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Review

Lactate dehydrogenase in sickle cell disease

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ABSTRACT

Lactate dehydrogenase (LDH) activity is elevated in many pathological states. Interest in LDH activity in sickle cell disease (SCD) has developed out of an increased comprehension of the pathophysiological process and the clinical course of the disease. Elevated LDH activity in SCD comes from various mechanisms, especially intravascular hemolysis, as well as ischemia-reperfusion damage and tissular necrosis. Intravascular hemolysis is associated with vasoconstriction, platelet activation, endothelial damage, and vascular complications. LDH has been used as a diagnostic and prognostic factor of acute and chronic complications. In this review we have evaluated the literature where LDH activity was examined during steady-state or acute conditions in SCD.

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1. Introduction

Human lactate dehydrogenase (LDH) is a major cytoplasmic enzyme in the glycolytic anaerobic pathway that catalyzes the reduction of pyruvate to L-lactate with the concurrent oxidation of its cofactor NADH to NAD^+ [1]. There are five isoenzymes of LDH according to their electrophoretic migration. LDH is found in all tissues, but each isoenzyme is predominant in a specific tissue: LDH-1 and LDH-2 are mainly in the heart, the reticulo-endothelial system, and red blood cells (RBC); LDH-3 is mainly in the lungs; LDH-4 is mainly in the kidneys, the placenta, and the pancreas; and LDH-5 is mainly in the liver and skeletal muscles [2,3]. The routine analysis of serum LDH does not differentiate these isoenzymes.

LDH is a marker of tissue damage occurring in conditions such as myocardial infarction, lung or liver disease, or in acute pancreatitis. LDH is also used as a tumor marker because of the high turnover of cancer cells and its concentration can be monitored during cancer treatment [4]. Its relevance as a marker of intravascular hemolysis is of most interest in hemoglobinopathy, especially in sickle cell disease (SCD). The other markers of intra- or extra-vascular hemolysis that

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are used routinely include reticulocyte count, unconjugated bilirubin concentration, aspartate aminotransferase, serum haptoglobin, and plasma hemoglobin.

SCD is a group of hereditary hemoglobinopathies resulting from a mutation of the *β-globin* gene that leads to the production of hemoglobin S. Production of hemoglobin S can occur in a homozygous pattern (SS), which is called sickle cell anemia (SCA), or in a compound heterozygous pattern (e.g., hemoglobin S and another abnormal hemoglobin, such as hemoglobin C (SC), other rare hemoglobins (e.g., O, D punjad), or thalassemia (S beta-thalassemia)). The abnormal hemoglobin can polymerize in RBCs in different situations (hypoxemia, infection, cold, fever, dehydration, or acidosis) and can result in chronic hemolytic anemia, which can lead to acute complications, such as a vaso-occlusive crisis, acute chest syndrome, acute bone marrow necrosis, stroke, priapism, or splenic sequestration. Abnormal hemoglobin can also cause chronic organ injury, especially involving the heart, kidneys, eyes (retinopathy), skin (ulcers), or bones (aseptic osteonecrosis).

The challenge of caring for patients with SCD is to treat pain and to avoid lethal acute complications, especially severe acute chest syndrome or multiorgan failure, and to prevent chronic organ injury or to diagnose it at an early stage. The aim of this review was to give to the reader an overview of the literature covering the relevance of LDH as a biomarker in the SCD population and how this biomarker is used and interpreted in daily clinical practice.

2. Hemolysis and vascular complications

Intravascular hemolysis impairs the bioavailability of nitric oxide (NO), which is a major regulator of vascular homeostasis. Free hemoglobin released in plasma from RBC after hemolysis provokes consumption of NO, leading to vasoconstriction, endothelial expression of cell adhesion molecules and activation of hemostatic processes, such as platelet activation. The release of arginase, another RBC cytoplasmic enzyme, into the plasma during hemolysis induces a depletion of arginine by its conversion into ornithine. Arginine is a substrate of NO synthase activity, and its depletion also contributes to a reduced NO availability [5].

Recent studies suggest that inflammation is directly caused by hemolysis. Indeed, increased plasma levels of heme released by RBC during hemolysis may activate the innate immune response, notably through NLRP3 inflammasome activation, resulting in increased secretion of interleukine-1 [6].

Although LDH is ubiquitous in the body, it appears that LDH isoenzymes released from RBCs during intravascular hemolysis account for much of the serum LDH activity in SCD patients. Thus, LDH activity is used as a surrogate marker of plasma hemoglobin, NO consumption and its deleterious cascade toward endothelial damage and vascular complications [7].

3. LDH at steady state: a predictive value for chronic organ injury

3.1. Range of values at steady state

The LDH activity at steady state in patients with SCD is usually elevated, but the value depends on the type of SCD and on the type of disease-modifying treatments the patients are receiving. The median ranges of LDH activity were studied previously: 526 U/L [interquartile range: 384–691] in patients with SCA without disease-modifying treatment, 351.5 U/L [280.5–425.5] in patients with sickle cell anemia receiving long-term hydroxyurea [8], 261 U/L in patients with Hemoglobin SC disease [9], and 152 U/L [136–172] in healthy individuals [8]. In SCA, it has been shown that the range of hemolysis markers at steady state is predictive of the development or not of acute and chronic complications.

3.2. The chronic hyper-hemolysis phenotype

It has been shown that higher LDH activity at steady-state was associated with pulmonary hypertension (defined by tricuspid regurgitant jet velocity (TRV) >2.5 m/s or high N-terminal pro brain natriuretic peptide (NT-proBNP) levels) [10,11,12] and higher left ventricular mass index and diastolic dimensions, higher systemic pulse pressure [13], leg ulceration [14,15,16], priapism [17], and increased risk of death; this subgroup of patients would have fewer vaso-occlusive crises [18,19] and less osteonecrosis. These patients have significantly lower blood hemoglobin concentrations. This phenotype is called “the chronic hyper-hemolysis phenotype” [7,18,20]. The mean ranges of LDH activity were 610.6 U/L (Standard deviation 178.4) in the high hemolysis phenotype of SCA and 234.5 U/L (SD 30.5) in the low hemolysis phenotype [18]. In these studies, it has been shown that the predominant LDH isoenzymes were LDH-1 and 2, which are present in RBCs, kidneys and cardiac muscle, whereas LDH-4 and LDH-5, which are found predominantly in skeletal muscles and the liver, were within their normal range. However, further studies showed that there was no correlation between LDH activity and creatinine kinase or serum creatinine, suggesting a predominant RBC origin of elevated LDH activity at steady state [7]. Some factors were associated with a lower hemolytic component: the presence of alpha-thalassemia (single or double deletion), higher hemoglobin F, female gender, hydroxyurea therapy [20], and a single nucleotide polymorphism (SNP) in the Nitrogen Permease Regulator-Like 3 (*NPRL3*) gene [21]. This phenotype did not include an increased risk of stroke, which was shown to be correlated with low blood hemoglobin concentration (Hb <70 g/L) [22]. However, other studies also suggest that high LDH activity is an independent risk factor for abnormal cerebral velocities measured by transcranial Doppler, which predicts the development of cerebral vasculopathy [23, 24] and the occurrence of strokes [25].

The association between high LDH activity and pulmonary hypertension found in predominantly adult patients [7,18,20] was not confirmed in a pediatric cohort [26].

3.3. Hemolysis and sickle cell anemia-associated nephropathy

Kidney involvement in SCD patients is frequent and includes glomerulopathy, tubulopathy, hematuria, increased risks of urinary tract infections and renal medullary carcinoma. Glomerulopathy affects 80% of adult SCA patients older than 40 years of age [27], and it presents as microalbuminuria or macroalbuminuria and hyperfiltration [28]. The evolution of glomerulopathy leads to renal insufficiency and confers a bad prognosis. Several studies show a correlation between microalbuminuria or macroalbuminuria and increased LDH activity [28,29,30,31], suggesting that hemolysis is a major determinant of glomerular damage. One hypothesis is that intravascular hemolysis induces the release of plasma-free hemoglobin and arginase, impairing NO bioavailability, which results in a myogenic response of afferent arteriole dysregulation and to subsequent hyperfiltration [28]. However, the role of hemolysis in the development of glomerulopathy is controversial [32], implying that the mechanisms are likely to be more complex and multifactorial. It has been suggested that anemia itself would provoke renal vasodilation and cause glomerular damage by increasing blood flow. Moreover, glomerular damage could also be related to changes in rheology and to the stickiness of the sickle erythrocytes [27].

LDH has been correlated with other renal dysfunction, such as renal tubular phosphate metabolism that results in hyperphosphatemia [33] or metabolic acidosis due to a possible corticopapillary gradient, leading to impaired ammonium availability [34].

3.4. Other correlations between LDH at steady state and clinical or biological manifestations

Pulmonary changes are often observed in sickle cell patients, including obstructive changes, restrictive changes, or both. Obstructive