REVIEW

The Clinical Value of Lactate Dehydrogenase in Serum: A Quantitative Review

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Summary: The aim of this article is to describe guidelines for rational use of lactate dehydrogenase and its isoenzymes, in the diagnostic processes and during follow-up, based on a systematic review of relevant literature. Sources of data for this study were English-language scientific publications, obtained from the database of the National Library of Medicine (Medline), concerning the clinical application (diagnosis, monitoring or treatment of disease) of lactate dehydrogenase and lactate dehydrogenase isoenzyme measurements in serum in the following main clinical fields: cardiology, hepatology, haematology and oncology. For acceptance in the present review, studies had to include: a proper definition of the tested patient population, diagnostic criteria, sampling time, sampling frequency, and test characteristics.

Estimation of the relation between lactate dehydrogenase or lactate dehydrogenase isoenzymes and specific diseases expressed as sensitivity, specificity, survival or remission rate were extracted.

The application of serum lactate dehydrogenase is relevant in the diagnosis of myocardial infarction (late detection), haemolytic anaemia, ovarian dysgerminoma and testicular germ cell tumour. For monitoring the progress of a disease lactate dehydrogenase is relevant in establishing the survival duration and rate in Hodgkin’s disease and non-Hodgkin’s lymphoma, and in the follow-up of ovarian dysgerminoma. Rational use of lactate dehydrogenase can be achieved when requests for its determination are limited to the above mentioned conditions. No rationale could be found for measuring lactate dehydrogenase isoenzymes.

Introduction

A proper way to reduce the number of requests for diagnostic laboratory tests is to identify those clinical situations in which the requested test provides critically useful information. This can be achieved either by focusing primarily on the differential diagnosis or on the laboratory test itself. The former approach is included in textbooks of medicine, in which several diseases are described complete with the matching laboratory tests. We have chosen the latter approach, i.e. we have evaluated the usefulness of one laboratory test in different clinical situations.

There are several publications on the guidelines for evaluating diagnostic tests (1, 2), but the use of the test as the starting-point of the investigation is mentioned in only a few cases, each involving a different approach. Sox et al. (3) screened the literature on erythrocyte sedimentation rate, and their study resulted in guidelines for rational use. Veldhuyzen van Zanten et al. (4) performed a prospective study to test the clinical importance of routine measurement of liver enzymes, and the American Medical Association in its Diagnostic and Therapeutic Technology Assessment project started from the laboratory test itself, by establishing the efficiency of maternal serum a-fetoprotein testing in detecting Down’s Syndrome (5).

This article describes the results of a systematic review of relevant literature on the clinical value of the determination of lactate dehydrogenase¹ and its isoenzymes in serum, and gives an indication of when and when not to request this laboratory test.

¹ Enzymes mentioned in the text:
Lactate dehydrogenase:
L-lactate : NAD⁺ oxidoreductase, EC 1.1.1.27.
Creatine kinase:
adenosine triphosphate creatine N-phosphotransferase, EC 2.7.3.2.
Enolase:
phosphopyruvate hydratase, EC 4.2.1.11.
Alkaline phosphatase:
orthophosphoric-monoester phosphohydrolase, EC 3.1.3.1.
Searching Methods

According to six textbooks of medicine, there are four main clinical fields in which serum lactate dehydrogenase is applicable to the diagnosis and treatment of patients: cardiology, hepatology, haematology and oncology (6–11). Lactate dehydrogenase was evaluated by reviewing relevant literature obtained with the aid of the computerized bibliographic search systems, Compact Search Cambridge (cardiology and hepatology) and Silver Platter (Spirs) version 3.1 (haematology and oncology). The relevance of all selected papers was judged by applying pre-defined criteria for inclusion. Effectiveness of lactate dehydrogenase was in most clinical fields expressed by sensitivity and specificity. In haematology and oncology, however, remission and survival rate were frequently used test criteria. Our goal was to look for English-language scientific publications about the relation between lactate dehydrogenase and lactate dehydrogenase isoenzyme measurements in human serum and the four clinical specialities. The applied search strategies were:

Cardiology

First, the titles of the manuscripts published in 1987—1996 had to contain the terms “lactate dehydrogenase” and “myocardial”. Second, “lactate dehydrogenase”, “myocardial” and “creatine” had to be defined as major or minor subject headings, used in the title or used in the abstracts of manuscripts published in 1988—1996.

Hepatology

First, the title of the manuscript had to contain the terms “lactate dehydrogenase” and “liver”. Second, the major subject headings “liver function tests” and “liver disease” were combined with the major subject heading “lactate dehydrogenase”. Both strategies were used for searching the period 1983—1996.

Haematology

The medical subject heading (MeSH) term “lactate dehydrogenase” was combined with “leukaemia”, “anaemia” and “neoplasm invasiveness”, respectively, all from the Thesaurus list. The subject heading list contained the subjects “analysis, blood, diagnostic use” and “therapy”. In this way the years 1985—1996 were searched. With the search strategy of combining “lactate dehydrogenase” with “anaemia, megaloblastic, Hodgkin and non-Hodgkin”, respectively, and the subject headings “analysis, blood, diagnostic use and therapy”, the years 1985—1996 were searched. These MeSH terms were obtained from the Thesaurus list as well.

Oncology

The MeSH term “lactate dehydrogenase” was combined with “tumour-marker-biology” and “neoplasm invasiveness”, respectively, both from the Thesaurus list. The subject heading list contained the subjects “analysis, blood, diagnostic use” and “therapy”. In this way the period 1985—1996 was searched.

The references mentioned in all selected publications were the next source of information. Relevance of all papers was judged by applying inclusion criteria. We selected publications describing the clinical value (diagnosis, monitoring or treatment of the disease) of lactate dehydrogenase or lactate dehydrogenase isoenzyme measurements in serum. In these publications a proper definition of the tested patient population, diagnostic criteria (gold standard), sample time, sample frequency, and test characteristics like sensitivity and specificity of lactate dehydrogenase with regard to a specific disease had to be described. However, handling of these inclusion criteria depends on the clinical field for which lactate dehydrogenase was used. For cardiology (acute myocardial infarction) a proper definition of the tested population, sampling moment and frequency must be clarified, while in the case of tumour diagnosis the precise time and frequency of sampling are less important. In all studies confirmation of the disease (gold standard) without use of lactate dehydrogenase should be properly defined, in oncology for instance by use of histological investigation and in acute myocardial infarction patients by ECG and a typical creatine kinase MB1 value or pattern.

Results

Cardiology

The applied search criteria resulted in 34 publications. Ten publications plus 5 references (12—26), all about acute myocardial infarction, were included. The tested population of most studies consisted of consecutive patients admitted to a coronary care unit, but populations of geriatric patients and patients selected by the laboratory computer were also described. Criteria used for diagnosing creatine kinase MB differed strongly between the authors or were not even stated, as were sample time and frequency. In most manuscripts test characteristics like sensitivity and specificity were mentioned. In other cases they could be calculated, using data from tables and/or figures. Because the subject heading “creatine” was used in the second search, studies on lactate dehydrogenase and creatine kinase isoenzyme MB could also be included. After selection and combination of the most appropriate studies, validation of the lactate dehydrogenase determination and comparison with creatine kinase MB activity at different time intervals became possible (17, 23—26).

Loughlin et al. (17) did not specify their gold standard for acute myocardial infarction, but further information showed that they had used the diagnostic criteria from a preceding study, including positive creatine kinase MB activity (29). Galbraith et al. (23) used receiver-operating characteristic (ROC) curves to assess the diagnostic utility of lactate dehydrogenase, lactate dehydrogenase-1 and several isoenzyme ratios at 6 hour intervals up to 95 hours after the onset of a myocardial infarction, as did Jensen et al. for lactate dehydrogenase-1 on five consecutive days (24). Levinson et al. (25) showed ROC-curves for the lactate dehydrogenase-1/lactate dehydrogenase-2 ratio, lactate dehydrogenase-1 (U/l) and lactate dehydrogenase-1 (%) measured in samples obtained within 24 hours after admission, and Painter et al. (26) compared a new lactate dehydrogenase-1 assay with existing lactate dehydrogenase-1 methods. Because results of the lactate dehydrogenase-1/lactate dehydrogenase-2 ratio (25) and the existing lactate dehydrogenase-1 method (26) were used for diagnosing acute myocardial infarction, published characteristics based on these measurements are not presented in this review. After combining results of all authors, ROC curves could be drawn for the first 24 hours after onset of complaints, and also for the optimum time interval (see figs. 1 and 2). Serum lactate dehydrogenase and lactate dehydrogenase isoenzyme measurements at about 24 hours after the first onset of pain resulted in sensitivities of about 95% and specificities of less than 90%, with the excep-
Fig. 1 Sensitivity and specificity of lactate dehydrogenase (U/l), + lactate dehydrogenase-1 (U/l), lactate dehydrogenase-1 (%), lactate dehydrogenase-1/lactate dehydrogenase-2 and lactate dehydrogenase-1/lactate dehydrogenase-4 determined about 24 hours after the first onset of pain (17, 23–26).

Fig. 2 Sensitivity and specificity of lactate dehydrogenase and lactate dehydrogenase isoenzymes determined at their optimum time interval. □ lactate dehydrogenase (U/l), 19–24 h; + lactate dehydrogenase-1 (U/l), 19–24 h, 48 h; □ lactate dehydrogenase-1 (%), 67–72 h; △ lactate dehydrogenase-1/lactate dehydrogenase-2 43–48 h, 55–60 h; × lactate dehydrogenase-1/lactate dehydrogenase-4 31–60 h, 55–60 h (17, 23, 24).

Hepatology

The activity (U/g) of lactate dehydrogenase in liver cells (95% of which is lactate dehydrogenase-5) is about 1/3 of that of myocardial cells, but 1800 times that in serum (30). For this reason Lott et al. (30) and Zimmerman (31) considered lactate dehydrogenase as a possible enzyme test for the diagnostic use in liver disease, although the latter drew attention to the relatively moderate elevation of lactate dehydrogenase. Sherlock (32) pointed out the strong rise in activity in neoplastic liver disease and considered it to be a rather insensitive determination for other forms of liver disease. Johnson & McFarlane did not even mention lactate dehydrogenase in their work on “The Laboratory investigation of liver disease” (33).

The first screening in the search strategy resulted in 661 articles published between 1983 and 1996. Only a few of these indicated a close relation between lactate dehydrogenase, its isoenzymes and the liver. In three of the selected articles an overview was given of laboratory investigations in liver disease. Chopra et al. (34) considered the lactate dehydrogenase determination to be nonspecific; only a continuous elevation in combination with a high level of alkaline phosphatase \(^1\) could be taken as an indication of liver metastases. Reichling et al. (35) pointed out that lactate dehydrogenase is less specific than the transaminases and thus of smaller diagnostic value. Other authors reviewing the relevance of enzyme tests in liver disease never mentioned lactate dehydrogenase (36–38). Finally, an editorial in The Journal of the American Medical Association commented on lactate dehydrogenase as the least specific enzyme test in liver disease (39).

The two fields in which lactate dehydrogenase (and its isoenzymes) are claimed to contribute are tumour diagnostics and liver transplantation. On suspicion of liver metastases the determination of lactate dehydrogenase and lactate dehydrogenase isoenzymes was reported to give a valuable contribution to the final diagnosis (40). However, in the differentiation of a primary liver tumour from secondary metastases, the determination of \(\alpha\)-fetoprotein is more powerful (41). In orthotopic liver transplantation performed in paediatric patients, the lactate dehydrogenase-5/lactate dehydrogenase-2 ratio seems to be a good indicator of early graft function and complications (42).

Haematology

The search strategy resulted in 93 publications on the measurement of the activities of lactate dehydrogenase and lactate dehydrogenase isoenzymes in serum and all types of blood cells. Studies on serum lactate dehydrogenase measurements in four frequently reported leukaemias were included (acute- and chronic lymphatic leukaemia, and acute and chronic myeloid leukaemia), as
well as studies on anaemia (megaloblastic, haemolytic and iron deficiency), Hodgkin’s disease and non-Hodgkin’s lymphoma. These criteria resulted in 24 publications (43–64, 65, 68). Patients in whom non-Hodgkin’s lymphoma was diagnosed, were mostly classified according to the histopathological classification scheme of Kiel. Classifications according to Rappaport or Lennert (low-, intermediate- and high grade) were used too. Ann Arbor criteria, used for clinical staging (stage I–IV), were applied in 6 of the 10 selected manuscripts. Test characteristics used were mean serum lactate dehydrogenase activity, sensitivity, specificity, remission duration and rate, and survival duration and rate. Most authors divided the tested population into different groups based on the measured lactate dehydrogenase activity, the grade of malignancy or stage of disease, and established the remission- or survival rate subsequently. For comparison, we processed the data from these studies in the following way. First, the mean lactate dehydrogenase activity of the patient populations tested was divided by the upper reference limit. Hicsönmez et al. (45) did not give their reference interval; therefore we chose an arbitrary upper reference limit of 450 U/l. Second, the remission- and survival duration and rate of the patient population with a normal lactate dehydrogenase activity was divided by the duration and rate of the patients with an elevated lactate dehydrogenase activity. In this way different remission and survival intervals could be combined in one table.

Leukaemia

The highest lactate dehydrogenase activity and sensitivity was measured in acute lymphatic leukaemia. In chronic myeloid leukaemia, the activity and sensitivity of lactate dehydrogenase varied strongly: 1.9–3.9 times the upper limit of normal, and 33%–100%, respectively (tab. 1). Flanagan et al. (49) measured increased values in all their chronic myeloid leukaemia patients, but Kornberg et al. (43) only detected high values in samples of chronic myeloid leukaemia patients suffering from a blastic crisis; whether Flanagan’s population consists of patients with blastic crises is unknown. Patel et al. (50) measured in their chronic myeloid leukaemia population a mean lactate dehydrogenase value of 575 U/l which is 3 times the upper reference limit, and they calculated the sensitivity and specificity for leukaemia in general. The chronic myeloid leukaemia patients tested by Buchsbaum et al. (51) were divided into two groups, remission or not; sensitivity and specificity for lactate dehydrogenase-3 were 90% and 72%, respectively. In both acute myeloid- and chronic lymphatic leukaemia, lactate dehydrogenase activity was hardly elevated and a low sensitivity was found. A negative correlation between the duration of the remission and serum lactate dehydrogenase activity was demonstrated in acute lymphatic- and acute myeloid leukaemia patients (44, 47, 48).

Anaemia

In almost all megaloblastic and haemolytic anaemia patients a high serum lactate dehydrogenase activity was detected (52, 53). The highest values measured in megaloblastic anaemia were up to 29 times the upper reference limit. Carmel et al. (54) reported a study on serum transferrin receptor in megaloblastic anaemia due to cobalamin deficiency. Only 19 of their 32 patients had a pathological lactate dehydrogenase value. However, not all patients had megaloblastic anaemia as suggested in the title of their manuscript, and diagnostic criteria were not clearly defined. In iron-deficiency anaemia, the serum lactate dehydrogenase remained normal. Because of the high concentration in erythrocytes, lactate dehydrogenase is a good marker for haemolysis. A free haemoglobin concentration in serum of 6–12 μmól/l caused by disrupted erythrocytes, results in an increased lactate dehydrogenase activity of 10–20 U/l (55, 56).

Hodgkin’s disease

Two of the selected studies concerned Hodgkin’s disease (49, 59). Sensitivity was very low, and increased serum lactate dehydrogenase values were found only in very ill patients. Schilling et al. (59) demonstrated a significant reduction of survival with increasing serum lactate dehydrogenase activity. The median survival of Hodgkin patients with lactate dehydrogenase below the upper reference limit was 129 months, and above the upper reference limit the median survival was 39 months.

Non-Hodgkin lymphoma

In serum of low grade, stage I–II non-Hodgkin patients, both the mean serum lactate dehydrogenase activity and sensitivity were low. Increased activities were found in stage IV patients and high grade lymphoma (49, 60–62, 64, 65). However, Lindh et al. (64) measured a low lactate dehydrogenase activity in nearly all low grade non-Hodgkin patients whether they were classified stage I, II, III or IV. The correlation of an unfavourable histopathological classification with high serum lactate dehydrogenase activities has already been reported by Erickson & Morales in 1961 (66, 67). In all clinical situations, the sensitivity was less than 61%. Two authors determined lactate dehydrogenase isoenzymes in the serum of non-Hodgkin patients. Ricerra et al. (62) measured a disturbed ratio, namely decreased lactate dehydrogenase-1 and increased lactate dehydrogenase-3 fractions, which occurred in all stages and classifications of the disease, while Ferraris et al. (57) could not find any significant modification of the isoenzyme pattern.
Tab. 1 Clinical value of lactate dehydrogenase in haematology

<table>
<thead>
<tr>
<th>Disease (References)</th>
<th>Activity Multiple of upper limit of normal</th>
<th>Sensitivity (%)</th>
<th>Remission Duration</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphatic leukaemia (43, 44—46, 48, 50)</td>
<td>3.3—3.9</td>
<td>79</td>
<td>2—3 ns</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukaemia (43, 47, 50)</td>
<td>1.0—2.5</td>
<td>26—68</td>
<td>2 ns</td>
<td></td>
</tr>
<tr>
<td>Chronic lymphatic leukaemia (43, 49)</td>
<td>1.0</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic myeloid leukaemia (43, 49, 50) lactate dehydrogenase-3 (51)</td>
<td>1.9—3.9</td>
<td>33—100</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Anaemia: (52, 53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>megaloblastic</td>
<td>6.4</td>
<td>1.9—29.2a</td>
<td>88—100</td>
<td></td>
</tr>
<tr>
<td>iron deficiency</td>
<td>1.0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>haemolytic</td>
<td>2.4</td>
<td>1.2—13.7</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease (49, 59)</td>
<td>1.0</td>
<td>31—38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Hodgkin’s disease (49, 57—64) low gradeb</td>
<td>1.0—1.5</td>
<td>11—38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>high grade</td>
<td>3.0—3.3c</td>
<td>42—60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Activity is defined as measured activity divided by the upper limit of normal; remission- and survival duration or rate are defined as the duration or rate in the patient population with a normal lactate dehydrogenase activity divided by the duration or rate in the patient population with an elevated lactate dehydrogenase activity; rate: the percentage of patients who survived or attained remission; ns: the difference between the remission rate in patients with a normal lactate dehydrogenase and patients with an elevated lactate dehydrogenase was not significant;

The prognostic value of serum lactate dehydrogenase (in non-Hodgkin’s lymphoma was determined in two different ways: survival duration and survival rate (probability of survival). Ferraris et al. (57) divided their non-Hodgkin population into three groups with a low, median and high lactate dehydrogenase activity. The median survival of these groups was 72.5, 31.1 and 4.6 months, respectively. The survival rate was measured by six different authors after 2, 3 and 5 years. All demonstrated a negative correlation between the pretreatment serum lactate dehydrogenase activity and the probability of survival (58, 60, 51, 63—65). After autologous bone marrow transplantation lactate dehydrogenase was one of the main prognostic markers associated with a short disease-free survival. In transplanted patients, a high lactate dehydrogenase level was associated with a 2.5 times increase in relapse rate (68).

Oncology

The search criteria resulted in 208 articles covering a wide field and a variety of different diseases. From the relevant publications those neoplasms which were encountered twice or more were included. In this way 16 publications about ovarian dysgerminoma, small cell lung cancer and testicular germ cell tumour (seminoma and non-seminoma) were selected (69—73, 76—78, 80—83, 85—88).

Ovarian dysgerminoma

Four of the five publications on this rare disease were case reports; the remaining one was a small review (69—73). Because two of the selected publications contained results about α-fetoprotein, carcinoembryonic antigen and human chorionic gonadotropin measurements in dysgerminoma and primary carcinoma of the ovary, comparison of lactate dehydrogenase with these markers was possible (tab. 2). To assess diagnostic strength, two other studies about lactate dehydrogenase and lactate dehydrogenase isoenzymes in patients with primary carcinoma of the ovary have been included for comparison (74, 75). Sensitivity and specificity of lactate dehydrogenase was calculated by comparing 5 patients positive for ovarian dysgerminoma with 69 patients suffering from all other kinds of malignant and benign ovarian tumours (70). Kikuchi et al. (75) determined sensitivity and specificity in 57 patients with primary carcinoma of the ovary, and compared the obtained results with those from 220 patients with benign ovarian tumours. Other test characteristics used were median activity and response to therapy (tab. 2).
<table>
<thead>
<tr>
<th>Laboratory test (References)</th>
<th>Activity</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian dysgerminoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (69–73)</td>
<td>4.5 (1.1–109)</td>
<td>92–100</td>
<td>66a</td>
<td>100</td>
</tr>
<tr>
<td>Lactate dehydrogenase-1–3 (69, 70)</td>
<td>elevated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Fetoprotein (69, 71)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoembryonic antigen (69, 71)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human chorionic β gonadotropin (69, 72)</td>
<td>1–18.6</td>
<td>42–71</td>
<td>71a</td>
<td>93b</td>
</tr>
<tr>
<td>Other ovarian tumoursb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (70, 74, 75)</td>
<td>1.4</td>
<td>42–71</td>
<td>87b</td>
<td>66</td>
</tr>
<tr>
<td>Lactate dehydrogenase-1 (74)</td>
<td>1.1</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase-4 (75)</td>
<td>2.2</td>
<td>42</td>
<td>93b</td>
<td></td>
</tr>
</tbody>
</table>

Specificity based on:

a 74 ovarian tumours (different types) including 5 dysgerminoma; b 57 primary carcinoma and 220 benign tumours of the ovary; c serous cystaden-, mucious cystaden-, endometroid-, meso-nephroid- and clear cell carcinom;

In all the reported cases of ovarian dysgerminoma only one patient had a normal serum lactate dehydrogenase while the others showed elevated values up to 109 times the upper reference limit. Thus, sensitivity is nearly 100%, but specificity only 66% (70). After removal of the tumour, serum lactate dehydrogenase decreased, and recurrence of the disease was accompanied by re-elevation of lactate dehydrogenase (72, 73). Measurement of the isoenzymes showed an elevated lactate dehydrogenase-1 to lactate dehydrogenase-3, or changing fractions, depending on the progress of the disease (69, 73). In one case, an elevated β human chorionic gonadotropin was reported (69), while in that of Pressley et al. both β human chorionic gonadotropin and α-fetoprotein were negative (72). Sensitivity of lactate dehydrogenase and lactate dehydrogenase isoenzymes for other ovarian tumours was less, but a specificity of nearly 90% or even 93% was found for lactate dehydrogenase-4.

Small cell lung cancer

Seven of the eight manuscripts were included. In these studies small cell lung cancer was histologically proven. In the remaining one the authors mentioned only that they had reviewed the cases of 103 small cell lung cancer patients (79). In five studies the change of lactate dehydrogenase as an indicator of response to therapy was determined. One author calculated the relation between the response to therapy and the lactate dehydrogenase level at presentation (81). Other test characteristics used were median activity, sensitivity, specificity and survival rate. In several studies the patient population was divided into two groups, depending on the spread of the tumour: limited (local) disease and extended disease. Starting from these groups, test characteristics were determined. Four authors also measured neuron-specific enolase1) in addition to serum lactate dehydrogenase activity (78, 80–82). Compilation of these results in table 3 enables a comparison between the two potential tumour markers.

An elevated mean lactate dehydrogenase activity was found only in the serum of small cell lung cancer patients with extended disease (results not shown). The sensitivity is therefore low (78, 80, 82). Cerny et al. (77) and Lassen et al. (83) reported a survival rate of patients with an elevated lactate dehydrogenase which was about half that of the group with a normal lactate dehydrogenase. In the population of Johnson et al. (81), all patients with an elevated lactate dehydrogenase died within two years, while 23% of the group with a low lactate dehydrogenase survived. Progression of the disease was associated with an increase in lactate dehydrogenase in only 56% of the patients. In 93% of the patients progression was associated with an increase in neuron-specific enolase (82). The sensitivity and survival rate for neuron-specific enolase, like its ability to indicate the response to therapy, exceed those of lactate dehydrogenase (82). On the other hand, lactate dehydrogenase levels above normal when measured at presentation were significantly associated with a low response to therapy, while neuron-specific enolase levels did not correlate with the response to treatment.

Testicular germ cell tumour

Of the five selected manuscripts about testicular germ cell tumour, three were published by von Eyben et al. (84, 85, 88). In two of these manuscripts the same patient population was described, we therefore ruled out the oldest one (84). The two remaining studies concerned testicular germ cell tumours (seminoma and non-seminomas). Munro et al. (87) and Fosså et al. (86) selected patients suffering from pure seminomas. Except
Table 3: Clinical value of lactate dehydrogenase in oncology: Small cell lung cancer

<table>
<thead>
<tr>
<th>Laboratory test (References)</th>
<th>Stage of disease</th>
<th>Sensitivity (%)</th>
<th>Survival (rate)</th>
<th>Response to therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Id + ed</td>
<td>37–58</td>
<td>2–23</td>
<td>33–96</td>
</tr>
<tr>
<td>Lactate dehydrogenase (76–83)</td>
<td>Id</td>
<td>21–38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ed</td>
<td>42–68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuron specific enolase (78, 80–82)</td>
<td>Id + ed</td>
<td>77–85</td>
<td>27</td>
<td>98–100</td>
</tr>
<tr>
<td></td>
<td>Id</td>
<td>69–87</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ed</td>
<td>83–86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Id: limited disease; ed: extended disease; survival rate is defined as the rate in the patient population with a normal lactate dehydrogenase activity divided by the rate in the patient population with an elevated lactate dehydrogenase activity; rate is the percentage of patients who survived.

For the latter publication, diagnosis of testicular germ cell tumour was histologically proven by all authors. Three authors included a reference population in their study: patients with a benign testis disorder, and people without disease (85, 86, 87). In one study the patient population was divided randomly into two groups: one group to obtain a data set for generating work hypotheses/strategies based on the performance of the measured tumour markers, and the second one as a test set to investigate the generated hypotheses. The results obtained from the data generating set were given by ROC curves from which the sensitivity and specificity of the tumour markers could be read (87). The test characteristics (likelihood ratio, true positive and false positive rate) obtained with the strategy which performed best (a combination of β human chorionic gonadotropin and lactate dehydrogenase and placental alkaline phosphatase) were recalculated to the matching sensitivity and specificity. Other test characteristics used were mean activity and survival rate.

Sensitivity of all tumour markers including lactate dehydrogenase in testicular germ cell tumour is low (table 4).

The best results (71%) were obtained with lactate dehydrogenase-1. The specificity of most markers was quite high, especially for lactate dehydrogenase-1 and β human chorionic gonadotropin. A combination of β human chorionic gonadotropin or lactate dehydrogenase and placental alkaline phosphatase, did not result in much extra information when compared with a single β-human chorionic gonadotropin measurement. When comparing initially β human chorionic gonadotropin negative patients with patients who have elevated pre-treatment β human chorionic gonadotropin, no significant difference in survival was measured. Using lactate dehydrogenase as a marker, patients with a low starting value seem to have a poorer prognosis than the patient population with an elevated lactate dehydrogenase activity (86). However, in a study of von Eyben, lactate dehydrogenase-1 was found to be a significant predictor of survival. After 3 years, 100% survival was measured in testicular germ cell tumour patients with pre-treatment normal lactate dehydrogenase-1 versus 60% survival in the patient population with an elevated lactate dehydrogenase-1.

Table 4: Clinical value of lactate dehydrogenase in oncology: Testicular germ cell tumour

<table>
<thead>
<tr>
<th>Laboratory test (References)</th>
<th>Activity Multiple of upper limit of normal</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase (86–88)</td>
<td>2.5</td>
<td>40–60</td>
<td>93b–95c</td>
<td>0.6 p = 0.08</td>
</tr>
<tr>
<td>Lactate dehydrogenase-1 (85, 88)</td>
<td>1.5</td>
<td>71</td>
<td>100a</td>
<td>1.7</td>
</tr>
<tr>
<td>α-Fetoprotein (85, 88)</td>
<td></td>
<td>29–45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human chorionic gonadotropin (85–88)</td>
<td>4.7</td>
<td>24–50</td>
<td>99–100</td>
<td>1.4 p = 0.17</td>
</tr>
<tr>
<td>Placental alkaline phosphatase (87)</td>
<td>3.3</td>
<td>45</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Human chorionic gonadotropin or lactate dehydrogenase and placental alkaline phosphatase (87)</td>
<td>3.3</td>
<td>54</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

Activity is defined as measured activity divided by the upper limit of normal; survival rate are defined as the rate in the patient population with a normal lactate dehydrogenase activity divided by the rate in the patient population with an elevated lactate dehydrogenase activity; rate: the percentage of patients who survived; specificity based on:

a 25 benign and 21 malignant tumours,
b 22 patients suspected of testes cancer with benign histology and 105 malignant tumours,
c 1717 samples from patients known to be disease free,
d human chorionic gonadotropin > 61 U/l or lactate dehydrogenase > 400 U/l and placental alkaline phosphatase > 60 U/l.
Discussion

The enzyme lactate dehydrogenase is distributed widely in the body. This fact, together with the general trend towards rationalization of laboratory requests, raises doubts about the relevance of lactate dehydrogenase in medicine. To identify clinical situations in which the determination of lactate dehydrogenase and its isoenzymes in serum are of real value, we reviewed relevant literature obtained by a computerized bibliographic search system. In trying to structure the evaluation process we defined four main clinical fields: cardiology, hepatology, haematology and oncology. We realize that working in this way probably excludes a few clinical applications of lactate dehydrogenase, but they concern only a very minor fraction of all lactate dehydrogenases measured in our laboratory.

A systematic literature search like this presents the state of the art over a short period of time. In all applications reported technical progress can lead to better diagnostic tools. These may change the diagnostic efficiency of lactate dehydrogenase; the diagnosis of Pneumocystis carinii pneumonia serves as an example. Thus, in both “Internal medicine” by Stein et al. and the “Cecil textbook of medicine” (9, 11) lactate dehydrogenase is mentioned as a sensitive marker of Pneumocystis carinii pneumonia, based on a publication of Zaman et al. (89). This study appeared in 1988 which for Pneumocystis carinii pneumonia is a long time ago. In the early days of acquired immunodeficiency syndrome (AIDS), the diagnosis of Pneumocystis carinii pneumonia was established in a late stage, since clinicians were at the time unacquainted with this disease. Therefore, the lungs were already damaged, which resulted in high levels of lactate dehydrogenase. Nowadays, Pneumocystis carinii pneumonia is diagnosed in an early stage by detecting Pneumocystis in bronchoalveolar lavage fluid. So, the increased clinical experience resulted in a lower sensitivity of lactate dehydrogenase, which rendered lactate dehydrogenase obsolete as a diagnostic tool in Pneumocystis carinii pneumonia.

In cardiology the measurement of lactate dehydrogenase and lactate dehydrogenase isoenzymes is a good method for the late detection (>36–48 hours after the first onset of complaints) of a myocardial infarction (see figures 1 and 2). In particular, the lactate dehydrogenase-1/lactate dehydrogenase-2 ratio with a diagnostic efficiency of 93%–98% gives the best information. For an early diagnosis, the determination of creatine kinase MB is superior, particularly in its specificity, to the lactate dehydrogenase and lactate dehydrogenase isoenzyme determination.

To monitor non-cancer disease in the liver neither lactate dehydrogenase nor its isoenzymes make a real contribution to the diagnostic process. Ample alternatives with higher sensitivity and specificity exist. Although little has been published on the use of lactate dehydrogenase and lactate dehydrogenase isoenzymes in liver malignancies, the enzyme does not emerge as the method of choice in this field of clinical enzymology at all.

In haematology lactate dehydrogenase is of little diagnostic value. It makes a substantial contribution only in megaloblastic- and haemolytic anaemia. However, lactate dehydrogenase-3 isoenzyme seems to be a useful marker for detecting chronic myeloid leukaemia and monitoring changes of active disease into remission. Prognostic value could be attributed to lactate dehydrogenase for Hodgkin’s disease and non-Hodgkin’s lymphoma survival; duration and rate decrease with a higher pre-treatment lactate dehydrogenase activity.

Presumably because dysgerminoma is a rare disease, no extensive studies on the diagnostic value of lactate dehydrogenase were found during the literature search. However, from the few case reports and the review it can be concluded that lactate dehydrogenase is valuable in diagnosis and follow up of therapy control.

In cases of small cell lung cancer, lactate dehydrogenase performs less than neuron-specific enolase; both markers have a prognostic value in survival and can be used in monitoring the therapy. The only advantage of lactate dehydrogenase over neuron-specific enolase seems to be the correlation between the marker level at presentation and the response to therapy.

In testicular germ cell tumour, lactate dehydrogenase-1 isoenzyme shows the best sensitivity and specificity, as well as prediction of survival. A good alternative is β human chorionic gonadotropin. Combination of β human chorionic gonadotropin, lactate dehydrogenase and placental alkaline phosphatase increases the low sensitivity (50%) by only 4%.

The final conclusions concerning relevant indications for the determination of total serum lactate dehydrogenase and in some cases its isoenzymes are: determination of serum lactate dehydrogenase is significant in the late detection of myocardial infarction, diagnosis of megaloblastic and haemolytic anaemia, establishing the survival duration and rate in Hodgkin’s disease and non-Hodgkin’s lymphoma, and diagnosis and follow up of ovarian dysgerminoma. Lactate dehydrogenase-1 isoenzyme is a rather sensitive marker in the diagnosis of testicular germ cell tumour. When the indications for lactate dehydrogenase are confined to the above clinical situations, lactate dehydrogenase will no longer be used in a non-specific manner as the “erythrocyte sedimentation rate of clinical enzymology”.

In our opinion in clinical chemistry this kind of systematic review should be performed for the top 50, and possibly more, determinations. We realize this is a complex
task, especially when the test of choice, in this case lactate dehydrogenase, is used in nearly all medical disciplines. On the other hand, we think that especially these generally used laboratory tests need to be examined.

Only then will clinical chemistry be able to present itself as a clinical discipline with clear indications of how to use the data it produces.

References


Received February 14/May 16, 1997
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