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Original Research Paper

Physiology

THE EMERGENCE OF LDH AS A BIOMARKER : PATHOPHYSIOLOGY OF LDH IN COVID-19

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INTRODUCTION

Lactate dehydrogenase (LDH) has recently gained more popularity as a prognostic biomarker in Covid-19. LDH being an intracellular enzyme is released in circulation following tissue injury. Many clinicians opt to use it as a particular marker of lung injury. LDH could be a hydrogen transfer enzyme that's found within the cytoplasm of most of the cells of the body. (1)

IMPORTANCE OF LDH

Biochemistry of LDH

LDH is an intracellular enzyme which catalyzes a reversible biochemical reaction which involves either oxidation of reduction. It belongs to a category of oxidoreductases within which pyruvate is reduced to lactate or lactate is oxidized to pyruvate.

LDH contains a molecular weight of 134,000 and it occurs as five tetrameric isoenzymes composed of two different kinds of subunits. Subunits M (for muscle) and H (for heart) are encoded by loci in chromosomes 11 and 12, respectively. Two subunits utilized in the formation of a tetramer yield five combinations: H4(LDH-1), H3M(LDH-2), H2M2(LDH-3), HM3(LDH-4), and M4(LDH-5). However, the tissue distribution of LDH isoenzymes is variable. For instance, LDH-1 and LDH-2 are the principal isoenzymes in heart, kidney, brain, and erythrocytes; LDH-3 and LDH-4 predominate in endocrine glands (e.g., thyroid, adrenal, pancreas), lymph nodes, thymus, spleen, leukocytes, platelets, and nongravid uterine muscle; and LDH-4 and LDH-5 predominate in liver and skeletal muscle tissue. In tissue injury or insult, the acceptable tissue isoenzymes appear in plasma; thus, determination of LDH isoenzyme composition has diagnostic significance. (1)

LDH is an intracellular enzyme which is cosmopolitan throughout the body and is found at high levels in tissues that utilize glucose for energy; it is therefore not organ specific. Isoenzymes are predominantly distributed within the tissue specific manner. LDH-1 and LDH-2 are predominantly present in cardiac muscles, kidney, and erythrocytes. Enough care should be taken while taking samples for the LDH analysis for myocardial infarct as sample hemolysis may give erroneous results. LDH-4 and LDH-5 isoenzymes are predominant in liver and skeletal muscle. LDH2-4 is found in many other tissues like the spleen, lungs, endocrine glands, and platelets. As a result of this distribution, a rise in LDH can reflect damage to a variety of different tissues (skeletal or cardiac muscle, kidney, liver). (2)

CLINICAL IMPLICATIONS OF LDH

Normal levels of LDH

Typical ranges for LDH levels (4)

LDH levels vary based on age and also the individual laboratory. Infants and young children will have much higher normal LDH levels than older children or adults. LDH is usually reported in units per liter (U/L). In general, normal ranges for LDH levels within the blood are as follows:

Age	Normal LDH level
0 to 10 days	290–2000 U/L
10 days to 2 years	180–430 U/L
2 to 12 years	110–295 U/L
Older than 12 years	100–190 U/L

ROLE OF LDH AS A DIAGNOSTIC TOOL

1) Myocardial Infarct

LDH-1: Present primarily in cardiac myocytes and erythrocytes.

Usually LDH isoenzyme levels increase 24–72 hours following myocardial infarct and reach a peak concentration in 3–4 days. The levels remain elevated for 8 to 14 days, making it a late marker for myocardial infarct. Normally, concentration of LDH-1 is lower than LDH-2, but after myocardial infarction, LDH-1 concentration becomes elevated and exceeds the concentration of LDH-2. This phenomenon is named as flipped LDH pattern. (5)

2) Megaloblastic Anaemia

Total serum LDH levels over 3000IU/L are diagnostic of megaloblastic anemia. Reversed LDH isoenzyme pattern (LDH1 >LDH2) by chloroform inhibition test is an adjuvant in the diagnosis where total serum LDH levels are between 451-3000IU/L and may also differentiate megaloblastic anemia from hemolytic anemia. (6)

3) Exercise

4) Renal disease

LDH could function as a biomarker to predict renal insufficiency in patients. (7) Serum levels of several commonly measured enzymes are abnormal in patients with end-stage renal disease (ESRD). (8)

5) Pulmonary embolism

In patients with pulmonary embolism, LDH can be a good prognostic marker for predicting in-hospital death. (9) LDH is a predictor of both in-hospital and all-cause mortality at follow-up after acute Pumonary Embolism. (10)

METABOLIC ASPECTS OF LDH

LDH is a very important diagnostic biomarker for some common diseases like cancer, thyroid disorders, tuberculosis, etc. In general, LDH plays a key role in the clinical diagnosis of varied common and rare diseases, as this enzyme

encompasses a prominent role in active metabolism. (11)

the levels of lactate represent a chemical marker of severity of illness under all conditions. As an example, in case of sepsis, lactate levels are considered as a robust predictor of mortality (3)

LDH AS A BOMARKER IN COVID 19

Elevated LDH levels were related with a ~6-fold increase in odds of developing severe disease and a ~16-fold increase in odds of mortality in patients with COVID-19. (12)

LDH was related to poor prognosis in patients with COVID-19. (13)

LDH may be a favorable prognostic biomarker with high accuracy for predicting in-hospital mortality in severe and critically ill patients with COVID-19. This could direct physicians worldwide to effectively prioritize resources for patients at high risk of death and to implement more aggressive treatments at an earlier phase to save patients' lives. (14)

LDH can be identified as astrong predictive factor for early recognition of lung injury and severe COVID-19 cases. (15)

Abnormal values cannot only result from cardiac damage or hemolysis but also from multiple organ injury and decreased oxygenation with upregulation of the glycolytic pathway. Because LDH is present in lung tissue, elevated levels seen in COVID-19 and other viral respiratory infections, such as Middle East Respiratory Syndrome, may represent the extent of lung injury that influences clinical outcomes. (16)

Serum LDH may represent a rapidly measured, efficacious, affordable, and widely available biomarker which will predict patients at the highest risk, allowing them to be prioritized and potentially reducing the death rate. (17)

BNP along with hs-TNI, - HBDH, CK-MB and LDH act as a prognostic biomarker in COVID-19 patients with or without pre-existing coronary artery disease. (18)

Henry et al. (19) showed that elevated lactate dehydrogenase (LDH) values were associated with 6-fold increased odds of severe COVID-19 disease. Meta-analysis confirmed that lactate dehydrogenase level can be used as a COVID-19 severity marker and is a predictor of survival. (20)

LDH, CRP and ALB are useful prognostic marker for predicting nucleic acid turn negative within 14 days in symptomatic patients with COVID-19. (21)

Early detection of acute respiratory failure is mandatory to promplty identify critically ill COVID19 patients. Elevated LDH and CRP serum concentrations are associated to respiratory failure in CoVID-19 patients. (22)

Serum LDH was validated for its potential usefulness as markers for evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia. (23)

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