Diagnostic Value of Plasma D-Lactate Level in Acute Intestinal Ischemia

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Abstract

Acute Intestinal Ischemia (AII) is one of the most wide spread problems physicians face in the routine medical practice. In most situations, the physician's task is to recognize the condition in an early stage prior to tissue necrosis and resultant multiple organ failure. Detailed history, physical exam and laboratory findings are often nonspecific in suspected adult patients. There is a bulk of evidence to approve that D-lactate is useful in the diagnosis of AII. It can be used routinely in patients with undifferentiated abdominal pain in the emergency setting. However, based on the current literature data, this marker may not prove useful for making a decision of operation in patients with AII. This review article is written to underline the value of D-lactate to predict AII.

Keywords: Acute abdomen; Acute intestinal ischemia; Mesenteric infarction; Biomarker; D-lactate; Diagnostic value

Abbreviations

AMI: Acute Mesenteric İschemia; AUC: Area Under the Curve; NOMI: Nonocclusive Mesenteric İschemia

Introduction

Acute Abdominal Conditions (AAC) is one of the hardest challenges for the physician working in the acute setting. Expedient diagnosis and emergency surgery are vital in patients with abdominal pain. Early diagnosis of the patients shows the success of the EDs. At the same time, early diagnosis efforts might help to reduce overcrowding in the EDs.

Resuscitation and therapeutic intervention related to AAC is also difficult to determine by laboratory analysis alone. Nonetheless, some critical interpretations can still be made. An elaborate clinical history and examination should be of great help in reaching a diagnosis and narrowing the differential diagnoses in these difficult patients. Intestinal arterial occlusions are associated with chronic mesenteric ischemia symptoms prior to acute onset, often located near the origin of the Superior Mesenteric Artery (SMA) [1]. Many circulating biomarkers have been evaluated in the clinical setting of AAC. For example, serum lactate measurement has long been among the most frequently employed laboratory workup to diagnose AII. Likewise, Intestinal Fatty Acid Binding Protein (i-FABP) I-FABP has gained popularity for use in the prediction of the same entity in the last three decades.

In most aspects, Acute Mesenteric (İntestinal) İschemia (AII) is one of the hardest to recognize among AAC in the Emergency Department (ED). The mortality rate is reported to remain high, even more than 50% [2]. The lack of specific symptoms in its early phase and its detrimental course in the case of missed or late diagnosis prompted researchers to seek for an early diagnostic marker to beware of complications.

Nonocclusive Mesenteric Ischemia (NOMI) is associated with a high death toll of 80% and is still an important diagnostic challenge, because of its insidious onset in a majority of patients [3,4]. The physician should distinguish those with NOMI and those who warrant intestinal resection. D-lactate and i-FABP was found promising in the diagnosis of AII [5-9].

The aim of this review is to provide current status on the search for an accurate plasma biomarker, including D-lactate and others in prediction of AII among other causes of AAC.

Treskes et al. [10] performed a systematic review and meta-analysis on diagnostic accuracy studies on I-FABP, α-Glutathione S-Transferase (α-GST), D-lactate, Ischemia Modified Albumin

Table 1: Studies investigating the relationship of serum lactate levels and Acute Mesenteric (Intestinal) Ischemia (AII) in the last fifteen years.

Study feature	Acosta et al. [1]	Cronk et al. [8]	Matsumoto et al. [13]	Shi et al. [14]	van der Voort et al. [19]	Demir et al. [28]	Studer et al. [32]	Hong et al. [36]	Nuzzo et al. [37]	Ambe et al. [38]
Setting	Hospital	Surgery	ED	Surgery	Hospital	Mixed	Surgery	Surgery	Surgery	Surgery
Subject Group	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult
Design	Retrospective study patients with acute mesenteric artery occlusion	Prospective study validation cohort of patients admitted for mechanical small bowel obstruction	Prospective, observational (diagnostic)	single-center prospective cohort study on patients with acute abdomen	Prospective observational cohort study	Systematic review	A retrospective study of patients with pathologically confirmed AMI.	Prospective study on intestinal infarction after cardiac surgery.	single-center prospective cohort study on patients with AMI.	Retrospective study on the patients undergoing laparotomy for suspected AMI within 24 hours of presentation
No. of Subjects	55	21	208	272	120	7 studies, 386 patients	91	20	67	75
Measured laboratory parametres	lactate and troponin I	serum L-lactate and i-FABP levels	I-FABP, WBC, D-lactate, CRP, based eficit, lactate de hydrogenase	I-FABP and D-lactate	Endoscopy, CT-scan. LDH, creatine kinase, ALAT, lactate and I-FABP	Serum lactate	Serum lactate level	Plasma levels of D-lactate, i-FABP, and Smooth Muscle Actin (SMA)	Serum lactate levels	serum L-lactate
Major outcome variable	To identify potential diagnostic laboratory pit falls at admission in patients with acute Superior Mesenteric artery (SMA) occlusion.	comparison of serum L-lactate with i-FABP Levels causes.	Biomarkers' usefulness in the early diagnosis of AMI of different	The clinical usefulness of serum I-FABP and D-lactate levels in the early diagnosis of AII.	The prognostic value of biochemical tests in critically ill patients with multiple organ failure and suspected bowel ischemia.	Value of serum lactate to diagnose AMI in clinical practice	The correlation of repeated preoperative serum lactate with bowel necrosis and to identify risk factors for a lethal outcome in patients with AMI.	Plasma levels of biomarkers were measured in post-cardiac surgery patients undergoing laparotomy for suspected NOMI.	To identify predictive factors for Irreversible Transmural Intestinal Necrosis (ITIN) in AMI and establish a risk score for ITIN.	To investigate the association between preoperative serum lactate level and these verity of tissue ischemia in those with AMI.
Results	Elevated lactate in 12 out of 27 patients.	Elevated lactate in 1 out of 3 patients with gut necrosis false negative elevation in 5 out of 18 patients without gut necrosis.	Most biomarkers' levels (except WBC and CK) were higher in the vascular ischaemia group than in the others. None of the biomarkers differed between patients with non-vascular AII and those with non-ischaemic disease.	The mean serum I-FABP and D-lactate levels in the patients with AII were higher than those with non-intestinal is chemia and with levels in the healthy control group. AUC for I-FABP and D-lactate were 0.85 and 0.69, respectively.	Patient groups proven and likely ischemia together compared to unlikely and no-ischemia together showed significant higher L-lactate (p =0.001) and higher D-lactate (p =0.003).	Serum lactate is an unspecific marker of tissue hypoperfusion and undergoes significant elevation only after advanced mesenteric damage.	Less than or equal to six hours prior to surgery, the mean serum lactate level was significantly higher and the mean pH significantly lower compared to >6 h before surgery.	D-lactate increased between the two laparotomies in nonsurvivors. Plasma i-FABP and SMA significantly decreased after the bowel resection.	Factors associated with ITIN in multivariate analysis were: organ failure (hazard ratio: 3.1, serum lactate >2 mmol/l, and bowel loop dilation on CT.	Elevated serum lactate might permit an early suspicion and thus influence the clinical decision-making with regard to prioritization of surgery in patients with suspected AMI.
Conclusion & Interpretation	normal lactate may not be infrequent after mesenteric artery occlusion	Small cohort to draw firm conclusions on the value of serum lactate in bowel necrosis. 33% Sensitivity 72% specificity.	Serum biomarkers may be useful in the diagnosis of vascular, but not non-vascular, intestinal ischaemia. Among them, I-FABP shows promise for detecting vascular ischaemia.	Serum I-FABP and D-lactate can improve the diagnosis of AII in patients with acute abdomen who are at risk.	Measurement of LDH, CK, and ALAT did not discern the critically ill with proven AII from those with definite diagnosis no-ischemia. Lactate levels were higher in those with AII and need further study just as I-FABP.	Based on current evidence, the level of no single serum marker, including serum lactate, is elevated early and specifically enough in the serum to diagnose AMI.	The value of serial lactate and pH measurements to predict the length of necrotic bowel is very limited. Length of necrotic bowel and lactate values are independent risk factors for mortality.	None of the biomarkers were accurate enough to diagnose AII. High values of SMA predicted AII. An increasing D-lactate after intestinal resection suggests impending death.	Organ failure, serum lactate >2 mmol/l and bowel dilation >2.5 cm at time of diagnosis are predictors of irreversible intestinal necrosis.	A linear relationship between serum lactate and the extent of bowel ischemia could not be established in this study.

(IMA), and citrulline and found that the novel serological biomarkers I-FABP, α-GST, IMA and citrulline may offer improved diagnostic accuracy of AII. Pooled sensitivity and specificity for investigated biomarkers were: I-FABP; 79.0 (95% CI 66.5 to 88.5) and 91.3 (87.0 to 94.6), I-FABP; 75.0 (67.9 to 81.2) and 79.2 (76.2 to 82.0), D-lactate; 71.7 (58.6 to 82.5) and 74.2 (69.0 to 79.0), α-GST; 67.8 (54.2 to 79.5) and 84.2 (75.3 to 90.9), IMA; 94.7 (74.0 to 99.9) and 86.4 (65.1 to 97.1), respectively.

LDH: Lapsekili et al. [11] indicated in their experimental study that plasma Lactate Dehydrogenase (LDH), levels higher than 1900 IU/L may be a useful marker in the early diagnosis

of acute mesenteric obstruction.

CRP: CRP is also referred to as a nonspecific inflammatory mediator. Many studies have also found in the literature on this subject. Jaye et al. [12] cited that mixed results had been yielded on the diagnostic value of CRP and Erythrocyte Sedimentation Rate (ESR) in patients with suspected AAC.

I-FABP: Matsumoto et al. [13] investigated the use of I-FABP and traditional biomarkers in the diagnosis of AII of different causes. They concluded that serum biomarkers may be useful in the diagnosis of vascular, but not non-vascular, intestinal ischaemia. Among them, I-FABP shows promise for detecting vascular ischaemia (area

under the curve 0·88). Shi et al. [14] evaluated the clinical value of I-FABP and D-lactate measurements in the early diagnosis of AII in 272 consecutive patients with a clinical diagnosis of acute abdomen. They concluded that Serum I-FABP and D-lactate can improve the diagnosis of AII in these group of patients. Area under the curve for I-FABP and D-lactate were 0.85 and 0.69, and cut-off values of 93.07 ng/mL and 34.28 ug/mL, respectively.

D-Lactate is the biomarker most frequently investigated in the diagnosis of acute abdomen and related entities [13-17]. D-Lactate is normally present in the blood of mammals at nanomolar concentrations due to methylglyoxal metabolism [18]. D-lactate is a product of anaerobic metabolism which is released in increased amounts in hypoxic conditions.

van der Voort et al. [19] evaluated usefulness of several biomarkers in critically ill patients with multiple organ failure and suspected bowel ischemia and showed that L-lactate and D-lactate levels were higher in patients with proven or likely bowel ischemia. The levels of D-lactate are reportedly found higher than controls in certain gastrointestinal entities, *e.g.,* AII and some infections. Literature data pointed out that D-lactate may be a highly specific and sensitive test for bacterial infections, mostly *via* intestinal production [20-26]. L and D- stereoisomers have long been recognized as biomarkers to predict AII. L-lactate is the end-product of glycolysis, accompanied by poor perfusion and suboptimal oxygen delivery. L-lactate is rapidly metabolized by the liver, thus early peaks of L-lactate generally go unnoticed. Elevated levels of L-lactate mostly indicate AII at a late stage; in which hypoperfusion has triggered infarction associated with metabolic acidosis [27]. On the other hand, D-lactate is a product of normal bacterial biochemical metabolism. Therefore, elevations of D-lactate can be seen in conditions not associated with critical illness, such as gastric bypass surgery, short gut syndrome, and probiotic usage [28]. D-lactate levels are expected to rise in accord with the mucosal injury and loss of homeostasis of the gut flora. However, pooled research records sensitivities of 82%, but substantially lower specificities, as low as 36% [28,29]. D-lactate, therefore, could be an ineffective marker for the hyper acute phase of AII.

Boosts in D-lactate levels are encountered rarely during the early phase of ischemia/reperfusion; however, at later periods (43 hours), authors reported peaked D-lactate levels, which can persist for around two days [30]. This may represent the severity of functional impairment and extent of mucosal damage associated with the ischemia. In primate studies, elevated D-lactate levels at 48 hours were postulated to be suggestive of pending poor outcome [31]. On the other hand, Studer et al. [32] reported that in their cohort, the serial lactate measurements added no benefits in the evaluation of severely ill patients with AMI.

Systematic reviews on the topic: In 2009, Evennett et al. [33] performed a systematic review of the articles on the markers of intestinal ischemia. They concluded that novel markers of intestinal ischemia such as D-lactate, GST, and i-FABP may offer improved diagnostic accuracy. Acosta et al. [34] published a literature review to provide current status on the search for an accurate plasma biomarker for AII. They noted that none of the proposed plasma-derived tests for AII has as yet entered routine clinical practice. The proposed biomarkers need to be evaluated in a prospective clinical research project in patients with acute abdomen.

Derikx et al. [35-38] summed up the literature with regard to

human biomarkers for AII reported between 2007 and 2017. They concluded that classic, general markers, *e.g.,* lactate, white cell count, base excess, showed poor diagnostic accuracy for intestinal ischemia. Preliminary results for IMA and inflammatory marker procalcitonin are promising. Best diagnostic accuracy is described for D-dimer, a-Glutathione S-Transferase (a-GST) and I-FABP.

Studies investigating the topic in the literature and main findings have been listed in Table 1.

Conclusion

It is known that D-lactate increase in bacterial proliferation and ischemic injury in most intraabdominal diseases. Because of the time is an important factor in overcrowded EDs, this biomarker appears to be useful in diagnosis of AAC. There are conflicting results to draw precluding a firm conclusion as to rely on lactate measurements in the diagnosis of AII in the emergency setting or not.

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