Lactate dehydrogenase: An enzymatic biomarker in oral health and disease
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Introduction
Lactate dehydrogenase (LDH) is a ubiquitous enzyme, which has the pivotal role in the clinical diagnosis of many disease processes. LDH is known to catalyze the oxidative conversion of the substrate pyruvate to lactate and has been used as an inflammatory marker. LDH is routinely present in the cytoplasm of the cell that gets released into the extracellular environment upon cellular lysis and cell death.[1] Thus, LDH represents a marker to cell death and tissue breakdown and its raised level often signifies a disease process.

LDH Isolation and Activity
LDH displays different isoenzyme profiles in different body fluids including serum, saliva, cerebrospinal fluid, etc. It is observed LDH-1 and LDH-2, which predominate in plasma, could be detected to only a limited extent in saliva secreted under resting conditions, whereas LDH-1 in saliva could barely be detected under stimulated conditions. Isoenzymes LDH-4 and LDH-5 were found to predominate in saliva, with higher specific activity than in plasma.[2] LDH is a ubiquitous enzyme that plays an important role in the clinical diagnosis of pathologic processes. Monitoring of LDH total enzyme activity and isoenzyme profiles in plasma is considered as an important clinical tool for detecting the nature and severity of various pathologies.[3]

Abstract
Lactate dehydrogenase (LDH), a metabolic enzyme catalyzing the anaerobic glycolysis has been a non-specific indicator of diseases such as myocardial infarction, liver disease (being particularly high in toxic hepatitis with jaundice), megaloblastic anemia’s, and renal disease. LDH is an intracellular enzyme detectable in the cellular cytoplasm of all the cells in the human body, which becomes extracellular upon the cell death. Therefore, its extracellular presence is related to the cell death and tissue destruction. The LDH concentration in saliva, as an expression of cellular necrosis, could be a more specific indicator of the oral lesions that affect the integrity of the oral mucosa. This article thus reviews LDH as an enzyme marker of oral health and disease with a note on its isolation and storage.

Keywords: Biomarker, lactate dehydrogenase, oral cancer

Approximately, 75% of the LDH in the whole saliva does not originate from the major salivary glands. Stimulating the major salivary glands and consequently increasing their secretions and their relative volumetric part in whole saliva, resulting in a profound diluting effect of the whole salivary LDH, with a 76% reduction of total activity (P < 0.01). This adds credence to the conclusion that the major source for whole-saliva LDH is non-glandular.[4] LDH activity in the whole saliva is a better indicator and a useful biochemical marker for health and disease. [5] De La Peña et al., 2004 studied the enzyme activity in saliva at a different temperature to establish a standardized protocol for isolation, quantification, and storage of the enzyme. It was found that salivary LDH without any additives was suitable to be stored at 4°C for 3 months. At −20°C, they found a significant decrease in the LDH activity after only 30 min of storage.[6]

Polyethylene glycol can be used as a preservative for LDH storage which represents the best additive for salivary LDH storage at all temperatures whereas; ethylenediaminetetraacetic acid is suitable only at room temperature for a week.[2]

LDH and the Disease Process
Raised LDH activity in saliva is often related to tissue inflammation and damage to oral tissues, commonly caused...
by gingivitis and periodontitis. Numabe et al., 2004 stated that LDH activity was reduced after an individual undergoes the periodontal therapy (with significant reduction with just phase 1 therapy). Thus, LDH in saliva has been a suitable indicator and diagnostic tool to assess the periodontal health.[6]

Todorovic et al., 2006 in their study observed that the activities of LDH enzyme in saliva which was significantly increased in the patients with periodontal disease in comparison to those healthy patients.[9]

Furthermore screening of oral lichen planus can be performed by measuring salivary LDH, which may be a feasible, simple, and convenient approach that does not require expert examiners.[10,11]

**LDH and Oral Cancer**

Oral cancer is the neoplastic process that usually begins with normal epithelium progressing through hyperplasia to dysplasia to carcinoma in situ and invasive carcinoma. Early diagnosis improves the overall survival rate and prognosis which is determined by the ability of oral health care professionals to detect the relevant potentially malignant lesions or cancerous lesions at their earliest or most incipient stage.

Such a goal could be achieved by increasing public awareness about the importance of regular oral screening or case finding examinations to identify the small, otherwise asymptomatic cancers, and pre-cancers.

Though immunohistochemical procedures have become more popular, histochemical techniques are still used in the diagnosis of tumors. Using enzyme-histochemistry, metabolic activities of malignant and premalignant cells differ from those of the tissue of origin can be demonstrated. Both qualitative, i.e., presence, raised or lowered activity, changes in is enzyme pattern, and quantitative evaluation is possible. One fundamental metabolic change in the many premalignant and malignant cells is a shift from predominantly aerobic respiration to anaerobic glycolysis.[12,13]

Shpitzer et al., 2007 conducted a comprehensive salivary analysis to evaluate the biochemical parameters as potential markers in the diagnosis of oral squamous cell carcinoma (OSCC); it was found these salivary markers including LDH was significantly higher in the patients with OSCC compared to the control group.[14]

Similar findings in a study by Nagler et al., 2001 showed a profound increase in this enzyme profile (salivary LDH) which is mainly derived from the exfoliated epithelial cells (in this case OSCC cells) which may represent a general salivary marker of the diseased oral mucosa. As a further interest the author also suggested future studies to be developed in order to establish a correlation between the level of salivary LDH and the aggressiveness of oral OSCC lesion, as the mitotic rate of more aggressive lesions is higher, and thus the salivary LDH may also be expected to increase.[15]

**LDH and Tumor Differentiation**

Squamous cell carcinoma usually exhibits a heterogeneous cell population with a difference in the degree of differentiation. As the presence of metaseses is highly correlated with survival, histopathologic grading of tumors has therefore been used for many years to predict the outcome of a tumor, although with varying prognostic value.[16]

Several studies related to tumor differentiation and the levels of the enzyme activity in serum have been reported.

Giartromanolaki et al., 2000 in their study of 76 patients with lung cancers observed an overexpression of LDH activity in serum in the advanced cancers.

Thus concluded expression of this biochemical marker in serum can predict the aggressiveness of the tumor and thus the prognosis.[17]

Similar studies by Mall et al., 2002 revealed serum LDH could be correlated to the advanced stages of small cell cancers of the lungs, similar findings have been reported in ovarian cancers by Yüce et al., 2001.[18,19]

Poorly differentiated head and neck cancers have also demonstrated high LDH levels suggesting a correlation between LDH levels and tumor differentiation.[20]

**Conclusion**

LDH, a metabolic enzyme represent a disease indicator in several systemic conditions including myocardial infarction, liver disease, malignancies, etc. In particular, salivary LDH is a marker of oral health and tissue integrity. Its raised levels in saliva[21] are thus attributed to cell death and tissue breakdown in terms of periodontitis, carcinoma, and other mucosal conditions with tissue destruction. Thus, in future, the salivary LDH estimation can evolve as a non-invasive technique for routine screening in assessing oral diseases.

**References**

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