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Pathophysiology, The Biochemical and Clinical Significance of Lactate Dehydrogenase

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ABSTRACT: Lactate dehydrogenase (LDH) is a family of enzymes that catalyzes oxidation-reduction enzymes, the interconversion between pyruvic acid and lactic acid. It is an enzyme that terminates the final catabolic reaction in which glucose id hydrolyzes anaerobically (glycolysis) resulting in lactate from pyruvate. These varied biochemical characteristics significantly influence its specificity to cells, tissues, and organs. Although LDH is mainly found in the cytoplasm, it is also located in multiple organelles. The presence of blood LDH implies an enzyme marker, and it may be a sign of death for many conditions such as ARDS, severe COVID-19, and some cancers. When LDH levels in the blood are increased they can reflect liver disease or anemia plus heart attack in addition to bone fracture — and muscle trauma. This also includes cancerous formations; infections like encephalitis or meningitis — along with HIV.

1. INTRODUCTION

A single marker, LDH, paints the diagnostic picture for a myriad of conditions— from HIV to cancer, and everything in between. These illnesses find their common ground through this enzyme as it plays a crucial role in active metabolism; hence, clinical detection using LDH reaches far and wide among disease spectra (Khan et al., 2020). With tissues teeming with LDH and even microbial identification possible through it-the ubiquitous nature underscores its significance in diagnostics like never before (Qin et al., 2023).

Oxygen is indeed important: very crucial for the cell, keeping it healthy and functional. The failure of multiple organs can result in untreated tissue hypoxia, which leads to death ultimately. In critical care settings where tissue oxygenation plays a vital role in ensuring prompt therapy aimed at restoring adequate oxygen delivery, we need to closely monitor it; however, skeletal muscles along with the heart plus the brain are major lactate producers — their levels come down if there is a decrease in blood flow alongside oxygen (which can happen during physical activity or due to certain disorders like heart failure). By convention, lactic acid has been considered a byproduct of cellular metabolism: an issue that develops when areas inflamed lack enough oxygen (Gupta, 2022).

LDH-A promotes the reversible transformation of pyruvic acid into lactic acid within cells. On the other hand, LDH-B facilitates the transformation of lactic acid into pyruvic acid (Gupta, 2017). It is possible that having elevated levels of LDH in persons who have been diagnosed with gastric cancer (GC) is linked with both overall survival (OS) and disease-free survival (DFS). LDH is a useful indicator of overall survival, however it does not provide any information regarding survival without the presence of certain diseases (Chen & Zou, 2023).

LDH is an indication that operates indiscriminately on tissue turnover, which is a natural metabolic process. Several types of cancer result in a widespread elevation of LDH levels or its isozymes. LDH is a nonspecific tumor marker; however, it can be used because it does not reveal the specific kind of cancer accurately. Cancer cells are identified by their high energy demands due to rapid cell growth, which in turn arises from a hyperglycolytic environment and generation of lactic acid even under normoxic conditions. The metabolic changes in fast-dividing cancer cells are predominantly related to increased glucose uptake with the production of large amounts of lactate through LDH — leading to elevated levels of LDH that can be detected in blood samples from cancer patients even before other clinical symptoms become apparent. A high LDH value indicates poor prognosis as well as resistance towards common chemotherapeutic agents so its assessment forms an integral part not only in diagnosing malignancies

but also in gauging response to anticancer treatment strategies: hence, determination of LDH has now become widely adopted practice for both detection of malignancy and evaluation of cancer treatment's success (Forkasiewicz et al., 2020).

BIOCHEMISTRY

An enzyme found in the cytoplasm, LDH is widely distributed in nearly all tissues throughout the body with particularly high concentrations in the liver, kidney, and muscles; notably red blood cells also contain significant amounts of this enzyme. LDH consists of five isomeric forms often referred to as isozymes which are tetramers made up of either muscle (M) or heart (H) subunits— these forms denoted as LDH-1 through LDH-5 differ in their expression levels across different organs. The varying expression patterns exhibited by these isozymes make LDH an important clinical diagnostic marker (Read et al., 2001).

The LDH-1 isozyme, predominant in heart tissue and consisting of four heart subunits denoted by 4H. Both the reticuloendothelial system and red blood cells contain LDH-2 as the major isozyme: it comprises three heart subunits (3H) and one muscle subunit denoted by 1M (3H1M). LDH-3, most important in the lungs, is made up of two heart subunits plus two muscle subunits; its chemical formula reads 2H2M. The presence of LDH-4 indicates primary organs in kidneys with one heart subunit and three muscle subunits (1H3M). LDH-5, despite being comprised of four muscle subunits, demonstrates high expression levels in both liver and skeletal muscle. The five isoforms differ in terms of their affinity towards substrates, concentration of inhibitors, isoelectric point and electrophoretic mobility even while they perform the same catalytic process (Khan et al., 2020).

The LDH subunits M and H have the same active site structure with similar amino acids involved in the process; however, alanine in the M-chain is replaced by glutamine in the H-chain at a tertiary structural level. Alanine is hydrophobic and has a low molecular weight while glutamine is polar with a positive charge— this structural difference imparts distinct biological characteristics to the two subunits. As a result, even though the H-subunit binds faster than the M-subunit and demonstrates catalytic activity (which is not comparable to that of other enzymes) due to its primary structure consisting mainly of amino acid sequences for binding, it does not show similarities to typical enzyme structures. The LDHA subunit has a net charge of -6 and demonstrates a higher attraction towards pyruvate than other subunits. Consequently, it catalyses the conversion of pyruvate into lactate, while simultaneously converting nicotinamide adenine dinucleotide plus H+ (NADH) into nicotinamide adenine dinucleotide (NAD+). In contrast, LDHB possesses a positive net charge and exhibits a greater attraction towards lactate, resulting in the transformation of lactate into pyruvate and NAD+ into NADH (Read et al., 2001).

PHYSIOLOGY

Lactate Dehydrogenase is the enzyme that catalyze the transfer of H (oxidation - reduction), which stimulate the interconversion between pyruvic acid and lactic acid using NADH. Principally, this enzyme anaerobically participates in the catabolism of glucose according to the equation:

Pyruvic acid + NADH + H+ ---> Lactic acid + NAD+

When cells experience anaerobic or hypoxic conditions, their ability to generate ATP through oxidative phosphorylation is impaired. As a result, cells must resort to alternative metabolic pathways to produce energy. LDH levels are elevated in order to fulfil the increased need for energy generation caused by these conditions. Nevertheless, lactic acid generated from the anaerobic degradation of glucose cannot undergo further metabolism in the majority of tissues, with the exception of the liver. As a result, lactate is released into the bloodstream and carried to the liver, where LDH facilitates the reverse reaction, turning lactate back to pyruvic acid through the lactic acid cycle (Passarella & Schurr, 2018).

During vigorous physical actions, when muscles deplete oxygen, pyruvic acid is converted to lactate by the enzyme lactate dehydrogenase. In red blood cells, pyruvate remains in the cytoplasm without further metabolism due to the absence of mitochondria, ultimately transforming into lactate. This process entails the chemical reaction in which NADH is oxidised to NAD+. Ensuring elevated intracellular levels of NAD is crucial for commencing the initial stage of glycolysis (Schurr & Payne, 2007).

Upon binding, NADH makes use of certain residues on LDH in order to improve the interaction with lactate. This leads to the development of two tertiary complexes, which are formed very quickly: LDH-NAD+-lactate and LDH-NADH-pyruvate. Pyruvate is released first and NAD+ is released next; in this process, the rate at which NADH and NAD+ dissociate from each other plays a major role as the primary limiting factor. The production of lactate from pyruvate— via an independent pathway that regenerates NAD+ — is energetically favorable at this point (Shi & Pinto, 2014).

LDH-A is capable of oxidizing 2-hydroxybutyrate (2HB); however, it is not the preferred substrate as in the case of lactate. 2-hydroxybutyrate is generated when 2-ketobutyrate (2KB) is synthesized. Enzymes like lactate dehydrogenase (LDH) or 2-hydroxybutyrate dehydrogenase (2HBDH), a specific type of LDH found in the heart, assist in this synthesis process. The activity of these enzymes is associated with high NADH/NAD+ ratio which acts as a consistent biomarker related to insulin sensitivity and various cardiovascular diseases that influence lipid oxidation and oxidative stress due to their correlation with type 2 diabetes (Sousa et al., 2021).

CLINICAL IMPORTANCE

The clinical importance of LDH assessment lies in the differential levels of LDH isozymes present in blood serum— these can reveal specific types of tissue pathology. It's interesting to note that LDH levels could continue to rise over a seven-day period post injury based on the tissue type involved. An increase in serum LDH is indicative of organ damage where typically a large number of cells die leading to loss of cytoplasm; this can happen due to various conditions such as acute myocardial infarction, anaemia or pulmonary embolism among many others which result in significant tissue damage. In the same way, liver injury results in high concentrations of LDH-5. An increased LDH-5, when contrasted with LDH-4, is an appropriate indicator for hepatic damage: cases of hepatitis or cirrhosis (Feng et al., 2018).

Serous effusions — such as those found in pericardial and peritoneal fluids — typically exhibit elevated LDH levels. But apart from these scenarios, another condition that results in significantly high LDH levels is intracranial haemorrhage— where LDH can shoot up by more than 40 U/L, a figure commonly associated with disorders like CNS lymphoma, leukaemia, or metastatic cancer. When different sources of tissue injury can be implied based on increased concentrations of various LDH isoenzymes (e.g., pneumonia co-occurring with a heart attack), reading the signs becomes an art. High LDH levels are flags waving towards severe illness or organ failure but interestingly enough LDH happens to be the lone ranger among blood biomarkers useful for detecting metastatic melanomas— hence its star status as an indicator for metastasis sites especially in the liver. And while we're at it, let's not forget that LDH also likes to play fortune teller; patients bearing high levels usually have bleak survival rates — just something else this little molecule can tell us about what lies ahead (Mishra & Banerjee, 2019).

Lactate dehydrogenase (LDH) is a single marker for both acute and chronic pathologies. Any increase in LDH blood levels will determine certain patterns of specific isoenzymes, each revealing the presence of a particular disease; thus, high LDH activity can act as a prognostic marker in the advancement of cancer including cutaneous lymphoma and determining the effectiveness of anticancer therapy. Overall, LDH serves well: as a diagnostic tool for those with metastatic neoplasms; and when other enzymes are joined together (like creatine kinase), they help follow up progressions of different disease conditions (muscular dystrophy or HIV infection) (Mori et al., 2019; Livesey et al., 2023).

Lactate dehydrogenase (LDH), in sports medicine, acts as an indicator showing how muscles react to training. It shows increased levels in skeletal and cardiac muscles within 3-5 hours post exercise: hence the appearance of a myocardial infarction is when the LDH-1/LDH-2 ratio is more than one, with it remaining raised for about ten days after reaching its peak value 24–48 h later. A substantial increase in LDH— specifically both LDH-1 and LDH-2 — more than fifty times normal indicates megaloblastic anaemia; on the other hand, elevated LDH-5 levels are used as an indication of muscular dystrophy when found in high amounts in blood. If the serum LDH level is tenfold higher than usual, toxic hepatitis can be confirmed if jaundice is also present. Increased LDH-3 levels are associated with significant platelet breakdown, which is observed in diseases such as pulmonary embolism. LDH plays a crucial role in assessing the makeup of fluids found in the pleural, peritoneal, or pericardial cavities. It helps differentiate between exudate and transudate effusions by comparing the amounts of LDH in these fluids to that in the bloodstream. LDH is employed as a stage marker (S classification) in cases of non-seminomatous testicular cancer. LDH levels that are unusually low are extremely uncommon and generally considered to be non-pathological (Farhana and Lappin, 2023).

CONCLUSIONS

Lactate dehydrogenase (LDH) is s group isoenzymes that are found in nearly all body organs. Disorders that may result in high LDH levels in the blood may include HIV, encephalitis, meningitis, encephalitis, infections such as cancers, muscle trauma, bone fractures, heart attack, anemia, liver disease, tuberculosis, thyroid disorders, and cancer. It performs the interconversion of pyruvic avid to lactic acid using NADH. LDH are present in five isomeric forms named LDH-1 to LDH-5. LDH-A could also stimulate the oxidation of 2-hydroxybutyric acid (2HB). LDH acts as a non-specific biomarker of chronic and acute diseases. High levels of serum LDH xhibit specific patterns of isoenzymes that are typical in different diseases. LDH is valuable for assessing patients with metastatic cancer.

REFERENCES

1) Chen, J., & Zou, X. (2023). Prognostic significance of lactate dehydrogenase and its impact on the outcomes of gastric cancer: a systematic review and meta-analysis. Frontiers in oncology, 13, 1247444. https://doi.org/10.3389/fonc.2023.1247444
2) Farhana A and Lappin SL. (2023) Biochemistry, Lactate Dehydrogenase. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557536/
3) Feng, Y., Xiong, Y., Qiao, T., Li, X., Jia, L., & Han, Y. (2018). Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy. Cancer medicine, 7(12), 6124–6136. https://doi.org/10.1002/cam4.1820
4) Forkasiewicz, A., Dorociak, M., Stach, K., Szelachowski, P., Tabola, R., & Augoff, K. (2020). The usefulness of lactate dehydrogenase measurements in current oncological practice. Cellular & molecular biology letters, 25, 35. https://doi.org/10.1186/s11658-020-00228-7

5) Gupta G. S. (2022). The Lactate and the Lactate Dehydrogenase in Inflammatory Diseases and Major Risk Factors in COVID-19 Patients. Inflammation, 45(6), 2091–2123. https://doi.org/10.1007/s10753-022-01680-7
6) Gupta GS. (2017) Lactate: Metabolic hallmark of cancer in 21st century. Clinics in Oncology.;2:1375–1377
7) Khan, A. A., Allemailem, K. S., Alhumaydhi, F. A., Gowder, S. J. T., & Rahmani, A. H. (2020). The Biochemical and Clinical Perspectives of Lactate Dehydrogenase: An Enzyme of Active Metabolism. Endocrine, metabolic & immune disorders drug targets, 20(6), 855–868. https://doi.org/10.2174/1871530320666191230141110
8) Livesey, A., Garty, F., Shipman, A. R., & Shipman, K. E. (2020). Lactate dehydrogenase in dermatology practice. Clinical and experimental dermatology, 45(5), 539–543. https://doi.org/10.1111/ced.14134
9) Mishra, D., & Banerjee, D. (2019). Lactate Dehydrogenases as Metabolic Links between Tumor and Stroma in the Tumor Microenvironment. Cancers, 11(6), 750. https://doi.org/10.3390/cancers11060750
10) Mori, K., Kimura, S., Parizi, M. K., Enikeev, D. V., Glybochko, P. V., Seebacher, V., Fajkovic, H., Mostafaei, H., Lysenko, I., Janisch, F., Egawa, S., & Shariat, S. F. (2019). Prognostic Value of Lactate Dehydrogenase in Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. Clinical genitourinary cancer, 17(6), 409–418. https://doi.org/10.1016/j.clgc.2019.07.009
11) Passarella, S., & Schurr, A. (2018). l-Lactate Transport and Metabolism in Mitochondria of Hep G2 Cells-The Cori Cycle Revisited. Frontiers in oncology, 8, 120. https://doi.org/10.3389/fonc.2018.00120
12) Passarella, S., & Schurr, A. (2018). l-Lactate Transport and Metabolism in Mitochondria of Hep G2 Cells-The Cori Cycle Revisited. Frontiers in oncology, 8, 120. https://doi.org/10.3389/fonc.2018.00120
13) Qin, F., Li, J., Mao, T., Feng, S., Li, J., & Lai, M. (2023). 2 Hydroxybutyric Acid-Producing Bacteria in Gut Microbiome and Fusobacterium nucleatum Regulates 2 Hydroxybutyric Acid Level In Vivo. Metabolites, 13(3), 451. https://doi.org/10.3390/metabo13030451
14) Read, J. A., Winter, V. J., Eszes, C. M., Sessions, R. B., & Brady, R. L. (2001). Structural basis for altered activity of M- and H-isozyme forms of human lactate dehydrogenase. Proteins, 43(2), 175–185. https://doi.org/10.1002/1097-0134(20010501)43:2<175::aid-prot1029>3.0.co;2#-
15) Schurr, A., & Payne, R. S. (2007). Lactate, not pyruvate, is neuronal aerobic glycolysis end product: an in vitro electrophysiological study. Neuroscience, 147(3), 613–619. https://doi.org/10.1016/j.neuroscience.2007.05.002
16) Shi, Y., & Pinto, B. M. (2014). Human lactate dehydrogenase a inhibitors: a molecular dynamics investigation. PloS one, 9(1), e86365. https://doi.org/10.1371/journal.pone.0086365
17) Sousa, A. P., Cunha, D. M., Franco, C., Teixeira, C., Gojon, F., Baylina, P., & Fernandes, R. (2021). Which Role Plays 2-Hydroxybutyric Acid on Insulin Resistance?. Metabolites, 11(12), 835. https://doi.org/10.3390/metabo11120835
18) Valvona, C. J., Fillmore, H. L., Nunn, P. B., & Pilkington, G. J. (2016). The Regulation and Function of Lactate Dehydrogenase A: Therapeutic Potential in Brain Tumor. Brain pathology (Zurich, Switzerland), 26(1), 3–17. https://doi.org/10.1111/bpa.12299.