Clinical Utility of Lactate Dehydrogenase
A Historical Perspective

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Lactate dehydrogenase (LD), an enzyme in the glycolytic pathway (EC1.1.1.27; L-lactate: nicotinamide adenine dinucleotide [NAD+] oxidoreductase), catalyzes the oxidation of L-lactate to pyruvate with the mediation of NAD+ as the hydrogen acceptor, with the reaction being reversible.1,2 This reaction forms the basis of the measurement of LD activity in the clinical laboratory with the rate of NADH production determined spectrophotometrically at 340 nm.3 LD has a molecular mass of 134 kDa; is a tetramer of two subunits, H and M; and hence has five isoenzymes, LD1 to LD5. While LD1 comprises four H subunits (H4), LD5 comprises only M subunits (M4), and the other isoenzymes LD2 to LD4 comprise H3M, H2M2, and HM3, respectively. It is a ubiquitous enzyme present in the cytoplasm of all cells, but the isoenzyme composition varies in various tissues. LD1 is predominant in heart, erythrocytes, and the kidney, while LD5 is predominant in liver and skeletal muscle. The other isoenzymes derive mainly from leukocytes, lymph nodes, lung, and spleen.1,2

Previously, the greatest indication for LD isoenzymes in serum was for the late diagnosis of myocardial infarction, in which one observed a “flipped pattern” (ie, LD1:LD2 >1.0). However, as we showed in 1996, the advent of the troponin assays rendered this labor-intensive and time-consuming test irrelevant.4 Furthermore, this flipped pattern can occur in hemolytic diseases, renal infarction, and germ cell tumors, and hence it also lacks specificity. However, it was useful in the diagnosis of myocardial infarction if the clinician ruled out these other disorders in the pretroponin era in a patient with chest pain. Today, there is no use for LD isoenzymes in the diagnosis of myocardial infarction.5

Before we consider the utility of LD in clinical medicine, we need to consider what the correct abbreviation is for this enzyme. While clinical chemists use the abbreviation LD, others, including the International Union of Biochemistry and Molecular Biology (IUBMB), find LDH an acceptable abbreviation, especially in biological sciences (personal communication with IUBMB secretary, Michael Walsh, PhD, FRSC, September 23, 2014).

So what are the indications for requesting a serum LD level? Its use in the assessment of liver function should be largely discouraged given its widespread distribution and the superiority of transaminases and alkaline phosphatase. However, with space-occupying lesions of the liver, there is an increase in both LD and alkaline phosphatase without any appreciable increases in transaminases.2 Also, it has no value in assessing muscle disease since the creatine kinase assay is far more specific and hence superior. It appears at present that the best indications are for confirming clinical hemolysis and using it to stage and guide management of certain tumors as a biomarker.

Given the relative abundance of LD in erythrocytes, preanalytic handling that results in hemolysis causes a spurious elevation, which invalidates the clinical utility. However, with regard to in vivo hemolysis, it can prove to be a useful marker in addition to an increased indirect bilirubin, reduced haptoglobin, and increased reticulocyte count.6 Also, in megaloblastic anemias, levels can be very high due to an increase in erythroid precursor turnover in the bone marrow.

The other important clinical indication of LD measurement is in the prognosis and management of certain tumors. Its greatest value appears to be with testicular germ cell
tumors. LD1 is the isoenzyme most frequently increased in testicular cancers. Coupled with both α-fetoprotein (AFP) and human chorionic gonadotropin (HCG), LD is an important serologic marker for diagnosis, staging/prognosis, and recurrence and monitoring of germ cell tumors. Preorchietomy, the American Joint Committee on Cancer Staging recommends assaying AFP, HCG, and LD for determining a serum tumor marker status. LD activities for stages 0, 1, 2, and 3 are within the reference range, less than 1.5 times the upper limit of the reference range, 1.5 to 10 times the upper limit of the reference range, and more than 10 times the upper limit of the reference range, respectively. LD also plays an important role in advanced melanoma, a devastating disease with a very poor survival. Surprisingly, despite a host of biomarkers having been studied, serum LD levels appear to be the best available prognosticator in metastatic melanoma, with increased levels associated with decreased survival. Its significance is such that it is the rare serum biomarker included in TNM staging, with the stage of M1c being assigned when distant metastasis is present and LD is elevated. LD is also recommended in the workup of multiple myeloma and other malignancies, including non-Hodgkin lymphoma and lung cancer. However, its ubiquitous distribution is a severe handicap to its greater clinical utility.

Serum LD in combination with LD measured in pleural fluid aids in distinguishing exudative from transudative effusions. Exudates exhibit one or more of the following, termed Light criteria: (1) pleural fluid/serum protein ratio of more than 0.5, (2) pleural fluid LD/serum LD ratio of more than 0.6, or (3) pleural fluid LD activity more than two-thirds the upper limit of the serum reference range. However, this is not uniformly accepted, and the British Thoracic Society recommends only the measurement of the pleural fluid to serum ratio when the protein levels in the fluid are indeterminate (25-35 g/L). LD similarly has utility in characterizing effusions in other serous body fluids such as pericardial and peritoneal fluids. LD in cerebrospinal fluid may be used to differentiate a traumatic tap from intracranial hemorrhage as well as distinguish bacterial from viral meningitis, with an increase in LD observed in the bacterial form. Increases in LD activity, with a 40-U/L upper limit of normal, can also be seen in central nervous system leukemia, lymphoma, and metastatic carcinoma.

In conclusion, this enzyme, LD, has had an interesting journey, but today its clinical utility has been relegated to confirm hemolysis and serve as a tumor marker.

References