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ASSOCIATION OF SERUM LACTATE LEVELS WITH CREATINE KINASE – MB AND LACTATE DEHYDROGENASE IN PATIENTS WITH MYOCARDIAL INFARCTION

Biochemistry

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ABSTRACT

Objectives: Myocardial infarction is the most common form of coronary heart disease, the commonest cause of worldwide mortality. The present biochemical markers take atleast 6 hours for elevation following an episode of myocardial infarction. There is a need for sensitive marker for early diagnosis and prognosis. Lactate, the end product of anaerobic glycolysis is found to be elevated in many critical illnesses. Thus the study was undertaken to assess the levels of serum lactate in patients with myocardial infarction and to correlate it with the frequently used enzymatic markers for the diagnosis of myocardial infarction, i.e creatine kinase – MB and lactate dehydrogenase

Methods: Fifty age and sex matched controls and fifty cases of myocardial infarction were included in the study. Serum creatine kinase – MB, lactate dehydrogenase and lactate were estimated in these subjects.

Results: The serum lactate levels were significantly higher among cases when compared to controls. The serum lactate levels positively correlated with serum creatine kinase – MB among cases but not with lactate dehydrogenase.

Conclusions: We conclude that serum lactate is altered in patients with myocardial infarction and may be considered as a prognostic risk factor in these patients. Further studies are needed to find the cut-off value of serum lactate for assistance in the hemodynamic management of these patients.

KEYWORDS

Myocardial infarction, lactate, biomarkers, creatine kinase – MB, lactate dehydrogenase

1. INTRODUCTION

Coronary heart disease is a common cause of death worldwide. The major manifestations of coronary heart disease are stable angina pectoris, cardiac failure and acute coronary syndrome, which includes unstable angina pectoris, myocardial infarction and sudden cardiac death. The most common form of coronary heart disease is myocardial infarction. At present, diagnosis of myocardial infarction is done by electrocardiogram and biochemical markers such as troponins and creatine kinase – MB. However, the initial electrocardiogram is diagnostic in only 50% of the cases[1] Biochemical markers such as creatine kinase, creatine kinase – MB and troponins are often initially normal and may take 6 - 8 hours to reach the diagnostic levels. Investigations such as echocardiography, exercise electro cardiography, and nuclear imaging, though more sensitive lack specificity and are not easily available in many health care centres[2]. Thus, there is a need for a sensitive marker that can be used for diagnosing myocardial infarction and assessing the prognosis.

Lactate is the end product of anaerobic glycolysis, which occurs predominantly during tissue hypoperfusion [3]. Regional hypo perfusion is frequently seen in myocardial infarction. Blood lactate levels are extensively studied in critically ill patients. Blood lactate level is an indicator of hemodynamic impairment and is a predictor of outcome in patients with shock [4]. Acute myocardial infarction is one of the most common causes of circulatory shock. When tissue perfusion is decreased, the impaired oxygen supply induces the muscle cells to use glycolysis anaerobically and produce lactate.

Though the negative prognostic role of hyperlactatemia is well established in several critical illnesses such as sepsis [5,6], data in patients with myocardial infarction are limited and controversial. So, the present study was undertaken to assess the levels of blood lactate in patients with acute myocardial infarction. We also studied the association of blood lactate levels with the common enzymatic markers of myocardial infarction, creatine kinase –MB (CK-MB) and lactate dehydrogenase (LDH)

2.MATERIALS AND METHODS

This is a case control study involving 50 cases of acute myocardial infarction and 50 healthy controls conducted at Thanjavur Medical College Hospital, Tamil Nadu, India. The study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine. The age of the study subjects ranged from 38 – 70 years. There were 25 males and 25 females in each group. The ethical committee approval was obtained for the study.

The patients with the following features were excluded from the study

- Age less than 25 years
- Cardiac arrest prior to blood sampling
- Traumatic cases
- Liver diseases
- Diabetes mellitus on metformin
- Inability to provide history
- Unavailability for follow up
- More than three emergency department visit for chest pain during the study period
- Referral from other institutions directly to the cardiology department

As liver disorders can affect the lactate clearance, patient with liver dysfunction were excluded from the study. Also diabetic patients on metformin were specifically excluded as metformin is known to increase the lactate levels in the body.

After obtaining informed consent from the study subjects, 5 ml of venous blood was collected under aseptic precautions. Serum lactate was estimated by colorimetric assay for the determination of lactate in serum/plasma – Monoreagent using Lactate PAP fluid. The principle of the test can be explained as under L-Lactate is oxidized to pyruvate and hydrogen peroxide by the enzyme lactate oxidase.

$$\text{L-Lactate} + \text{Oxygen} \xrightarrow{\text{Lactate oxidase}} \text{Pyruvate} + H_2O_2$$

Hydrogen peroxide reacts with p-Aminophenazone and p-chlorphenol in the presence of peroxidase to form a red coloured chromogen.

$$H_2O_2 + \text{p-Aminophenazone} + \text{p- chlorphenol} \xrightarrow{\text{Peroxidase}} \text{Chromogen} + H_2O$$

The increase in absorbance at 546 nm is proportional to the lactate concentration and can be measured photometrically.

The reference range for serum lactate is <19.8mg/dl or <2.2 mmol/L. Estimation of creatine kinase-MB was done by kinetic immuno inhibition method. It is based on the principle that the major creatine kinase activity in normal serum is due to creatine kinase-MM and creatine kinase- MB isoenzymes, found mainly in skeletal muscle and heart muscle respectively. Creatine kinase -BB is usually present in serum at low concentration. Both creatine kinase isoenzymes are dimers formed by the association of two sub-units from muscle (M) and nerve cells (B). The immunoinhibition from a specific antibody of both, MM sub-units and the single M sub-unit of creatine kinase-MB, allows the determination of the B sub-unit. The CK-B activity corresponding to half of CK-MB is measured by the increasing rate of

absorbance resulting from the following coupled reaction

Creatine phosphate + ADP $\xrightarrow[(pH\,6.5)]{\text{Creatine Kinase(AMP,NAC)}}$ Creatine + ATP

ATP + Glucose $\xrightarrow{\text{Hexokinase}}$ Glucose-6 phosphate + ADP

Glucose-6 phosphate + NADP + H2 $\xrightarrow{\text{G6-PDH}}$ Gluconate -6 Phosphate + NADPH + H+

(G6-PDH: Glucose-6-phosphate dehydrogenase)

The reference range for creatine kinase-MB in adults is 2 IU/L to19.5 IU/L

Estimation of lactate dehydrogenase (LDH) was done by modified IFCC method which is based on the principle that the enzyme lactate dehydrogenase catalyzes the reduction of pyruvate, forming NAD from NADH. The rate of oxidation of NADH to NAD is measured as a decrease in absorbance which is inturn proportional to the lactate dehydrogenase activity in the sample. The reference range for lactate dehydrogenase is 100 – 200 IU/L.

Statistical analysis was performed using SPSS Statistics version 16 (SPSS Statistics Inc., Chicago, US). Data was expressed as mean (SD) or median (range). Unpaired t test or Mann-Whitney test was used to compare the parameters between control and study groups for parametric and non-parametric data respectively. Pearson or Spearman correlation was used to correlate the parameters among the cases for parametric and non-parametric data respectively. 'p' value less than 0.05 ($p<0.05$) was considered as statistically significant.

Table 1: General Characteristics Of The Study Subjects

Parameters	Controls	Cases	p-value
Age , mean (SD), years	52.1 (9.23)	54.12 (8.55)	0.259
Gender Male Female	 25 25	 25 25	 1
Weight, mean (SD), kg	66.68 (6.99)	68.46(10.06)	0.307
BMI, mean (SD), kg/m^2	23.51(1.85)	26.34(4.25)	<0.0001

Table 2: Biochemical Parameters In The Study Subjects

Parameters	Controls	Cases	p-value
Serum Lactate , mean (SD), mg/dL	15.72 (1.96)	39.34 (14.34)	<0.0001
Serum CK-MB, mean (SD), IU/L	14.72(4.19)	104.74 (58.91)	<0.0001
Serum LDH, mean (SD), IU/L	115.98 (9.02)	141.9 (22.93)	<0.0001
Serum total cholesterol, mean (SD), mg/dL	166.8 (17.93)	202.8 (41.82)	<0.0001
Serum Triglyceride, median (range), mg/dL	126.5 (65 – 170)	124 (102 – 198)	0.877
Serum HDL-cholesterol, mean (SD), mg/dL	43.8 (9.68)	39 (10.04)	0.017
Serum LDL-cholesterol, mean (SD), mg/dL	97.2 (22.58)	137.87 (42.61)	<0.0001
Serum VLDL-cholesterol, median (range), mg/dL	25 (13 – 34)	24.8 (20.4 – 39.8)	0.931

Table 3: Correlation Of Serum Lactate With Ck-mb And Ldh In Cases

Parameter	r	p value
CK-MB	0.602	<0.0001
LDH	0.071	0.625

3.RESULTS

Out of 100 subjects included in the study, 50 had acute myocardial infarction and 50 were healthy controls. The mean age of the study subjects was 54.12 ± 8.55 years and 52.1 ± 9.23 years for cases and controls respectively. The general characteristics of the study subjects are depicted in Table 1. There is no statistical difference in age and body weight between the two groups. However, the mean body mass index (BMI) of cases is higher than mean BMI of the control group (26.34 ± 4.25 vs 23.51±1.85) ($p<0.0001$).

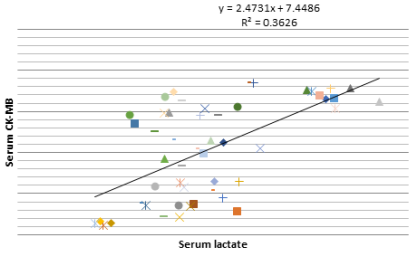

Figure 1: Correlation Between Serum Lactate (mg/dl) And Serum Creatine Kinase –mb (iu/l) In Cases

The mean serum lactate level in the study group is higher than the mean level in the control group which is statistically significant (39.34±14.34 mg/dl vs 15.72±1.96) ($p < 0.0001$). As expected, the mean levels of creatine kinase – MB and lactate dehydrogenase were significantly higher among the cases. The lipid profile is also altered between the two groups. The serum total cholesterol and the serum low density lipoprotein –cholesterol (LDL-Cholesterol) are significantly elevated while the serum high density lipoprotein –cholesterol (HDL-Cholesterol) is significantly decreased among the cases when compared to controls. However, the serum triglycerides and serum very low density lipoprotein –cholesterol (VLDL-Cholesterol) are not significantly altered between the two groups. (Table 2)

In our study, serum lactate levels were positively correlated with serum creatine kinase – MB ($r = 0.602$; $p<0.0001$) (Figure 1). No significant correlation was seen between serum lactate and the enzyme, lactate dehydrogenase (Table 3).

4.DISCUSSION

In our study, in patients with myocardial infarction, the serum levels of lactate are significantly higher when compared to controls. In myocardial infarction, the tissue perfusion is decreased and the oxygen supply to the myocytes is reduced. Consequently, the muscle cells oxidize glucose anaerobically producing lactate from pyruvate, instead of utilizing pyruvate for mitochondrial energy production. This is responsible for increased serum lactate levels in patients with myocardial infarction. In addition, the ability of the ischemic myocardium to extract lactate from the circulation is also compromised. This further adds to the hyperlactatemia in these patients [7]

Under normal circumstances, serum lactate through pyruvate accounts for 10 - 40 % of the myocardial fuel supply, making heart an important net consumer of lactate. Impaired supply of oxygen can turn the heart into a lactate producer instead of lactate consumer [8,9]. Stress, hypotension and glycometabolic dysregulation may also be responsible for increased serum lactate level in these patients [10]

In states of hypoperfusion, the blood supply to vital organs like liver and kidneys are also affected. This would in turn affect the clearance of lactate by these organs, contributing to increased serum lactate levels. The effects of hyperlactatemia and lactic acidosis on cardiovascular system are particularly pernicious and include decreased cardiac output, reduced arterial blood pressure, centralization of blood flow and reduced blood supply to various organs of the body[11]. Thus, a vicious cycle is formed, hyperlactatemia reducing the blood supply to the various organs which in turn increases the serum lactate levels.

Our study is in line with few other studies. The study by Kulshrestha et al. done on 30 patients with myocardial infarction also showed that the serum lactate level is significantly higher among the cases [12] Gatien et al.[13] demonstrated that venous lactate level at presentation is highly sensitive for the diagnosis of acute myocardial infarction, especially in patients with more than two hours of chest pain.

Lactate is a metabolite that can be easily and quickly assessed, and has been studied over the years in critical illnesses [14] Hyperlactatemia is associated with adverse outcomes in critical illnesses[15]. In patients with ischemic cardiac disease, the amount of lactate released by the myocardium is related to the severity of the disease[8].

In a study done on 253 non-diabetic patients with ST-elevation myocardial infarction (STEMI) submitted to percutaneous coronary intervention (PCI), Lazzeri et al. found that lactate level at admission was an independent predictor of intensive cardiac care unit mortality [10]. Gjsedal et al. showed that blood lactate is a predictor of short-term mortality in patients with myocardial infarction complicated by heart failure in the absence of cardiogenic shock [16]. According to study by Kawase et al., higher levels of arterial lactate at admission were associated with high mortality in patients with acute decompensated heart failure with or without acute coronary syndrome[17]. In a study done on 229 patients admitted to coronary care unit, the lactate levels at admission showed the highest predictive power for development of shock [18]. Nichol et al showed in a multicentric study that relative hyperlactatemia, defined as blood lactate concentrations more than 0.75 mmol/L could identify patients at higher risk for death. They further confirmed in their study that lactate levels more than 2 mmol/L strongly associated with higher hospital mortality[19]. Hyperlactatemia is considered as a marker of metabolic stress response and the severity of hyperlactatemia is associated with increased mortality in patients with critical illnesses.

Further, in our study we have found that serum lactate levels are correlating with serum creatine kinase-MB levels ($r = 0.602$; $p<0.0001$). Creatine kinase – MB is an indicator of myocardial necrosis, which inturn depends on the extent of myocardial ischemia [20]. More severe cardiac injury due to ischemia aggravates tissue hypoperfusion and consequently rises the serum lactate levels as well. However, no positive correlation is seen with serum lactate dehydrogenase. This could be explained by the fact that creatine kinase -MB and lactate rise in blood in the initial hours of myocardial infarction while lactate dehydrogenase starts rising in 12 – 24 hours. In our study, most of the samples were collected within 6 hours of onset of symptoms and patients who underwent treatment elsewhere before coming to our institution were excluded from the study. Also we measured total lactate dehydrogenase level which is non-specific and measurement of lactate dehydrogenase -1isoenzyme would have been more appropriate.

5.CONCLUSION

The levels of serum lactate are increased in patients with myocardial infarction. This might have prognostic implications for assessing the morbidity and mortality in these patients. Further studies are needed in this regard find the cut-off value of serum lactate for assistance in the hemodynamic management of these patients

Limitations of the study

Serial measurements of serum lactate could have given more information on the prognostic value of hyperlactatemia in myocardial infarction. Estimation of cardiac troponin and its correlation with lactate was not done. Further investigations are required with larger number of patients to find the cut-off value of serum lactate for better management of the condition.

6.REFERENCES

1. Young GP, Green TR. The role of single ECG, creatine kinase and CKMB in diagnosing patients with acute chest pain. Am J Emerg Med. 1993; 11:444–9
2. Ioannidis JPA, Salem D, Chew PW, Lau J. Accuracy of imaging technologies in the diagnosis of acute cardiac ischemia in the emergency department: a meta-analysis. Ann Emerg Med.2001; 37:471–7
3. Stacpoole PW. Lactic acidosis. Endocrinol Metab Clin North Am 1993; 22: 221 – 45
4. Vermeulen RP, Hoekstra M, Nijsten MWN, Van der Horst IC, Van pelt J, Jessurun GA et al Clinical correlates of arterial lactate levels in patients with ST-segment elevation myocardial infarction at admission: a descriptive study. Crit Care.2010; 14(5): R164.
5. Vernon C and Le Tourneau JL. Lactic acidosis: recognition, kinetics and associated prognosis. Crit Care Clin 2010; 26: 255 – 283
6. Juneja D, Singh O and Dang R. Admission hyperlactatemia: causes, incidence, and impact on outcome of patients admitted in a general medical intensive care unit. J Crit Care 2011; 26(3):316 – 320
7. Hattori R, Takatsu Y, Yui Y, Sakaguchi K, Susawa T, Murakami T, et al. Lactate metabolism in acute myocardial infarction and its relation to regional ventricular performance. J Am Coll Cardiol. 1985; 5: 1283 – 91
8. Gertz EW, Wisneski JA, Neese R, Bristow JD, Searle GL, Hanlon JT. Myocardial lactate metabolism: evidence of lactate release during net chemical extraction in man. Circulation 1981; 63:1273-1279
9. Stanley WC, Chandler MP. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. Heart Fail Rev 2002,7: 115-130.
10. Lazzeri C, Sori A, Chiostri M Gensini GF, Valente S. Prognostic role of insulin resistance as assessed by homeostatic model assessment index in the acute phase of myocardial infarction in nondiabetic patients submitted to percutaneous coronary intervention. Eur J Anaesthesiol 2009; 26 (10): 856 – 862
11. Orchard CH and Kentish JC. Effects of changes of pH on the contractile function of cardiac muscle. Amer J. Physiol. 1990; 258: 967 – 981
12. Kulshrestha MR, Tiwari V, Tripathi P. Serum lactate level as a potent biomarker in acute myocardial infarction. Int J Clin Biochem Res 2019; 6(3):353-355
13. Gatien M, Stiell I, Wielgosz A, Ooi D, Lee JS. Diagnostic performance of venous lactate on arrival at the emergency department for myocardial infarction. Acad Emerg Med 2005; 12: 106−113
14. Lazzeri C, Valente S, Chiostri M, Gesini GF. Clinical significance of lactate in acute cardiac patients. World J Cardiol 2015; 7(8): 483-489
15. Khosravani H, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. Crit Care 2009; 13: R90
16. Gjesdal G, Braun O, Smith JG, Schhersten F and Tyden P. Blood lactate is a predictor of short-term mortality in patients with myocardial infarction complicated by heart failure but without cardiogenic shock. BMC Cardiovasc Disord 2018; 18: 8
17. Kawase T, Toyofuku M, Higashihara T, Okubo Y, Takahashi L, Kagawa Y et al. Validation of lactate level as a predictor of early mortality in acute decompensated heart failure patients who entered intensive care unit. J Cardiol 2015; 65: 164 – 170
18. Mavric Z, Zaputovic L, Zagar D, Matana A, Smokvina D. Usefulness of blood lactate as a predictor of shock development in acute myocardial infarction. Am J Cardiol 1991; 67: 565 – 568
19. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care 2010; 14: R25.
20. Ali F, Naqvi SAS, Bismillah M, Wajid N. Comparative analysis of biochemical parameters in diabetic and non-diabetic acute myocardial infarction patients. Indian Heart J 2016; 68: 325 -331