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Lactate dehydrogenase as an indicator of liver, muscular and cancer diseases

Ali Abdul Hussein Sadeq AL-Janabi*, Zahraa Qasum Ali, Zahraa Muhammed Noree

Department of Clinical Laboratories, Collage of Applied Medical Sciences, University of Karbala, Karbala, Iraq

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ABSTRACT

Objective: To determine lactate dehydrogenase (LDH) level as an indicator of liver, muscular or cancer diseases in patients of more than 40 years of age.
Methods: Ninety-one patients (43 females and 48 males) had been tested for LDH and liver function tests (LFTs). Creatine kinase (CK) levels were measurement only in patients who had high levels of LDH.
Results: As an indicator for liver diseases, high levels of LDH and one or more of LFTs, especially alkaline phosphatase, had been observed in 12 patients (8 females and 4 males). For muscular damage, measurement of CK in patients with elevated levels of LDH and normal levels of LFT revealed that CK values elevated in three males and one female. Whereas high LDH levels, as an indicator for cancer diseases, were found in three males and one female who had normal values of LFTs and CK.
Conclusions: LDH can be regarded as a good biomarker for diagnosis of liver, muscular and cancer diseases. There is little variable between males and females in the elevated value of LDH. Patients who had high values of LDH, although they had normal levels of LFTs and CK are proposed to have unidentified cancer disease.

1. Introduction

Lactate dehydrogenase (LDH) found in different types of human tissues is an oxidoreductase enzyme (EC 1.1.1.1.27). Although LDH is tetrameric enzyme, only two subunits have been determined: H for heart and M for muscle[1]. The main function of LDH is converting pyruvic acid, the final product of glycolysis, to lactic acid and vice versa in muscle through production of cellular energy[2]. However, it is normally located in small amounts in most of active organs. Thus, high level of this enzyme may indicate unusual conditions that can result from liver, muscular disorder (*e.g.* acute myocardial infarction)[3] and even from cancer disease. Moreover, total LDH level may elevate in blood of patients suffering from various diseases such as allergy[4], but not in patients with chronic obstructive pulmonary disease[5].

In the absence of liver and muscle diseases, high level of LDH is considered to be one of more specific indicator for different types of cancer. In patients with breast cancer, early and late stage of this type of cancer can also be monitored by LDH[6,7]. High level of LDH also described in other types of cancer, such as in 13.5% of non-small cell lung cancer patients[2] and in children with Hodgkin lymphoma[8].

The measurement of LDH as indicator for liver or muscular disorder or as biomarker for cancer disease in suspected patients was the main aim of this study.

2. Materials and methods

2.1. Patients

Ninety-one out and in patients (43 females and 48 males) in AL Hussein General Teaching Hospital at Karbala Province (Iraq) were involved in our study from July to August 2014. All patients age up to 40 years old. The clinical examination by physician confirmed that all patients showed signs of abnormal liver functions. Thus, liver function tests (LFTs) were suggested for those patients.

2.2. Reagents

Alanine transaminase (ALT); aspartate transaminase (AST), and alkaline phosphatase (ALP) were purchased from Abbott

*Corresponding author: Ali Abdul Hussein Sadeq AL-Janabi, Department of Clinical Laboratories, Collage of Applied Medical Sciences, University of Karbala, Karbala, Iraq.

E-mail: aljanabi_bio@yahoo.com

Diagnostics (USA), creatine kinase (CK) and LDH were purchased from Human Gesellschaft für Biochemica und Diagnostica mbH (Germany).

2.3. Samples collection

Serum of all patients was analyzed for ALT, AST and ALP levels as LFTs by automatic instrument of Architect plus, C 4000 from Abbott Diagnostics (USA) with reagents of the same company. LDH levels were measured by using liquid UV method that modified based on the recommendations of the Scandinavian Committee on Enzymes. Briefly, 20 μL of each patient serum was mixed first with 1 000 μL of buffer (pH 7.35) supplied by the manufacturing company and incubated for 1-5 min at 25 ℃. A volume of 250 μL of substrate that composed of nicotinamide-adenine dinucleotide (0.75 mmol/L) and sodium azide (0.095%) was added to the mixture. After mixing, the absorbance at 340 nm was read by UV-visible spectrophotometer (CECiL, CE 1021, England) after 1 min. CK levels were assayed according to Humazym M-test as described by the instructions of the produced company.

2.4. Statistical analyses

Data of all biochemical tests were expressed as mean ± SD. The value were analyzed statistically with paired *t*-test between test value of patient and normal individual. The minimum level of *P* value was < 0.01 considered as significant level.

3. Results

From Tables 1 and 2, the values of LDH and LFT in males and females were variable. From 91 patients, 27 females and 28 males showed normal levels of LDH and LFT. Most of patients (9 males and 6 females) who had normal LDH levels revealed elevation values of one or more of LFTs, while high LDH and LFTs level observed in large number in females (8 patients) than in males (4 patients). Otherwise, normal level of LFTs that associated with high level of LDH was clearly observed in males (7 patients) than in females (2 patients) with a significant difference from normal patients.

Table 1
Values of LDH in females with high levels of one or more of LFTs.

LFTs	Patients No.		Total No.
	Normal LDH	Abnormal LDH	
AST (IU)	1.0 ± 0.9	-	1
ALT (IU)	-	-	-
ALP (IU)	2.0 ± 0.2	4.0 ± 0.7*	6
AST and ALT (IU)	2.0 ± 1.0	1.0 ± 0.4	3
AST and ALP (IU)	-	2.0 ± 0.5	2
ALT and ALP (IU)	-	-	-
AST, ALT and ALP (IU)	1.0 ± 0.6	1.0 ± 0.6	2
Normal liver test	-	2.0 ± 0.6	2
Normal individual	27.0 ± 4.0	-	27
Total number	33	10	43

Mean ± SD; - : No patients; *Significant at $P < 0.01$.

Table 2
Values of LDH in males with high levels of one or more of LFTs.

LFTs	Patients No.		Total No.
	Normal LDH	Abnormal LDH	
AST (IU)	4.0 ± 2.0	-	4
ALT (IU)	-	1.0 ± 0.6	1
ALP (IU)	1.0 ± 0.7	1.0 ± 0.1	2
AST and ALT (IU)	1.0 ± 0.4	1.0 ± 0.2	2
AST and ALP (IU)	1.0 ± 0.6	-	1
ALT and ALP (IU)	-	-	-
AST, ALT and ALP (IU)	2.0 ± 1.0	1.0 ± 0.7	3
Normal liver test	-	7.0 ± 2.2*	7
Normal individual	28.0 ± 3.0	-	28
Total number	37	11	48

Mean ± SD; - : No patients; *Significant at $P < 0.01$.

Four females possessed high levels of ALP and LDH, while 1 male had such high values. Moreover, non of patients had abnormal levels of ALT and ALP when they measured together (Tables 1 and 2).

Increased LDH levels in blood could not be indicator for liver diseases only, but it may be resulted from damage in muscular tissues. Ten females and eleven males who possessed high level of LDH were investigated for CK, as monitor for muscular injury, and LFTs. High values of LFTs with normal CK were observed in females. As indictor for muscular damage, males with elevated LDH levels whom revealed normal levels of LFTs with high values of CK appeared to be in a great number (3 patients) comparing with females (one patient) (Tables 3 and 4). For more specific test of LFTs, ALP alone or with AST revealed high level in females with abnormal value of CK (Table 3). Additionally, two patients (male and female) showed increased levels of LDH and all of LFTs, but the value of CK in their blood were elevated which means they may sever from muscular damage (Tables 1, 2, 3 and 4).

Table 3
Values of CK and LFTs in females with high levels of LDH.

LFTs	Patients No.		Total No.
	Normal CK	Abnormal CK	
AST (IU)	-	-	-
ALT (IU)	-	-	-
ALP (IU)	2.0 ± 0.4	2.0 ± 0.5	4
AST and ALT (IU)	1.0 ± 0.5	-	1
AST and ALP (IU)	1.0 ± 0.2	1.0 ± 0.1	2
ALT and ALP (IU)	-	-	-
AST, ALT and ALP (IU)	-	1.0 ± 0.3	1
Normal liver test	1.0 ± 0.2	1.0 ± 0.2	2
Total number	5	5	10

Mean ± SD; - : No patients; *Significant at $P < 0.01$.

Table 4
Values of CK and LFTs in males with high levels of LDH.

LFTs	Patients No.		Total No.
	Normal CK	Abnormal CK	
AST (IU)	1.0 ± 0.3	-	1
ALT (IU)	-	1.0 ± 0.2	1
ALP (IU)	-	1.0 ± 0.3	1
AST and ALT (IU)	-	1.0 ± 0.2	1
AST and ALP (IU)	-	-	-
ALT and ALP (IU)	-	-	-
AST, ALT and ALP (IU)	-	1.0 ± 0.4	1
Normal liver test	3.0 ± 0.6	3.0 ± 0.2	6
Total number	4	7	11

Mean ± SD; - : No patients; *Significant at $P < 0.01$.

None of our patients revealed abnormal levels of LFTs and LDH that associated with normal level of CK which eliminated the possibility of severing from liver cancer disease. However, three males and one female who had high level of LDH showed normal levels of LFTs and CK which increase the possibility for those patients to sever from one types of cancers with excluded liver cancer disease (Table 4).

4. Discussion

LDH plays an important role in human body represented by anaerobically converting of pyruvic acid to lactic acid and vice versa[2]. Under normal conditions, LDH produced in human body in little amounts with low monitory value. There are many factors responsible for increasing LDH levels in blood stream that distributed between temporary conditions such as prolonged exercise[9] and some of physiological disorder *i.e.* severity of preeclampsia[10], ascites[11] and allergy[4].

For clinical values, LDH is useful for diagnosis or as an indicator for many diseases in liver and muscles and also for cancers. The main goal of our study is to determine if the increasing levels of LDH may result from either liver, muscular or cancer diseases in patients of more than 40 years of age. In addition to LDH, three tests for evaluating of liver functions including ALT, AST, and ALP found to be more useful to diagnosis the liver state. Most of patients had elevated level of LDH in associated with one or more types of LFTs either when they tested alone or with each others. Burke classifieds liver diseases into two categories of injury: cell necrosis (acute and chronic) and cholestasis[12]. Elevation of ALT and AST with less increase or normal ALP may indicate for cell necrosis, whereas the reverse points is to cholestasis. Moreover, ALT values in acute hepatic injury are usually higher than AST[12]. The usage of LDH in addition to those liver tests increase the accuracy of diagnosis of liver diseases. The ALT-LDH index is the other form of LDH to predict the prognosis of acute liver injury at their early stages[13] and also to differentiate between typhoid hepatitis and acute viral hepatitis[14]. Acute liver failure can also detect by determining the amount of LDH production in hepatocytes based on biopsy examination[15].

In contrast with females whom showed elevated levels of LDH and LFTs, large number of males had high levels of LFTs with normal value of LDH which means that the measurement of LDH is not significant to diagnosis liver diseases in male comparing with female. Thus, it's recommended to include LDH test with the list of LFTs to limit the confounding results about evaluation of liver diseases in both gender.

The present of LDH in muscle regarded to play a very important role for muscular tissues through its ability to convert muscular lactic acid into pyruvic acid, an essential step in producing cellular energy[2]. Moreover, LDH is not restricted in specific type of muscle, it can be found in various types of muscle, especially skeletal and cardiac muscles. These muscles are also known to contain CK rather than LDH which may release in blood with greater levels as result from various muscular diseases such as skeletal muscle necrosis[16], and Duchenne muscular dystrophy[17]. Thus, If we need to confirm that high level of LDH is resulted from muscular disorder and not from other things, it's important to measure the CK level. CK is a better indicator of heart or muscular damage. Therefore, estimation of CK along with LDH may serve as suitable diagnostic marker for muscular damage *i.e.* Rhabdomyolysis, cardiac manifestations that associated with organophosphorus poisoning[18], acute myocardial infarction[3] and patients with prosthetic heart valves[18]. However, in the present of normal CK levels, it's unlikely that the elevated levels of LDH derive from myocardial necrosis[19].

In our patients with high level of LDH, greater value of each of CK and all types of liver enzymes (except ALT and ALP in both sex and AST and ALP in males) was observed. Although ALT, AST, and ALP mainly located in liver, human muscles are also contain these enzymes even in little amounts and can release it into the blood stream following different muscular damages[16,20]. Thus, elevated levels of these enzymes in the absence of liver disease should lead to consideration of muscular injury which is confirmed by elevating of CK and LDH as we showed in both gender. Nathwani *et al.* recorded that ALT, AST, and ALP rate had been greater in 16 patients who had muscular necrosis without evidence of liver disease[16].

Gender appeared to be a confounding factor while interpreting LFT and CK. Equal number of males and females revealed high level of CK in associated with various LFTs. From all patients, there is no one showed abnormal level of AST and CK which is in agreement with the results of Khan *et al.*[3].

The patients who revealed abnormal levels of LFTs and LDH that associated with normal level of CK can eliminate the possibility of their severing from liver cancer disease. Three males and one female who had elevated level of LDH revealed normal value of CK and LFTs. Thus, if we excluded the liver diseases as indicator by negative LFTs and muscular damage as indicator by negative CK, the probability to explain elevated LDH level may return to the present of one of cancer diseases. Many types of cancer diseases could increased LDH level without any effect in liver functions such as breast cancer[6,7,21], and children with Hodgkin lymphoma[8]. While, some of cancer metastasis in liver or arrived to liver causing elevation in the levels of its enzymes as noted in breast cancer[22].

There are many explanations for increasing LDH level in blood of patients whom suffering from cancer diseases. First, the increase number of cells during cancer development will consume great amount of glucose to get energy by glycolysis which increasing

LDH level when the condition is anaerobic[23]. Second, growing cancer cells will destroy other tissues and causing release of intracellular enzyme like LDH into the blood stream by the injury or dying cells[24]. Third, increase LDH level by activating its production by tyrosin phosphorylation mechanism in cancer cells[25].

In conclusion, LDH can use as a good biomarker for diagnosis of liver, muscular and even cancer diseases. There is little variable between males and females in the elevated values of LDH. Patients with normal values of LFTs and CK and high level of LDH suggested to have unidentified cancer disease, except liver cancer, and for that other specific tests are required.

Conflict of interest statement

We declare that we have no conflict of interest.

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