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Original Research Article

Level of serum lactate dehydrogenase in oral submucous fibrosis

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ABSTRACT

Background: Oral cancer is one of the most common form of malignancies in India. In many cases it develops at the site of premalignant lesion. Of all oral premalignant conditions, oral submucous fibrosis (OSMF) is of greater concern because of its disabling nature and relative greater chances of malignant transformation. Transformation of normal tissue to premalignant lesion and further to oral cancer results in alteration in glycolytic pathway and hence the lactate dehydrogenase (LDH) levels. The aim of this study was to estimate the LDH levels in serum of subjects with OSMF and to compare them with healthy controls and to correlate the relationship between pathogenesis of OSMF and the LDH enzyme.
Methods: It is a case control study. The study included 40 diagnosed cases of OSMF and 40 matched healthy controls. Venous blood of 3 ml was collected in both cases and controls. Serum was separated by centrifugation and LDH was estimated by using standard kits. Statistical analysis was done using student 't' test. Pearson's correlation was performed to establish the relationship between study variables.
Results: It was observed that serum LDH levels were significantly increased in cases of OSMF as compared to controls ($p < 0.005$).
Conclusions: Serum LDH was significantly increased in OSMF and can be used as a valuable biochemical marker in prognosis of OSMF.

Keywords: OSMF, LDH, Premalignant, Oral cancer, Glycolytic pathway

INTRODUCTION

The term oral cancer includes all malignancies that originate in the oral tissues and remains a major public health problem.[1] In India, the incidence of oral cancer is about three to seven times more common as compared to developed countries. India tops in prevalence of oral cancer in the world and oral cancer remains the commonest cancer among male population. Oral cancer is the third-most common cancer in India after cervical and breast cancer among women.[2,3] The OSMF is a precancerous condition or premalignant condition- a generalized pathological state of the oral mucosa associated with a significantly increased risk of cancer according to world health organization (WHO).[4] It is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx.[5] Occasionally it is preceded by and/or associated with vesicle formation and is always associated with juxta-epithelial inflammatory reaction followed by progressive hyalinization of lamina propria.[6,7]

The later subendothelial and submucosal myofibrosis leads to stiffness of the oral mucosa and deeper tissues with progressive limitation in the opening of the mouth and prostrusion of the tongue, thus causing difficulty in eating, swallowing and phonation.[8] There may be marked epithelial atropy.

The enzyme lactate dehydrogenase (LDH) is an ubiquitous enzyme that was discovered in early periods of enzymology. This enzyme catalyses the reaction of lactate production via pyruvate reduction during anaerobic glycolysis. This enzyme is found in mostly all body tissues but mainly concentrated in heart, liver, red blood cells, kidneys, muscles, brains and lungs. Lactate Dehydrogenase activity is mainly due to genomic changes during malignant transformation.

Recently the role of biochemical markers in management of head and neck cancer has received increased attention. Among all the body fluids, blood has been the media of choice for the study of the biochemical markers. Increased serum lactate dehydrogenase (LDH) activity is considered as a marker of cellular necrosis and serum LDH levels have been used as a biochemical marker in diagnosis in various cancers such as oral, laryngeal and breast cancer. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumour cells due to breakdown of glycoprotein. Studies have also suggested that increased levels of LDH in serum are seen in patients with oral leukoplakia (OL), OSMF and oral squamous cell carcinoma (OSCC).[9-11] Value of LDH elevates in OSCC and potentially malignant disorders; this finding can be used for benefit of the patient in predicting prognosis.[12-18]

The present study is aimed to evaluate the serum LDH levels in OSMF among the control individuals and to correlate the LDH levels in these selected cases using the relatively minimally invasive, easily available serum as the diagnostic tool.

METHODS

This was a case control study. The study was carried out on 40 cases of clinically diagnosed OSMF in the age group 20-50 years attending the otorhinolaryngology outpatient department of Koppal Institute of Medical Sciences (KIMS), Koppal. Forty (40) age and sex matched healthy subjects were taken as controls. The study was conducted over a period of one year from January 2015 to December 2015. Ethical clearance was obtained from the institute's ethical clearance committee. Informed consent was taken from the cases and controls after explaining the procedure. The 40 OSMF patients were clinically examined and diagnosed. Later they were confirmed histopathologically following punch biopsy.

Exclusion criteria were subjects not willing to participate in the study, patients on chemotherapy or radiotherapy or undergoing any surgery for OSMF, those with haemolytic anaemia, haemoglobin variants, pregnancy, hepatic disease and infectious diseases like tuberculosis, sarcoidosis, those with h/o multiple transfusions, overt thyroid dysfunction, chronic kidney disease, chronic liver disease, those on corticosteroid therapy, patients with h/o myocardial infarction in recent past (2 weeks) and patients on medications for arrhythmia, pulmonary infarction and cerebrovascular accident.

Biochemical analysis

A sample of 3 ml venous blood was collected under aseptic precautions. It was allowed to clot and serum was separated by centrifugation. Lactate dehydrogenase levels were evaluated in semi auto analyser (Chem 5 V2) using kits supplied by Erba diagnostics. It works on the principle that LDH catalyses the oxidation of lactate to pyruvate accompanied by the simultaneous reduction of NAD to NADH. LDH activity in serum is proportional to the increase in absorbance due to the reduction of NAD.[19-24]

$$\text{L-lactate} + NAD^+ \underset{\text{pH 7.4-7.8}}{\overset{\text{LDH, pH 8.8-9.8}}{\rightleftharpoons}} \text{Pyruvate} + NADH + H^+$$

Statistical methodology

Data was expressed in terms of mean ± SD. Chi- square test was applied to estimate the difference between the two groups of population. Unpaired 't' test was used to study the changes in serum Lactate dehydrogenase levels between the study groups. Pearson correlation was performed to establish the relationship between study variables. P value <0.05 was considered statistically significant.

RESULTS

This was a comparative case control study conducted on 40 cases of OSMF and 40 age and sex matched healthy controls (n=40). Serum LDH was estimated and analysed in cases and controls. The results were expressed as mean ± SD.

The age distribution of cases and controls is depicted in Table 1. The mean age (in years) of cases was 49.5 ± 11.7 years and that of controls was 46.2 ± 10.3 years and was not significant (p >0.05).

Table 1: Age distribution of cases and controls.

	OSMF cases	Controls	p value
Mean age (in years)	49.5 ± 11.7	46.2 ± 10.3	>0.05, ns

Table 2 shows the gender distribution. Out of 40 cases of OSMF, 31 (52%) were males and 29 (48%) were females. Out of 40 controls, 30 (45 %) were males and 30 (45%) were females and it was not statistically significant (p =0.38). In general, males were more commonly affected than females. The incidence of OSMF was most common seen between 2nd and 4th decade.

Table 2: Gender distribution of cases and controls.

Gender	Cases-OSMF n(%)	Controls- n (%)
Male	31 (52%)	30 (45)
Female	29 (48%)	30 (45)

χ^2 =4.165 p =0.38, Not significant

The serum LDH levels were found to be greatly increased in cases of OSMF as compared to controls. The mean serum LDH (IU/L) in cases of OSMF was 492.20 ± 16.41 IU/L, in controls was 117.23 ± 19.47 IU/L and was statistically highly significant (p <0.0001) as in Table 3 and Figure 1.

Table 3: Comparison of serum LDH levels between controls and OSMF.

	OSMF cases	Controls
Serum LDH (IU/L)	492.20 ± 16.41	117.23 ± 19.47

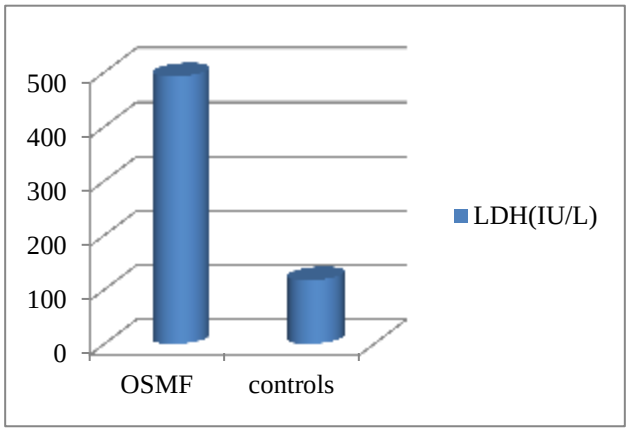

Figure 1: Comparison of serum LDH levels in between the groups.

DISCUSSION

This was a case control study conducted on 40 cases of diagnosed OSMF and compared with 40 matched controls. The results of the present study showed that there was a progressive increase in the serum LDH levels from well-differentiated to the poorly differentiated OSMF. This abnormality may be due to an altered amount of the enzyme forming tissue, an altered rate of synthesis of these enzymes within the tissue of origin, or an alteration in the permeability of the cell membrane brought about by the pathological condition. The mitotic differentiation is higher in moderately differentiated than the well-differentiated type and it is the highest in the poorly differentiated type. The present study was also aimed to assess the correlation between tumour differentiation and serum Lactate Dehydrogenase levels, which showed a positive correlation.

The early diagnosis of cancer is based on the fact that malignant transformation is a gradual process, and carcinoma develops over a long period going through intermediate stages of different biological significance. The treatment at an early stage offers the best prognosis and even a better chance of cure. Recently, tumour markers are receiving more attention in the early detection of the lesion.

Lactate dehydrogenase is a hydrogen transfer enzyme and is involved in the final step in the metabolic chain of anaerobic glycolysis. LDH catalyses the oxidation of L-lactate to pyruvate with nicotinamide-adenine dinucleotide (NAD) as a hydrogen acceptor. The enzyme is composed of four peptide chains of two types: M (muscle) and H (heart), each under separate genetic control. LDH, a cytoplasmic enzyme is present essentially in all major organ systems. The extracellular appearance of LDH is used to detect cell damage or cell death. Due to its extraordinarily widespread distribution in the body, serum LDH is abnormal in a host of disorders. It is released into the peripheral blood after cell death caused by, e.g. ischemia, excess heat or cold, starvation, dehydration, injury, exposure to bacterial toxins, after ingestion of certain drugs, and from chemical poisonings.[25,26]

Carcinogenic changes have tremendous influence in increasing LDH activity. These carcinogenic changes may lead to decreased lactate to pyruvate conversion resulting in an abnormality in the regeneration of NAD that may interfere with glycolysis part of carbohydrate metabolism. Malignant tumour tissue or contiguous tissue damaged by tumour liberates enzymes into circulation that contributes toward abnormal increase in enzyme levels. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumour cells due to breakdown of glycoprotein.

In our study there was a significant increase in LDH levels in cases, which was in accordance to studies done in Danish in south Indian population.

CONCLUSION

The present study revealed that the serum LDH levels were higher in OSMF patients when compared to the healthy controls. Serum LDH levels could be a valuable biomarker for detection of OSMF progressing to cancer, which is being easily available. Its alteration in histological tumour differentiation can be an indicator for the treatment and prognosis of oral cancer.

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