria. So, 25 articles were primarily selected to be reviewed and evaluated for quality. Finally, 19 articles were selected and analyzed according to the Newcastle–Ottawa checklist. A total of 642 HNSCC patients were reviewed. The meta-analysis showed salivary LDH levels in the HNSCC group were higher than the control group (mean difference = 0.675, standard error = 0.058) ($P < 0.001$). **Conclusions:** As the research results showed, a significant correlation was observed between salivary LDH levels and HNSCCs. So, LDH can be employed as a valuable and minimally invasive biomarker in head and neck cancer screening and prevention.

Keywords: *Head and neck squamous cell carcinoma, lactate dehydrogenase, saliva*

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Introduction

Malignancy is one of the biggest health problems in society. Head and neck cancers are the sixth most common cancers globally, affecting about 650,000 people annually.[1] They include cancers of the lips, tongue, mouth, cheeks, hard and soft palate, sinuses, larynx, oropharynx, and nasopharynx. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer, accounting for about 90% of cases.[2] The prevalence and mortality rate of this cancer is higher in developing countries than in developed ones, so the incidence varies according to geographical variations.[3] Also, its incidence is twice as high in men as in women. Risk factors for this cancer include alcohol consumption, tobacco, viruses, weakened immune system, radiation, familial and genetic predisposition, diet, and nutrition.[4]

Concerns with head and neck cancer are the lack of knowledge of specialists, the lack of early diagnosis, and late diagnosis. Head and neck cancers are usually diagnosed in advanced stages despite access to the oral cavity and surrounding area during a clinical examination.[5] Histopathologic examination following biopsy is the gold standard for diagnosing head and neck cancers with limitations. The relative complexity and low availability of this standard gold method for diagnosing head and neck cancers have highlighted the search for alternative or adjuvant diagnostic procedures, including the use of saliva and serum biomarkers. In recent decades, saliva has been used as a minimally invasive, accurate, cost-effective, simple, convenient, and reproducible in the diagnosis and follow-up of patients.[6]

One of the diagnostic biomarkers in the saliva is the enzyme lactate dehydrogenase (LDH), an essential cytoplasmic enzyme present in almost all body tissues and abundant in the liver, muscle, and kidneys. It has five isomeric forms. LDH is the most basic enzyme

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of glycolysis in conditions of hypoxia. It catalyzes the conversion of pyruvate to lactic acid under anaerobic glycolysis. Under anaerobic conditions, due to necrosis and cell death, the concentration of this enzyme in extracellular fluid and saliva increases.[7]

Research has shown that LDH is produced by the epithelial cells of the oral cavity. The level of this enzyme rises in pathological conditions such as OSCC due to cell death, necrosis, and an increase in cell proliferation. Cancer cells change metabolism. Unlike normal cells in the body, these cells increase the rate of anaerobic glycolysis instead of oxidative phosphorylation under hypoxic conditions to provide the energy needed for cell proliferation and cell survival and increase lactate production.[8-10]

The present study mainly investigates the possible relationship between salivary LDH levels in healthy individuals and HNSCC patients so that LDH can be used in saliva as a reliable biomarker for early diagnosis, prognosis, and treatment of HNSCC.

In cancers of various organs, such as the kidney, breast, and colon, systematic review articles and meta-analyses have examined the differences in LDH levels in healthy and sick individuals. Its role in the diagnosis and prognosis of cancer has been mentioned. However, no systematic review has been performed on the relationship between salivary LDH levels and squamous cell carcinoma of the head and neck. Some studies have also shown a significant difference between salivary LDH levels in patients with squamous cell carcinoma of the head and neck and healthy individuals. However, in some studies, such as Nagler *et al*.[11] and the review study of Reznick,[12] this difference in salivary LDH levels is less significant than the difference in serum LDH levels. This study aims to systematically examine the differences in the levels of this enzyme in the saliva of healthy individuals and patients with cervical squamous cell carcinoma. Doing such studies may contribute to the early detection of cancer, prevent its progression, and reduce treatment costs and side effects.

Methods

Research protocol

This systematic review was carried out based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement).

Statistical population

The research population includes case-control studies from 2000 until August 2021 which were selected and reviewed by two researchers.

Search strategy

To gather the data, first, the keywords, including LDH, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), or oral carcinoma and saliva, were defined based on PubMed and MeSh databases. Two researchers then searched the keywords in the databases PubMed, Google Scholar, Web of Science (WoS), Scopus, Embase and Cochrane, The reason for choosing these databases was their popularity for indexing the highest number of valid articles. The sources of the found articles were also searched manually, and no study that met the inclusion criteria was found. It should be noted that unpublished articles were not included in the study, and only those published up to August 2021 were included. In the first round, irrelevant and duplicate articles and those unavailable in the full text were excluded.

Inclusion and exclusion criteria

Inclusion criteria include 1- case-control articles in the case group of patients with HNSCC 2- measured salivary LDH levels; 3- articles published in English available in abstract and full text. Exclusion criteria include 1- case reports, short reports, and letters to the editor; 2- duplicate articles; 3- studies conducted on inhuman cases; 4- studies in languages other than English; 5- studies inconsistent in terms of population and the results; and 6) studies whose quality score was less than five according to the Newcastle-Ottawa Scale checklist.

Qualitative assessment of the articles

The quality of the selected articles was measured by the Newcastle-Ottawa Scale.[13] According to this protocol, a score of 0 to 9 was assigned based on having the above items recorded in the tables for each study. Two researchers scored each study, and if the study score did not match, the third researcher took it. Finally, the scores of the articles were collected: according to their final scores. They were classified as high-quality (score 6–9), medium-quality (score 3–5), and low-quality (score 0–2) articles. Then, the articles were reviewed for collecting the relevant data and analyzed based on their significance and quality degrees.

The researchers generally assessed the quality of the selected articles using the standard PRISMA checklist, consisting of 27 sections and evaluating various aspects of the methodology.[14]

Data collection

A table was set up to extract and record the data. The data such as author's name, year of publication, country, number of patients in a study, number of the control group, amount of LDH in saliva, saliva collection methods, statistical analysis, and results were collected by two researchers.

Statistical analysis

After entering the information in Excel software, the data were checked by comprehensive meta-analysis software

version 2.2.064 with a 95% confidence interval. TAU^2 and I^2 tests were used to evaluate the heterogeneity of data in a systematic review study. Diffusion bias was also investigated in the articles using funnel plots and Egger regression and Begg-adjusted rank correlation tests. After the final review, 19 articles were included in the meta-analysis.

Results

Selection of articles

According to keyword searching in diverse databases, 988 articles were found related to salivary LDH associated with HNSCCs. After excluding duplicate articles (665 articles), 323 were selected. Then, by reviewing their titles and abstracts according to the inclusion and exclusion criteria, 251 articles were excluded, and 72 were selected. After that, full texts of the selected articles were reviewed and scrutinized. So, 25 articles were selected, of which four were excluded due to the small number of participants in the experimental and control groups, and lack of mean expression, and standard deviation of LDH; and two ones due to cancer patients undergoing chemotherapy. Finally, 19 articles with sufficient scores based on the Newcastle-Ottawa checklist were included in the study [Figure 1].

Characteristics of the selected articles

All the selected case-control studies were published from 2007 to 2020. In total, the number of control groups was n = 663, and the number of case groups (HNSCC patients) was n = 642.

In 12 of the 19 articles, the case and control groups were matched, and in 7 ones, case and control groups were unmatched in terms of age and gender [see Table 1]. The average age of the subjects in the control group and the HNSCC group in all articles was reported to be between 45 and 60 years. 68.4% of the studies were conducted in India, 10.5% in Iran, 10.5% in Israel, 5.3% in Iraq, and 5.3% in Russia.

In all articles, unstimulated saliva was used for collecting specimens. The subjects' saliva was collected about 1 to 3 h after eating and put in special saliva collection tubes in a centrifuge at different speeds. The tubes were then placed in iceboxes and sent to a laboratory for determining the LDH levels.

Ten studies did not report information on enzyme levels in men and women. Among the other nine studies, there were 108 women and 168 men in the control group and 110 women and 174 men in the case group with HNSCC.[15,17,19,20,23,27,28,29,34]

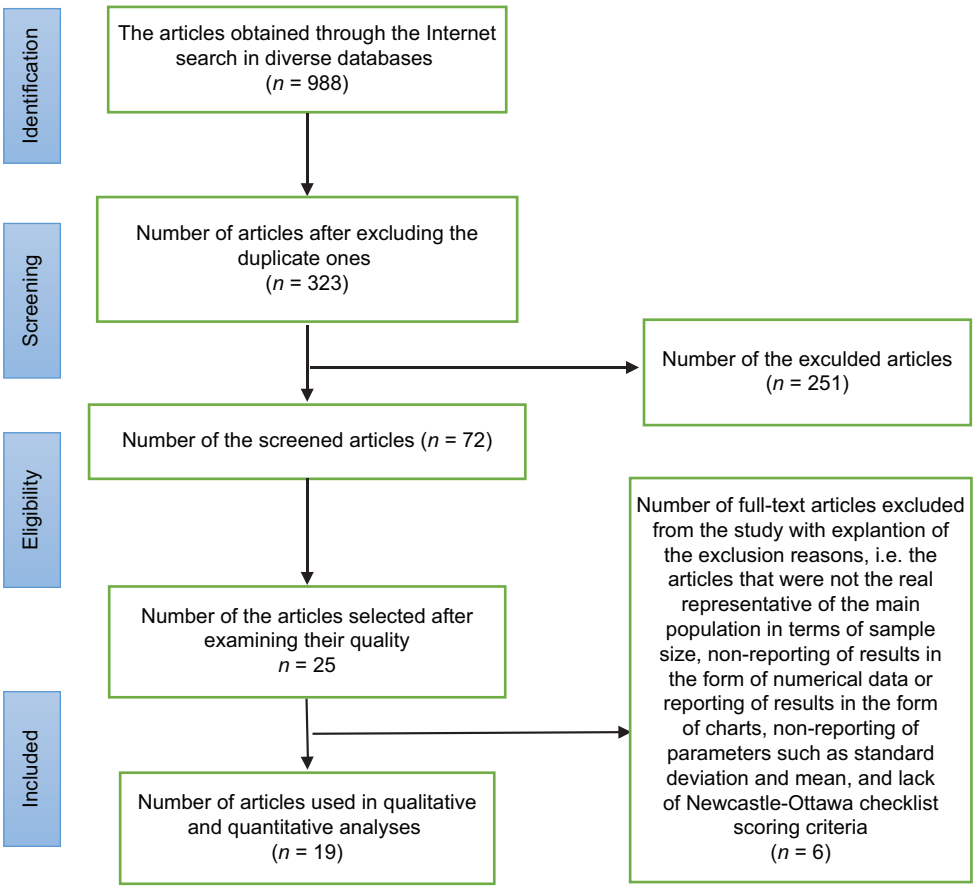

Figure 1: Flowchart of the process of selecting articles for meta-analysis

Table 1: Summary of studies included in systematic review and meta-analysis

Authors	Country	The sample size of the control group	The sample size of the HNSCC group	The LDH mean in the control group (in UI/L or µ/L)	The LDH mean in the HNSCC group (in UI/L or µ/L)	*P*	Matched/ unmatched in age and gender	The quality Scores of the articles
Shpitzer (2007)[15]	Israel	25	25	120	191.6	=0.002	Matched	5
Shpitzer (2009)[16]	Israel	19	19	390	725	=0.0002	Matched	6
Merza (2010)[17]	Iraq	20	20	244	525	<0.05	Unmached	5
Shetty (2012)[18]	India	25	25	48.77±4.83	79.5±4.66	=0.0001	Matched	7
Joshi (2014)[19]	India	30	30	262.2±10.17	788.7±24.56	<0.001	Matched	7
Dhivyalakshmi (2014)[20]	India	14	14	79.7	265.5	<0.001	Unmatched	6
Patel (2015)[21]	India	25	25	261.16±85.78	686.4±81.75	=0.001	Matched	7
Kadiyala (2015)[22]	India	20	20	126.7±58.2	515.7±257.8	=0.001	Matched	7
Kallali (2016)[23]	India	10	25	182.2±29.8	630.9±39.8	=0.0009	Unmatched	6
Lokesh (2016)[24]	India	20	30	497±51.57	1225.4±221.79	=0.0001	Unmatched	6
Dcruz (2016)[25]	India	30	30	117.3±19.37	486.79±18.7	<0.001	Matched	7
Rao (2017)[26]	India	30	30	201.3±8.1	906.4±23.4	<0.001	Unmatched	6
Preet singh (2018)[27]	India	62	62	456	887	=0.01	Matched	6
Mohajertehran (2019)[28]	Iran	44	44	771	1005	<0.01	Matched	7
Mantri (2019)[29]	India	30	30	86.12±7.05	592.9±28.57	<0.001	Matched	7
Samlin (2019)[30]	India	20	20	201.3±8.1	1172.5±45.87	=0.03	Matched	6
Goyal (2020)[31]	India	100	100	115	820	<0.01	Matched	7
Vbelskaya (2020)[32]	Russia	114	68	1008±607.9	1441±864.8	=0.0153	Unmatched	7
Gholizadeh (2020)[33]	Iran	25	25	3.83±1.14	98.83±49.32	=0.0001	Unmatched	6

Salivary LDH levels were also higher in men and women with squamous cell carcinoma of the head and neck than in men and women in the control group. In the present systematic review study, only in three studies, the mean level of LDH in the saliva of men and women with HNSCC was measured.[18,22,28]

The mean LDH level in all 19 articles in the HNSCC group was significantly higher than the control group ($P < 0.001$). In three studies, the mean LDH level in the poorly differentiated group was higher than in moderately differentiated and well-differentiated groups.[20,24,25] In one study, the poorly differentiated group's mean LDH level was less than the other two groups.[28] Also, in one study, the mean LDH level in the case Grade 3 (G3, poorly differentiated) group was less than in Grade 2 (G2, moderately differentiated) group.[32]

Results of a meta-analysis of changes in salivary LDH levels in HNSCC patients

Due to the unavailability of the standard deviation of the LDH level in all articles, the *P* value of the LDH level was meta-analyzed in the articles, and the strictly standardized mean difference was used as the effect size. In this index, the difference between the calculated means is divided by the standard deviation. As a result, 19 articles were included in the meta-analysis. For this purpose, Comprehensive Meta-Analysis software version 2.2.064 was used. Then, I^2 was employed for determining the matched and non-matched articles. Since the I^2 values were smaller than 0.5 for each of the 19 articles, the Fixed model was used. Also, in terms of age and gender homogeneity, the 19 articles were divided into matched and unmatched groups, of which 12 were matched and had an I^2 index of smaller than 0.5, for which the fixed model was employed. We had 7 heterogeneous studies with I^2 >0.5, for which we used a random model [Figures 2,3,4]. Three different meta-analyses were performed: in 12 studies that were matched in terms of gender and age. Salivary LDH levels were compared in the HNSCC group and control group (standard error = 0.052; std diff in mean = 0.514) [Figure 2]). In seven studies that were unmatched in terms of gender and age, salivary LDH levels were compared in the HNSCC group and the control group (std diff = 0.949; standard error = 0.178) [Figure 3]. In general, this comparison was made in 19 studies (standard error = 0.058 std diff in mean = 0.675) [Figure 4]. In all studies, salivary LDH levels were higher in the HNSCC group than in the control group.

Two methods were used to check the diffusion bias. At first, a funnel plot was drawn for each index. Then, Begg and Mazumdar rank correlation and Egger regression intercept indices were used. The significance of these indices indicates the existence of diffusion bias in the articles [Figure 5]. For this purpose, after reviewing Tweedie's trim and fill analysis, the standardized *P* values for all articles, matched ones, and unmatched ones were bigger than zero. Despite the diffusion bias, this value is bigger than zero. Therefore, it can be concluded that the

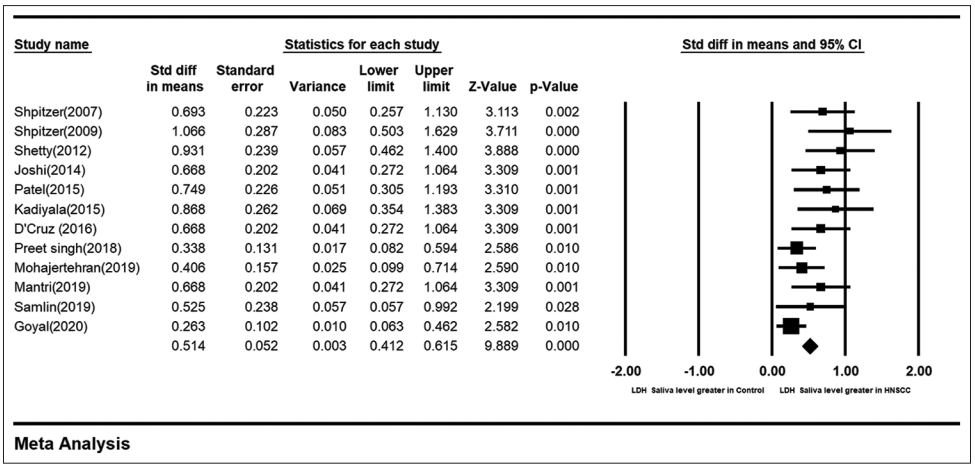

Figure 2: Accumulation graph of the strictly standardized mean difference in salivary LDH levels between HNSCC patients and healthy individuals for the matched articles based on the Fixed model with a 95% confidence interval for each article

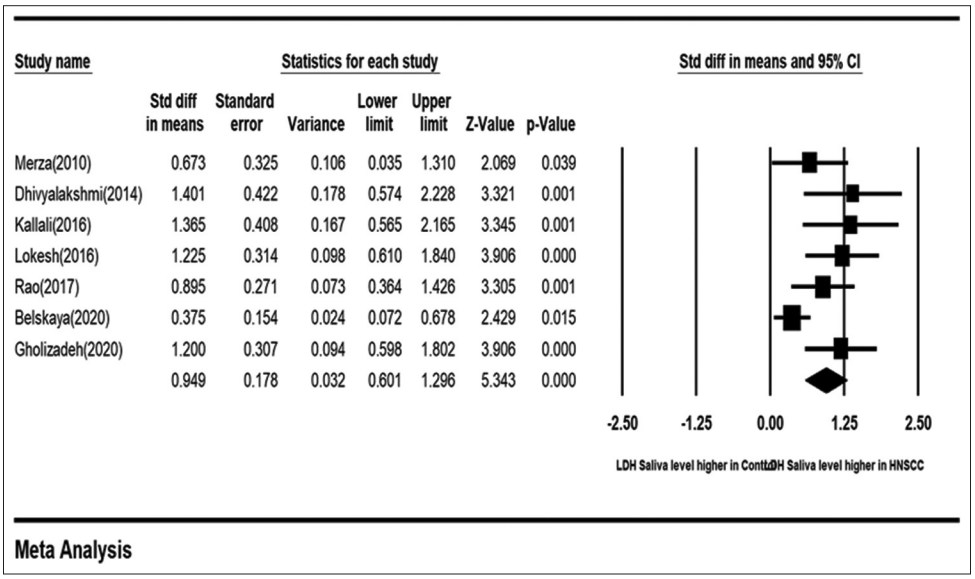

Figure 3: Accumulation graph of the strictly standardized mean difference in salivary LDH levels between HNSCC patients and healthy individuals for the unmatched articles based on the Random model with a 95% confidence interval for each article

salivary LDH levels in the HNSCC group are higher than in the control group.

Discussion

Head and neck cancer is the sixth most common cancer in the world. In recent years, many studies have been conducted on complex diagnostic and therapeutic technologies for this disease. The involvement of organs and tissues in this cancer is complex and diverse, making it challenging to decide on treatment. Therefore, a combination of a medical team is usually needed to treat this cancer.[1]

Cancer cells change metabolism: unlike normal cells in the body, these cells increase the rate of anaerobic glycolysis instead of oxidative phosphorylation in the absence of oxygen to provide the energy needed for abundant cell proliferation.[9]

This metabolic phenomenon is called the Warburg effect, the predominant metabolism in malignant cells.[9] The reversal of glycolysis in cancer cells is due to their dependence on energy and glucose to provide metabolites necessary for growth, such as nucleic acids and fatty acids.[10] Glycolysis is performed when the oxygen concentration is lower than average, and the enzymes that facilitate this reaction include LDH and glucose transporters (Glut-1/Glut-3).[10] The level of this enzyme in normal cells can also increase depending on the type of function and their response to pathogens such as hypoxia, necrosis, and hemolysis.

Studies have shown that salivary LDH isoenzymes are similar to the isoenzymes of oral mucosal cells, and measuring saliva LDH can be a promising biomarker for diagnosing and predicting oral pathological conditions.[9]

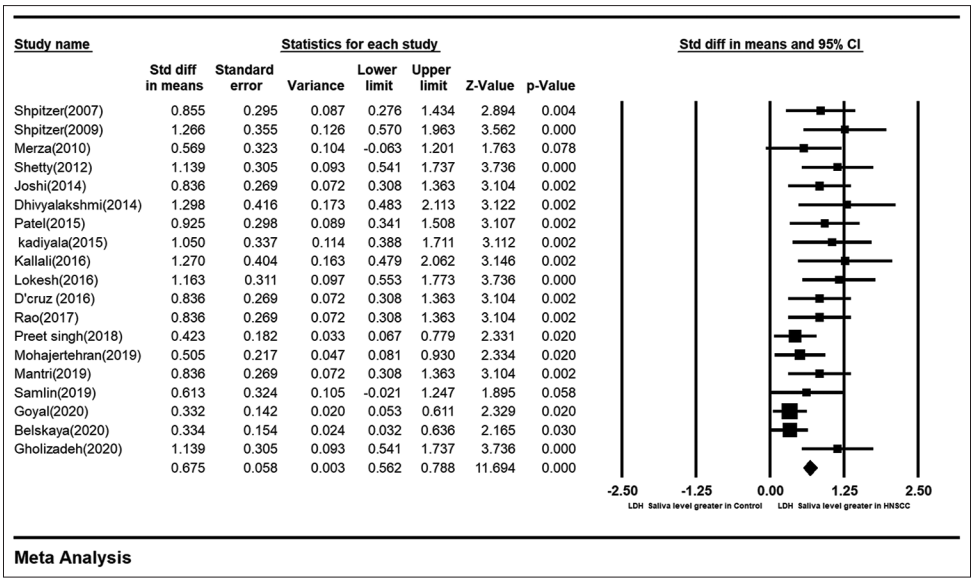

Figure 4: Accumulation graph of the strictly standardized mean difference in salivary LDH levels between HNSCC patients and healthy individuals for all articles based on the Fixed model with a 95% confidence interval for each article

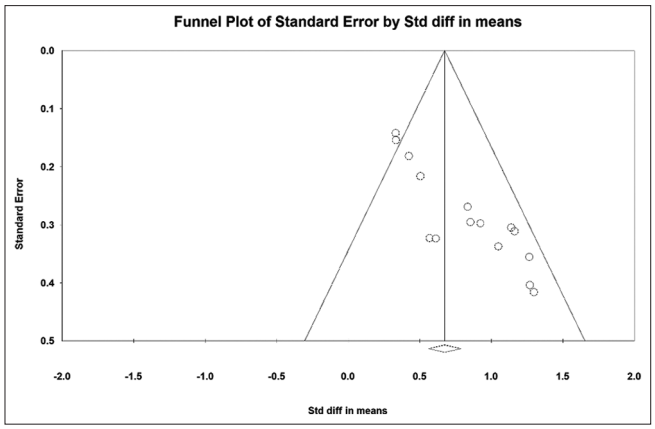

Figure 5: Funnel plot of all articles: results related to the between the strictly standardized mean difference of salivary LDH levels in the HNSCC and control groups

Salivary LDH has been studied in various dental studies. Todorovic *et al*. (2006)[34] showed that salivary LDH is a valuable biomarker in diagnosing and treating periodontal disease. During disease, due to pathological processes, the periodontium cells secrete the LDH into the saliva outside the cell. Also, the level of this enzyme is related to the amount of gingival index for the diagnosis of periodontal diseases, and it has been observed that after treatment, due to the repair of periodontal cells, the amount of LDH in saliva decreases.

Also, LDH levels in saliva in oral lesions such as lichen planus and lichenoid reaction lesions are higher than in healthy individuals. In this disease, the enzyme level in serum and saliva was increased.[34]

Patel *et al*. (2015)[21] conducted in India found that despite the convenience and accessibility of the oral cavity and head and neck for direct clinical examination, malignancies in these areas are diagnosed in the final stages, which reduces the quality of life. Because cancer cells undergo metabolic changes compared to healthy cells, biomarkers in cells and body fluids can be used to diagnose the disease earlier and better. This study reported that salivary LDH levels in patients with oral cancer were higher than in healthy individuals.

in India, Goyal (2020) showed that salivary LDH levels in people with head and neck cancer were higher than serum LDH levels in these individuals. Therefore, the amount of this enzyme in the saliva of individuals can be used as a marker for screening patients. Also, in this study, it was mentioned that the level of LDH in the saliva of patients with head and neck cancer is much higher than the amount of alkaline phosphatase (ALP) in the saliva of these people. Thus, biomarkers seem to be more accurate for screening patients.[31]

In contrast to the above studies, a study by Neglar *et al*.[35] In Israel, which did not enter our meta-analysis due to lack of inclusion criteria, examined the difference between unstimulated saliva LDH and stimulated saliva LDH and serum LDH in the diagnosis of oral diseases. They concluded that the LDH level of unstimulated saliva was less accurate in diagnosing and predicting oral malignancies than the other two because some of the free-reducing metal elements in saliva, such as copper and iron, reduced the level and activity of this enzyme in saliva. It comes to my head. In smokers, the presence of smoking compounds also has a destructive effect on salivary enzymes such as LDH and amylase, while serum does not have this destructive effect. To increase the activity of LDH in saliva, antioxidants such as glutathione and N-Acetylcysteine, and other antioxidants should be used to protect salivary enzymes against metals and compounds in cigarettes.[11]

Examining the effect of salivary antioxidants on the protection of salivary enzymes, Neglar *et al*.[35] in 2000. found out that some antioxidants, such as ascorbate (ASC), were inactivated in the presence of salivary-free metals such as iron, and had lower antioxidant effectiveness. It contributes to losing LDH activity in saliva while the iron is not freely present in serum and has no decreasing effect on the LDH activity and level.

In the present study, 19 articles were included in a meta-analysis to evaluate changes in salivary LDH levels in HNSCC. All 19 articles concluded that LDH levels in the HNSCC patients' saliva were higher than in healthy individuals. Reasons for increased LDH levels include increased mitosis in cancer cells and increased production of lactate products, cell destruction, and LDH exits from the cell and its entry into extracellular fluids such as saliva and the breakdown of glycoproteins and conversion to lactic acid.

Most of the studies included in our meta-analysis did not mention a specific relationship between the microscopic degree of head and neck cancer and salivary LDH levels. It seems that further studies with a large sample and a more accurate methodology are needed to investigate the microscopic relationship between HNSCC and salivary LDH levels.

Some studies have shown that salivary LDH levels are reduced after HNSCC patients' treatment. As a result, LDH can be used as a factor for screening and early diagnosis to evaluate the treatment process.[21]

Most of the studies included in our meta-analysis were conducted in India. To investigate the cause of this phenomenon, the prevalence of head and neck cancer was examined epidemiologically in India. The prevalence of head and neck cancer is very high in India and Southeast Asia. The International Agency for Research on Cancer reports that the incidence of cancer in India will increase from 1.2 million in 2012 to 1.7 million in 2035. more than five individuals die every hour due to oral cancer.[36] In countries like India, which have economic and cultural poverty, malnutrition, tobacco and alcohol consumption, health care, and lifestyle are affected. Many people in India do not have access to oral cancer screening, information, and treatment services due to low income and lack of awareness.[37]

In general, saliva is a biofluid containing many biological molecules, based on a review study by Amenabar *et al*. (2020).[38] Accordingly, it is better to use a variety of biological molecules in saliva in laboratory tests to achieve an accurate clinical diagnosis with high sensitivity.

Examination of salivary LDH enzyme in patients with head and neck cancer can be helpful as a biomarker for screening and early diagnosis and follow-up of the treatment process. It is noteworthy that the level of this enzyme may change in many diseases. Also, the type of isoenzyme measured in the studies was not specified. At present, changes in salivary LDH levels can only be used as an adjunct to other clinical and paraclinical methods for disease screening and diagnosis, prognosis, and follow-up of treatment.

It is suggested that the results of this systematic review can be made available to general dentists and specialists in oral and maxillofacial diseases and pathology because the use of saliva LDH as a simple, minimally invasive, and inexpensive tool for head and neck cancer screening will be efficient.

Research limitations

The limitations of this study include the following: selection of articles published only in English, the impossibility of full access to all articles related to the subject due to their non-indexing in databases, heterogeneity of research methods such as differences in sampling methods and sample sizes, different collection methods saliva and measurement of LDH, failure to study other isoenzymes of salivary LDH in articles, lack of geographical and genetic diversity among studies (most of them were done in India), and the need for doing uniform research in different parts of the world.

Conclusions

This systematic review and meta-analysis show that salivary LDH levels are higher in HNSCC patients than in healthy individuals. So, salivary LDH can be used as a simple minimally invasive biomarker to determine the prognosis and early diagnosis of head and neck cancer to screen high-risk patients and help dentists make proper decisions. However, the role of factors in unstimulated salivae such as free metals and smoking compounds in smokers should also be considered because these factors affect some salivary antioxidants, and their protective role for LDH is reduced; therefore, the LDH activity and level may decrease in unstimulated saliva. Given the research limitations, it is hoped that more extensive clinical trials would be conducted to improve and update the results.

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Conflicts of interest

There are no conflicts of interest.

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