Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 05, Page No: 151-155

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Serum Lactic Acid as a Prognostic Marker in Clinical Medicine

Praraj Jaiswal[1*], Sachin Agrawal[2], Sourya Acharya[3], Sunil Kumar[2], Vinisha Jaiswal[4]

Department of Medicine, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

ABSTRACT

Body tissues under stresses, such as hypoxia, inflammation, sepsis, and shock, trauma, and organ failure resort to anaerobic respiration under low oxygen availability. This prompts cells to resort to anaerobic respiration as a means of producing ATP. Lactic acid is one of the by-products of anaerobic respiration. It is an anti-inflammatory agent and inhibits formation of pro-inflammatory mediators such as interleukin 12 and TNF (Tumour Necrosis Factor) in tissues and increases formation of interleukin 10 (Anti-Inflammatory). Therefore, it can be postulated that an increase in lactic acid levels in the blood can indicate an increased level of inflammation in the body, since anti-inflammatory chemicals will be secreted in response to an increase in inflammatory mediators. A prognostic marker is a biochemical used to measure the progress of a disease. Based on the above hypothesis, one can measure lactic acid levels in conditions such as, sepsis, myocardial infarction, trauma, diabetic ketoacidosis, malignancies etc. and use them as a prognostic marker to alter the course of treatment. This article aims to explore the role of lactic acid as a prognostic biomarker based on current literature, emphasizing on patients with cancer, with sepsis, and critically ill patients in Intensive Care Units (ICUs). Malignancy is an anabolic state causing high oxygen demand and larger numbers of tissues undergo anaerobic glycolysis, thus causing an increase in lactic acid levels. Sepsis causes the release of a high amount of inflammatory mediators which in turn raise the anti-inflammatory chemicals such as lactic acid.

Key Words: Anaerobic respiration, Hypothesis, Prognostic biomarker

HOW TO CITE THIS ARTICLE: Praraj Jaiswal, Sachin Agrawal, Sourya Acharya, Sunil Kumar, Vinisha Jaiswal Serum Lactic Acid as a Prognostic Marker in Clinical Medicine, J Res Med Dent Sci, 2022, 10(5): 151-155.

Corresponding author: Praraj Jaiswal
E-mail: iprarajjaiswal@yahoo.in
Received: 21-Feb-2022, Manuscript No. JRMDS-22-49335;
Editor assigned: 23-Feb-2022, Pre QC No. JRMDS-22-49335 (PQ);
Reviewed: 9-Mar-2022, QC No. JRMDS-22-49335;
Revised: 22-Apr-2022, Manuscript No. JRMDS-22-49335 (R);
Published: 5-May-2022

INTRODUCTION

Lactic acid is conventionally known as the substance generated in skeletal muscles after rigorous exercise, producing a state of muscular cramps and fatigue. As our understanding of the physiologic processes in our body has advanced, it is being realised that lactic acid plays a much more integral role in the maintenance of homeostasis, as well as in the pathogenesis of some common but deadly conditions such as carcinomas.

In the human body, lactic acid or lactate, is derived from skeletal muscle (25%), skin (25%), brain (25%), red blood cells (20%), and intestine (10%) [1]. on an average 15 to 25 milliequivalents per kilogram per day of lactate is produced. 0.3-1.8 mmol/L of serum lactic acid is considered a normal value, which is a result of a delicate balance between its production and clearance *via* liver and kidney [2]. It acts through the MCT (Mono Carboxylate Transporter) receptors.

The most well-known function of lactic acid is its role in energy production. The glycolytic pathway, occurring in the cytoplasm, is responsible for the manufacturing of two molecules of pyruvate, which acts as a substrate for the enzyme lactate dehydrogenase to act on, producing two molecules of lactic acid, and two ATP (Adenosine Triphosphate) molecules which is the main fuel for cells. This process is known as fermentation [3]. And is classically understood to occur under anaerobic conditions [4]. Lactic acid production can also be seen in normal oxygen conditions, a phenomenon known as Warburg effect, and has been discussed later in this article.

MATERIALS AND METHODS

Lactate may potentially play a role in cognitive function by regulating prostaglandin mediated cerebral blood flow, enhancing neuronal plasticity and stimulating expression of certain genes in astrocytes that are responsible for long term memory [1].

Other functions of lactate include tissue injury and reconstruction *via* promoting production of procollagen factors and extracellular matrix, augment viral clearance *via* interferon activity, and immune modulation. Lactate is fundamentally an anti-inflammatory unit, as it promotes the yield of anti-inflammatory cytokines like interleukin-10 (IL-10), upregulates the expression of anti-inflammatory genes like tgfb, mg_{11} and CD_{206}, while downregulating pro-inflammatory elements such as IL-12, TNF (Tumour Necrosis Factor) and NK (natural killer) cells [1].

When its role at a cellular level is grasped, there is no room for doubt that lactic acid has an intricate relationship with acute as well as chronic illness. Being a molecule that is produced from multiple sites, under various circumstances, it can give a fairly accurate assessment of bodily function in times of physiologic stress or pathologic disease. Thus, its role as a prognostic marker is undeniable. The first use of lactic acid as a prognostic marker was done by Broder and Weil in 1964 [2]. A prognostic marker is a compound that is measured to assess the disease severity, so that possible outcomes can be anticipated. Such a marker is important to plan the course of treatment of a patient, as the duration of hospital stay, response to treatment and the possibility of cure or remission are all dependent on the prognosis.

In this review, we aim to examine the use of lactic acid as a prognostic marker in the three categories of patients; those having a diagnosed malignancy, those having sepsis or septic shock, those who are critically ill of an illness other than two mentioned before.

Lactic acid itself is not a toxic molecule. However, it is a direct product of a stress response in the body, due to its position as an anti-inflammatory substance. Lactic acidosis can be classified into type A and type B.

Type a lactic acidosis is seen in an environment of depleted oxygen, causing anaerobic glycolysis. Most causes of lactic acidosis directly or indirectly act through this mechanism, as any type of cellular insult, be it trauma, infection, or inflammation, impairs oxygen delivery to tissues [4]. Type B lactic acidosis can be further divided into three subtypes, B_1, B_2 and B_3.

B_1 hyperlactatemia or secondary lactic acidosis is seen when the normal clearance by the kidney and liver is diminished, as a response to chronic renal and hepatic illnesses or failure. B_2 subtype is a toxin or drug mediated acidosis. Some drugs and toxins implicated include beta-agonists, epinephrine, metformin, methanol and propylene glycol [4]. Lactic acidosis in the paediatric population can also be attributed to a wide array of inborn errors of metabolism, which may range from fatty acid oxidation disorders, glycogen storage disorders or defects of the urea cycle [5]. This is classified into subtype B_3.

It is clear now that lactic acid has numerous sources for generation which have a variety of stimulants. The production of lactic acid in an environment of stress almost always can be explained by more than one mechanism. However, this poses the disadvantage of being a highly non-specific marker. Cancer, sepsis and critical care are three arenas that are frequently encountered in the clinical practice, and the availability of lactic acid as an easily and inexpensively testable entity makes a difference in how risk stratification of each patient is done.

Lactic acid as a prognostic marker in cancer

With passing time, non-communicable ailments have surpassed infectious diseases in causing a great loss to life. Malignancies are becoming increasingly common. While some cancers are easily manageable and have a high remission rate, many carcinomas still remain undiagnosed till later stages because of wide ranging presentations. Definitive treatments have also not been found for many malignancies. In such cases, providing a prognosis is a crucial part of an oncologist's job.

Many biomarkers have come up in recent times for prediction as well as prognosis of tumours. Carcino Embryonic Antigen (CEA), Prostate-Specific Antigen (PSA), beta human chorionic gonadotropin (β-hCG), Alpha Feto Protein (AFP) is some examples [6].

One upcoming tumour prognostic marker is serum lactic acid. It is found, as a general rule that raised intracellular and extracellular lactic acid levels accompany any cluster of malignant cells, and can reach up to 40 mmol/L, compared to the normal 1.8 mmol/L [1]. Hyperlactatemia in malignancy can be explained by two ways: efflux of lactic acid from cancer cells, and increased lactic acid production. First described by Warburg, there is excessive glucose uptake and subsequent lactate production by cancer cells even when adequate oxygen is available [7-8]. And is appropriately named as the 'Warburg Effect'. Defective cell respiration and overexpression of glycolytic enzymes may be responsible for this effect [9].

Increased lactate levels are also partly responsible for cancer prognosis in another capacity. It promotes neovascularization of the tumour cell mass by stimulating the release of VEGF (vascular endothelial growth factor) [7]. The malignant potential of cancers is further increased by lactic acid as it promotes metastasis by increasing delivery of hyaluronic [9]. Suppressing immune cell response to tumour antigens and increasing motility of tumour cells [1]. Lactate can also contribute to the development of a radio resistant and chemo resistant nature of certain cancers due to its ant oxidative properties [9].

A unique issue faced in the backdrop of cancer is the risk of developing sepsis or tumour lysis syndrome, both of which are characterised by increased lactate and indicate a declining status of the patient [10]. Hence, it can be said that lactic acid is a valuable prognostic marker in carcinomas as it indicates the tumour cell burden, degree of malignancy and ability to metastasise. Lactate Dehydrogenase (LDH) enzyme deserves a special mention as a prognostic marker in certain haematological malignancies [11]. Its importance is derived from its action on the pyruvate substrate to form lactate in the glycolytic pathway.

Lactic acid as a prognostic marker in sepsis

Sepsis is the organ dysfunction occurring as a result of an uncontrolled host immune response towards an infection. Many criteria have been introduced over the years to define and gauge the severity of sepsis. As per the 2016 guidelines by Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), the SOFA (Sequential Organ Failure Assessment) score is recommended to assess the extent of organ dysfunction in a patient with sepsis, which includes parameters such as respiratory, cardiac, hepatic and renal functioning, coagulation profile and Glasgow Coma Score (GCS) [12]. The q SOFA (quick SOFA) score has also been introduced now, as a rapid bedside evaluation of the patient's status (Table 1).

Table 1: qSOFA score.

	Score
Systolic blood pressure	<100 mmHg
Respiratory rate	>22 breaths/minute
Glasgow coma scale	<15
≥ 2 is suggestive of sepsis	

Serum lactate testing is one of the first line investigations done in suspected septic patients [14]. A marker of impaired cellular metabolism and tissue hypo perfusion, lactic acid provides a picture of the patient's general condition. Lactic acidosis in a patient of sepsis can be attributed to both, type A and type B mechanisms. In case of a septic shock, lactate levels are elevated due to poor tissue oxygenation and perfusion, indicating that the cells have reverted to anaerobic glycolysis for energy generation [15]. However, it is also observed that raised lactate levels are seen even in patients with normal haemodynamic and adequate fluid resuscitation, implying that another mechanism is also at play [4]. This may be accounted for by damage to capillary endothelium by various circulating inflammatory markers, impairing the oxygen unloading and uptake by cells, leading to a kind of secondary hypoxia [4].

Lactic acid as a prognostic marker for septic patients serves suitably well. In patients who have not yet progressed to shock, lactate levels of more than 4 mmol/L are 96% specific in predicting mortality [16]. It also has the advantage of foreshadowing hyoperfusion, when clinical signs such as a fall in blood pressure have not appeared [17]. As the levels of lactate increase, a proportional increase in mortality is also noted, as seen in the study by Shapiro et al. Levels of ≥ 4 mmol/L had a mortality of 28.4%, while values of <2.4 mmol/L had a fatality of 4.9% [2]. Clinical outcome is also influenced by lactate clearance, as better prognosis is seen in those who clear an initially raised lactate within 24 hours [2]. And a worse outcome for those with persistently increased values [14].

Some discourse among the medical fraternity has suggested that 6 hourly repeated lactate measurements may be superior to a one time measurement [18]. As well as using lactate, SOFA score and APACHE II (Acute Physiology and Chronic Health Evaluation) in combination may provide a better idea of the short term and long term prognosis.

Lactic acid as a marker in critically ill patients

Critically ill patients in the ICU (Intensive Care Unit) undergo tremendous amounts of stress by various ongoing processes in the body such as inflammation and organ dysfunction. Most often, these patients are in a state of circulatory shock, resulting in severe tissue under perfusion, which may be regional like in cases of fractures, burns, traumatic limb injury or deep vein thrombosis. Systemic hypoxia is seen in conditions like respiratory infections, myocardial infarctions, organ failure, brain injury and metabolic imbalances. These tissues are where lactic acid production flourishes as the cells are dependent on anaerobic glycolysis for energy generation in the form of ATP. A critical partial pressure of oxygen is 35 mm Hg, beyond which lactic acid begins to increase to significant levels due to defective clearance by the kidney and liver [4].

It is also seen that lactic acidosis may be present even in patients with normal perfusion pressures, in cases where the oxygen delivery systems faulty, as is seen in patients of severe anaemia or endothelial damage.

RESULTS AND DISCUSSION

Cardiac Critical Care Unit (CCU) post-operative patients are found to have raised serum lactate levels, but it is unlikely that it has any correlation with surgical outcome. On the other hand, in a study of patients who have endured myocardial infarctions, initial lactate of less than 5 mmol/L had a mortality of 39%, while patients with an initial lactate level of more than 10 mmol/L had a mortality of 92% [2].

Trauma leads to hypovolemic shock, however, the typical clinical picture of tachycardia and hypotension seen in shock may be late to present if there is a concealed or occult source of bleeding. In such an event, lactic acid is a reliable indicator of hypo perfusion at the microvascular position [2]. Thus, if hyperlactatemia is detected during the primary investigations itself, a judgement about the prognosis of the patient can be made, as it will predict the requirement of fluid resuscitation and the degree of traumatic inflammation. Similarly, in a paper by it was said that the survival of severe burn patients can be estimated by the lactate levels on admission [19].

In the paediatric ICU, it was seen that twenty four hour raised lactate had a higher mortality (93%), than a lactate that normalised within few hours (30%) of initiation of management [14].

Excessive work of breathing is seen in respiratory pathologies like bronchial asthma and COPD (chronic obstructive pulmonary disease), promoting energy production *via* the anaerobic pathway. As a result, increased levels of serum lactic acid may be seen, but they seem to have no prognostic value in clinical disease progression [2].

Another recurring cause of admission in the ICU is of diabetic ketoacidosis. Found no link between the treatment duration or morbidity and lactic acid levels [20].

As hyperlactatemia is a direct result of deranged body metabolism, it is safe to assume that it may predict the magnitude of this derangement. Though it may not be a specific prognostic marker for most conditions, it does provide a vague, but accurate evaluation of the disease outcome.

CONCLUSION

Lactic acid is an important biochemical, participating in many physiologic as well as pathologic processes. Some of the roles of lactic acid include energy production for normal cells under anaerobic conditions, and under normoxic conditions in tumour cells. It is also an anti-inflammatory agent, anti-oxidative agent, immune cell modulator.

Clinical medicine is ever evolving. Potential molecules are always being studied for any practical benefit they may provide, in terms of diagnosis, management or therapy. Serum lactic acid is one such molecule. It is now being seen as a valuable prognostic marker in many common clinical conditions, due to its involvement in cellular metabolism at the most basic level. As it is easy to test in labs, affordable for patients, and constantly changing with the predicament of the patient, it may be considered a preferable biomarker for stating the prognosis of many diseases. It is seen that levels of serum lactic acid are a reliable prognostic indicator in malignancies. Septic patients may be given a more accurate outcome when lactic acid is used in collaboration with other scores such as SOFA and APACHE. For patients of the ICU, lactate as a prognostic marker should be determined on a case to case basis, depending upon the etiology and mechanisms of illness.

Overall, serum lactic acid can be considered a reliable, albeit non-specific predictor of patient outcomes in hospital scenarios and must be used in conjunction with complete clinical assessment and score.

REFERENCES

1. Sun S, Li H, Chen J, et al. Lactic Acid: No Longer an Inert and End-Product of Glycolysis. Physiology 2017; 32:453-463.
2. Mirzaei M, Karimi M. Etiology and Therapeutic Approach to Ascites in Iranian Traditional Medicine: The Avicenna’s Perspective. Hepatitis Monthly 2018; 18.
3. Rabinowitz J, Enerbäck S. Lactate: the ugly duckling of energy metabolism. Nature Metabolism 2020;2:566-571.
4. Pino R. Appropriate Clinical Use of Lactate Measurements: Erratum. Anesthesiology 2021.
5. Chakrapani A, Cleary M, Wraith J. Detection of inborn errors of metabolism in the newborn. 2021.
6. Lahoud R, O'Shea A, El-Mouhayyar C, et al. Tumour markers and their utility in imaging of abdominal and pelvic malignancies. Clin Radiol 2021; 76:99-107.
7. Brooks G. The tortuous path of lactate shuttle discovery: From cinders and boards to the lab and ICU. J Sport Health Sci 2020; 9:446-460.
8. Mirzaei H, Hamblin MR. Regulation of glycolysis by non-coding RNAS in cancer: Switching on the Warburg effect. Mol. Ther-Oncolytics 2020; 19:218-239.
9. Hirschhaeuser F, Sattler U, Mueller-Klieser W. Lactate: A Metabolic Key Player in Cancer: Figure 1. Cancer Res 2011;71:6921-6925.
10. Bouobda G, Gonzalez C, Phipps R, et al. Value Added Impact of Both Point-of-Care and Laboratory Lactic Acid Analysis When Emergently Evaluating Cancer Patients. Oncol Ther 2020; 8:277-284.
11. Elbossaty W. Lactate Dehydrogenase (LDH) as Prognostic Marker in Acute Leukemia Quantitative Method. J Blood Dis Transfus 2017; 8.
12. Marik P, Taeb A. SIRS, q SOFA and new sepsis definition. J Thorac Dis 2017; 9:943-945.
13. Waligora G, Gaddis G, Church A, et al. Rapid Systematic Review: The Appropriate Use of Quick Sequential Organ Failure Assessment (q SOFA) in the Emergency Department. J Emerg Med 2020; 59:977-983.
14. Marikar D, Babu P, Fine-Goulden M. How to interpret lactate. Archives of disease in childhood - Education & practice edition. 2020; 106:167-171.
15. Yang H, Du L, Zhang Z. Potential biomarkers in septic shock besides lactate. Exp Biol Med 2020; 245:1066-1072.
16. Liu Z, Meng Z, Li Y, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the q SOFA score for mortality among adults with Sepsis. Scand j trauma resusc emerg med 2019;27.
17. Khater W, Salah-Eldeen N, Khater M, et al. Role of supar and lactic acid in diagnosing sepsis and

predicting mortality in elderly patients. Eur J Microbiol Immunol 2016; 6:178-185.

18. Ryoo S, Lee J, Lee Y, et al. Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock Defined by Sepsis-3. Critical Care Med 2018;46:489-495.

19. Jeng J, Jablonski K, Bridgeman A, et al. Serum lactate, not base deficit, rapidly predicts survival after major burns. Burns 2002; 28:161-166.

20. Cox K, Cocchi M, Salciccioli J, et al. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care 2012; 27:132-137.