# Hyperlactatemia and Lactic acidosis – a review Nadeem Zaidi

#### INTRODUCTION

Lactic acid is considered as a metabolic waste whose production in the body is triggered primarily by a compromised perfusion and oxygenation state of tissues but physiologically it is an important source of energy for various cellular activities. Its production highlights human body's adaptive ability in a diseased or stressed state.

Swedish chemist Carl W. Scheele made his observation in 1780 that lactic acid is found in sour milk products.<sup>1</sup> Presently it is widely used in pharmaceutical and food industry as a preservative. In medicine it is one of the main components of crystalloid solutions (Ringer lactate and Hartmann's solution).

Since the middle of nineteenth century scientists have made their observations that lactic acid is present in dead tissues and its production in the animal's muscles is related to oxygen supply to the muscles. German chemist J. J. Scherer was the first one to demonstrate the presence of lactic acid in human blood with some pathological states.<sup>2</sup> In clinical practice lactic acid is considered as a biological marker of various disease processes especially shock and any shock like state where tissue perfusion and oxygenation is compromised.

Most of the time clinicians over react to the elevated blood lactate levels and make a clinical diagnosis of sepsis or septic shock. Health care professionals need to be aware that hyperlactatemia could be due to a variety of conditions and specific treatment should be directed to the underlying condition.

In this review we will discuss some very basic physiologic concepts about lactic acid production in the body, its physiological importance and clearance from the body. Pathophysiology regarding hyperlactatemia and lactic acidosis with a particular reference to sepsis will also be reviewed. Finally some general diagnostic recommendations regarding hyperlactatemia and metabolic acidosis will be made.

# **BASIC PHYSIOLOGICAL CONCEPTS**

Glucose is the principal source of energy for our body. Most of the cells in human body metabolize it into water and carbon dioxide. It is a two stage process. First phase is glycolysis in which glucose is broken down into pyruvate. Second phase is Krebs cycle and oxidative phosphorylation in which mitochondria converts pyruvate into water and carbon dioxide. This phase needs oxygen. The end product is adenosine triphosphate (ATP). Upon demand ATP is broken down with the release of free hydrogen ions. Through a series of reactions mitochondria mops up these free hydrogen ions to form either water or incorporates them back to form ATP. 1,3 These systems are working continuously providing not only the energy for various cellular activities but also maintain the electro neutrality of the blood. The main limiting factor for their smooth working is the supply of oxygen. 1, 4, 5

Under anaerobic conditions pyruvate formed at the end of glycolysis is converted to lactic acid (figure 1). Excessive lactic acid is cleared from the body either by converting back to pyruvate by lactic dehydrogenase or into glucose (gluconeogenesis) in the liver and kidney through Cori's cycle (figure 2). Myocardium and brain cells can use lactate as a source of energy when the metabolic requirements are high. Lactate also acts like a hormone that indirectly increases the efficiency of energy utilisation and metabolism.<sup>1, 4, 5, 6</sup> Figure 3 shows the interconversion and relationship between lactic acid and lactate

Metabolic acidosis which develops with hyperlactatemia is due to two reasons. Firstly is the formation of lactic acid which quickly dissociates to release H+ ions. The remaining compound either combines with sodium or potassium to form a stable salt called lactate while the H+ ions titrates with bicarbonate (HCO3).

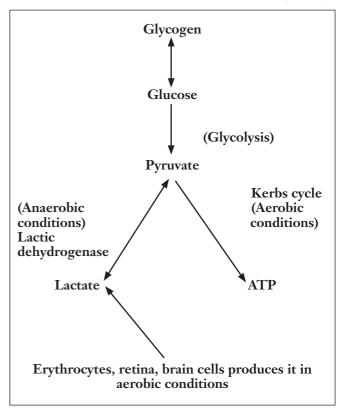
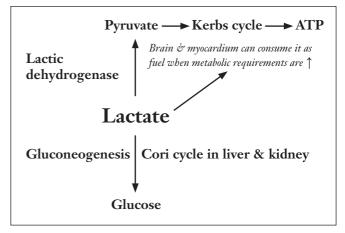


Figure 1: Lactic acid production in the body



**Figure 2:** Fate of lactate in the body

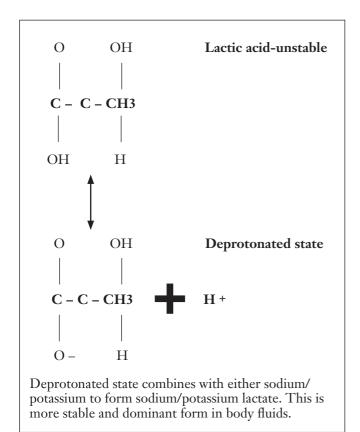


Figure 3: Interconversion of lactic acid and lactate

Consumption of HCO3 tilts the balance toward acidosis. Secondly in a hypoxic state the efficiency of Krebs cycle is reduced. Normally H+ ions produced with ATP hydrolysis are mopped up in Krebs cycle but in hypoxic state there is build-up of these H+ ions which changes the pH of the body fluids.<sup>6, 7</sup> Body maintains a tight balance between lactate production and its hepato renal clearance thus maintaining the pH of body fluids within a narrow range.

## CAUSES OF HYPERLACTATEMIA (TABLE 1)

Normal individuals produce 15 to 20 mmol/kg of lactic acid per day. At rest red cells, brain, muscles and skin produces excessive lactate. During pregnancy placenta also contributes to it. During exercise lactate is predominantly produces by muscles. In anaerobic conditions all tissues can produce lactic acid. Lactate exists in the body in two isomers (L & D -lactate). Human body produces primarily the L-isomer of lactate.

Normal blood lactate levels are 1-2 meq/Litre. Lactate levels greater than 2 meq/Litre represent hyperlactatemia, whereas lactic acidosis is a form of metabolic acidosis characterized by high serum lactate (>4 meq/L) with a change in pH (<7.36). Hyperlactatemia can occur with adequate tissue perfusion and an intact buffering system while lactic acidosis shows a more sinister underlying pathology. Hyperlactatemia or lactic acidosis happens primarily due to following two reasons, increase production of lactate or decrease clearance of lactic acid from the body Development of lactic acidosis in most of the clinical situations receives contribution from both of these processes. <sup>7,8</sup>

Physiological causes	Heavy exercise
Pathological causes	Prolonged seizures Excessive shivering Diabetic keto acidosis (DKA) Starvation Hypo perfusion states Malignancy Inborn error of metabolism Renal/hepatic failure
Side effects of medicine/toxins	Biguanides (Phenformin, Metformin) Acetaminophen over dose Linezolid Propofol (prolonged use) Cocaine Cyanide poisoning Nitropruside Isoniazid toxicity Anti-retroviral drugs Chronic alcohol toxicity Salicylates Strychnine Sulfasalazine Valproic acid B-adrenergic agents (epinephrine, terbutaline)

**Table 1:** Causes of hyperlactatemia

## **TYPES OF LACTIC ACIDOSIS (TABLE 2)**

Depending on etiology, there are two types of lactic acidosis (type A & type B) with type B being further subdivided into three subtypes (B1, B2 & B3). These were first described by Cohen-Woods. In certain clinical situations lactic acidosis may move form type A to type B over a course of treatment.

# HYPERLACTATEMIA IN SEPSIS

There are many haemodynamic variables and laboratory parameters which are being used to help in early diagnosis of sepsis and septic shock including lactic acid. Lactic acid measurement in sepsis is easy, quick and reliable with a diagnostic and prognostic potential. In sepsis and basic pathology is the imbalance between oxygen supply and tissues metabolic demand. Surviving sepsis campaign not only emphasised the importance of measuring lactic acid as a marker of tissue hypo perfusion but also suggested that all the resuscitation efforts should be aimed to normalize lactate levels. <sup>10</sup>

Shapiro<sup>11</sup> demonstrated the relationship between lactate levels and mortality of in hospital patients with infection. According to him the expected mortality was 4.9% when lactate levels were <2.5 mmol/L. It increases to 28.4% in patients with a lactate levels of >4 mmol/Litre. Lactate levels are also useful in the diagnosis of occult shock phenomenon. These patients are haemodynamically stable, normotensive but with persistently high lactate levels.<sup>12</sup>

Type A (there is some clinical evidence of impaired/inadequate tissue perfusion or oxygenation)	1) Carbon monoxide poisoning 2) Severe anaemia 3) Shock 4) Regional hypo perfusion 5) Prolonged seizures/fits 6) Heavy exercise, sprinting
Type B (there is no clinical evidence of impaired/inadequate tissue perfusion or oxygenation)	Type B1 Associated with systemic diseases Hepato renal failure Diabetic ketoacidosis (DKA) Malignancy  Type B2 Associated with drugs and toxins Biguanides Prolonged use of propofol Salicylates  Type B3 Associated with in born error of metabolism Glycogen storage disease Enzyme deficiency Pyruvate dehydrogenase deficiency Pyruvate carboxylase deficiency

Table 2: Classification/types of lactic acidosis

Bandon and Keith were of the opinion that the lactate generated in sepsis is not entirely due to anaerobic metabolism.<sup>13</sup> They suggested that other contributing mechanisms play an important part in this regard e.g. impaired hepatic clearance of lactate from the body, inhibition of lactic dehydrogenase enzyme activity and adrenergic stimulation. This stimulates glycolysis which generates more pyruvate (figure 1). Excess pyruvate is converted to lactate as mitochondria can't process this entire load through Krebs's cycle. Following a successful resuscitation, blood lactate levels remains high with a normal or near normal pH. This is termed as stress hyperlactatemia. Both venous and arterial samples can be used to measures lactate levels. Arterial sampling is preferred as it is more accurate, not effected by collection process and with the same sample blood gases can also be analysed.14

## HYPERLACTATEMIA IN TRAUMA

The basic pathology in most of the poly trauma patients is the blood loss. This impairs the tissue perfusion and oxygenation initiating the anaerobic cascade resulting in rise of blood lactate levels. Hyperlactatemia and its associated and metabolic acidosis promote coagulopathy and further blood loss. Triad of hypothermia, metabolic acidosis and coagulopathy are the main determinants of

High anion gap metabolic acidosis	Normal anion gap (hyperchloremic) metabolic acidosis
↓ acid production Lactic acidosis Diabetic ketoacidosis Starvation Chronic alcoholism	Loss of bicarb from the body Diarrhoea Ureteric diversion Carbonic anhydrase inhibitors Renal tubular acidosis- proximal
↓ renal excretion of acid Chronic kidney disease	↓ renal excretion of acid Renal tubular acidosis- distal hyperaldosteronism
Intake of Aspirin Alcohol – acute toxicity	

**Table 3:** Diagnostic approach to metabolic acidosis

outcome in a poly trauma patient. Most of the resuscitation efforts in the first hour (golden hour) in a poly trauma patient are directed toward restoration of blood volume. A trauma patient who fails to bring lactate value toward normal at 24 hours of injury carries a significantly higher mortality.<sup>15</sup>

#### **DIAGNOSTIC APPROACH**

Arterial blood gases not only help in quantifying the magnitude of hyperlactatemia and metabolic acidosis but through it we can calculate the anion gap. Anion gap is the difference between the measured cations and measured anions with normal value of 08-10 mmol/L.

Anion gap = measured cations – measured anions

Anion gap = (Na + K) - (HCO3+Cl)

The normal value of anion gap needs adjustment in case of hypoalbuminemia. Based on anion gap calculation metabolic acidosis is divided into two categories (table 3).

# ROLE OF ALKALIZATION IN SEVERE HYPERLACTATEMIA AND METABOLIC ACIDOSIS

To overcome the hemodynamic consequences of hyperlactatemia and metabolic acidosis some time various alkalizing agents are used to correct the pH with the aim that this will restore the cellular functions. The alkalizing agents used for this purpose are sodium bicarbonate, cardicarb and THAM (tris-hrdroxymethyle amino methane). Most of the literature in this regard is controversial. Sometimes base therapy is used in intensive care for symptomatic treatment of metabolic acidosis when the pH is <7.10. Main limiting factors regarding sodium bicarb use are paradoxical intra cellular acidosis and hypocalcemia. <sup>16, 17</sup>

#### CONCLUSION

Our understanding about lactic acid physiology has improved tremendously over the last many years. Presently we consider lactic acid as an important source of energy, an important modulator of energy utilization and performance whenever metabolic requirements are high. It also acts as a hormone which helps the human body to adopt in a pathological state.

Pathologically it is an important biological marker of illness with a diagnostic and prognostic potential. Hyperlactatemia and lactic acidosis can occur due a variety of reasons but most of the times it signifies an impaired tissue oxygenation and perfusion. While treating these patients health care professionals should keep all the differentials in mind and apply a rational diagnostic approach.

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