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BIOCHEMICAL DIAGNOSIS OF ACUTE PANCREATITIS

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ABSTRACTS

The diagnosis of acute pancreatitis requires the presence of at least two of the three diagnostic criteria – characteristic abdominal pain, elevated serum amylase or lipase, and radiological evidence of pancreatitis. Serum concentrations of amylase and lipase rise within hours of the pancreatic injury. A threshold concentration 2–4 times the upper limit of normal is recommended for diagnosis. Serum lipase is now the preferred test due to its improved sensitivity, particularly in alcohol-induced pancreatitis. Its prolonged elevation creates a wider diagnostic window than amylase. Laboratory testing of serum amylase and /or lipase levels are central to the diagnosis of acute pancreatitis (AP) as these tests are quick, cheap, reliable and perhaps the only objective criteria available at the bedside at the time of initial presentation. It is important to understand the physiology and biochemistry of these tests in order to get a clear grasp of their diagnostic utility. Lipase is more specific than amylase and stays elevated longer than amylase due to its longer half-life in serum resulting from renal tubular reabsorption. There is no advantage of testing lipase and amylase, as well as no advantage in serially trending them for monitoring the clinical progress of the patient. They have no role in determining the etiology or severity of acute pancreatitis. If the clinical suspicion for acute pancreatitis is high, imaging studies should be performed to confirm or rule out the diagnosis of acute pancreatitis even with low elevation or no elevation of these enzymes. This article is a comprehensive review of the existing literature on serum lipase and amylase as diagnostic tools for AP and their cut off levels used for the diagnosis of AP. Neither enzyme is useful in monitoring or predicting the severity of an episode of pancreatitis in adults. New biomarkers including trypsinogen and elastase have no significant advantage over amylase or lipase.

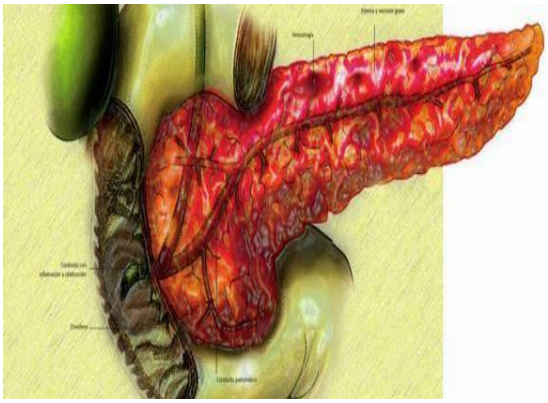
KEYWORDS: amylase test, lipase test, pancreatitis.

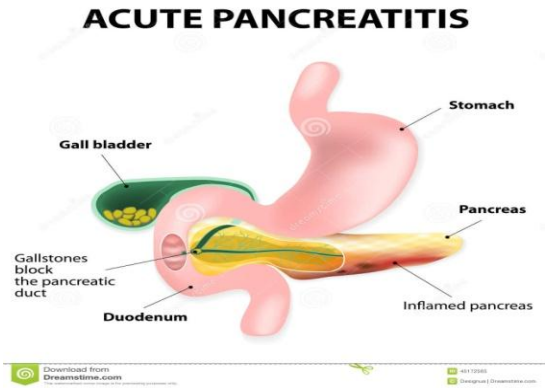
INTRODUCTION

Acute pancreatitis (AP) is a very common GI disorder. With increasing number of hospital admissions[1] for AP, the financial impact of this disease is huge.[2] In the year 2009, the total discharges with the principal diagnosis of acute pancreatitis in the United States were 274,119. This marked a 30% increase from the year 2000. The median length of stay was 4 days. The median cost per hospital admission was 6096 USD. The total number of in-hospital deaths due to AP was 2631, which is about 1% of the total admissions.[3] The American College of Gastroenterology (ACG) practice guidelines for the diagnosis and management of AP recommend that the diagnosis of AP be established by the presence of 2 of the following 3 criteria: 1) Abdominal pain consistent with AP 2) serum lipase and /or amylase greater than 3 times the upper limit of normal (ULN) 3) characteristic findings from abdominal imaging (Contrast Enhanced CT or MRI).[4]

Pain from AP is most commonly epigastric, but could also be in the left or right upper quadrant. It can radiate to the back, flanks or chest. It is usually constant. The intensity is variable, but is most often severe.[4] This description of the pain is somewhat non-specific. Pain may be absent or may be overshadowed by the early appearance of organ dysfunction. The history of pain may not be available in many patients - as for example in elderly patients or demented patients. The only two objective criteria for diagnosis are elevated serum lipase and/or amylase values and imaging findings characteristic of AP. Contrast Enhanced CT (CECT) of the abdomen is conventionally considered the gold standard for the diagnosis of AP. It is more than 90% sensitive and specific for the diagnosis of AP.[5] However, imaging evidence is often not available at the time of diagnosis.[6] If available, in a good number of patients with AP, CT scan can be normal, especially early in the course of the disease. Also, as per the practice guidelines of the ACG, it is not recommended to obtain a CT scan of the abdomen at the time of

admission. CECT is recommended when the diagnosis of AP is in doubt or if the patient fails to improve /worsens clinically after 48 hours of admission.[6] This is due to the cost involved and the lack of sensitivity of CT early in the course of the disease. Hence, the only objective diagnostic criteria routinely available at the time of initial patient contact are serum levels of pancreatic enzymes lipase and/or amylase.





Pathophysiology

Pancreatitis is thought to occur as a consequence of premature, intra-pancreatic activation of pancreatic proenzymes. These include chymotrypsinogen, procolipase, prophospholipase A2 and proelastase. The proenzymes are synthesised by the acinar cells and stored in vesicles known as zymogens. They are released into the pancreatic duct and activated at the brush border of the duodenal enterocytes. The specific mechanisms by which the various aetiologies of pancreatitis cause this premature activation of proenzymes are not well understood.[9] It appears that 'autodigestion' starts a local inflammatory response. The release of proinflammatory and chemotactic mediators, the activation of macrophages and the influx of other inflammatory cells damage the pancreas. Systemic complications such as bacteraemia, acute respiratory distress syndrome and a systemic inflammatory response syndrome may also occur if the various mediators enter the systemic circulation.[1,2]

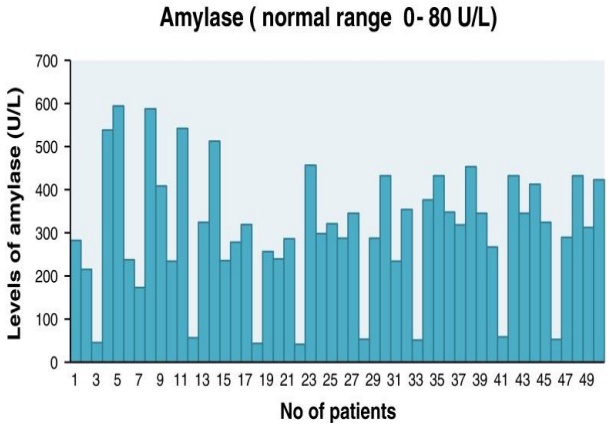


Figure: 1

Table: Causes of elevated serum amylase and lipase[2,5]

Causes	Amylase	Lipase
Abdominal conditions	Acute Pancreatitis, Pancreatic Trauma, Perforated Viscus, Intestinal Infarction And Obstruction, Peritonitis, Acute Cholecystitis, Appendicitis, Hepatitis, Abdominal Aortic Aneurysm, Ruptured Ectopic Pregnancy, Fallopian And Ovarian Cysts	Acute Pancreatitis, Pancreatic Trauma, Perforated Viscus, Intestinal Infarction And Obstruction, Peritonitis, Acute Cholecystitis, Appendicitis, Hepatitis, Abdominal Aortic Aneurysm, Malignancy (Especially Oesophagus, Stomach, Duodenum, Pancreas)
Extra-abdominal conditions	Salivary Disease, Renal Failure, Ketoacidosis, Pneumonia, Cerebral Trauma, Burns, Anorexia Nervosa And Bulimia	Renal Failure, Ketoacidosis, Fat Embolism, Bony Fractures
Drug induced	Azathioprine*, Colaspase, Sulphonamides, Tetracycline*, Didanosine, Methyldopa*, Oestrogens*, Frusemide, 5-Aminosalicyclic Acid*, Valproate*,	Adrenocorticotropic Hormone*, Tetracycline*, Oestrogens, Frusemide*, Valproate*, Thiazides*, Rifampicin*, Metronidazole*, Zalcitabine, Opioids, Methylprednisolone*, Indomethacin*

MATERIAL AND METHODS

Fifty diagnosed patients of acute pancreatitis at tertiary care hospital between December 2011 and May 2013 were included in the study from surgical wards. Data collected included full particulars of patients with biochemical parameters and radio imaging findings.

Samples were taken within 12–38 h of onset of abdominal pain. Biochemical analytes recorded were serum amylase, lipase, urea, and creatinine and liver enzymes. Estimated on autoanalyzer on AU 480.

Principle of the Test

The chromogen lipase substrate 1,2-0-dilauryl-rac-glycero-3-glutaric acid ester is cleaved by the catalytic action of alkaline lipase solution to form1,2-0-dilauryl-rac-glycerol and an unstable intermediate, glutaric acid-ester. This decomposes spontaneously in alkaline solution to form glutaric acid and methylresorufin. The color intensity of the red dye formed is directly proportional to the lipase activity and can be determined photometrically.

Normal range is: 13–60 U/L.

Amylase

CNP-G_3 Kinetic–ready to use kits from Siemens.

Principle of the Test & Description of Kit

2-Chloro-4-nitrophenyl-α-maltotriose (CNP-G3) is a direct substrate for determination of α-amylase activity, which does not require the presence of ancillary enzymes.

The rate of 2-Chloro-4-nitrophenol formation can be monitored at 450 nm and is proportional to the α-amylase activity in the specimen.

Normal range: Up to 80 U/L.

Diagnosis of Acute Pancreatitis

The diagnosis of acute pancreatitis requires two of the following three features:

a. Characteristic abdominal pain.
b. Levels of serum amylase or serum lipase, or both, that are three or more times the upper limit of normal.
c. Findings of acute pancreatitis on computed tomography.[1]

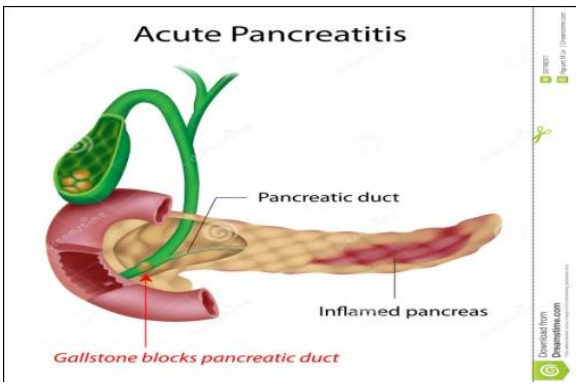
RESULTS

During the study period, a total of 50 patients were assessed with proven diagnosis of acute pancreatitis by radioimaging irrespective of etiologic. However, out of 50 patients, 42 patients had both amylase and lipase raised, remaining 8 patients had amylase normal but lipase raised (Table 1). Amylase was raised up to seven times of its upper limit of normal range (Fig. 1) and lipase was raised up to ten times its upper level of normal range (Fig. 2). Sensitivity of amylase in our study is 84% with confidence interval 0.74–0.94, whereas, sensitivity of lipase is 100%.

DISCUSSION

Originally the lipase assay used an oily substance which was not very suitable for automation. This is now not the case. Amylase has always been known to have poor specificity for diagnosis of acute pancreatitis. It also has the problem that low values are observed when the patient has hypertriglyceridemia; therefore both lipase and amylase were preferred to complement one another. Clinicians rely on the findings of serum amylase and serum lipase along with typical abdominal pain and CT findings for the diagnosis of acute pancreatitis. Several studies done in this field demonstrate different findings. Study done by Frank B et al[8] shows that a simultaneous determination of both amylase and lipase is recommended for the evaluation of patients with abdominal pain while some studies say both are not required for the same.[9] The diagnosis of pancreatitis should not solely be based on the arbitrary value of three or four times greater than normal of pancreatic enzymes, but interpreted together with the clinical presentation.[10] According to few studies, amylase levels may remain within normal range in 19 % of patients admitted with acute pancreatitis.[11,10] According to British Society of Gastroenterology guidelines for the management of acute pancreatitis, lipase is the main focus towards the diagnosis of acute pancreatitis.[7] Our studies go in accordance to the previous studies[4,5] which shows that serum lipase in a case of acute pancreatitis is better diagnostic marker than serum amylase. In a similar study done by Dhanwant Gomez et al.[11], majority of patients with acute pancreatitis had raised levels of both amylase and lipase (97%), however, raised lipase levels were seen between 95 and 100 % of patients based on the aetiology. In Our study, 84% of patients of acute pancreatitis had both amylase and lipase raised and 100 % of acute pancreatitis patients had lipase raised, irrespective of aetiology. Our study is in agreement with the study done by Agrawal et al.[5] and Thomson et al.[14]., who reported higher sensitivity and specificity of serum lipase in diagnosis of acute pancreatitis compared to serum amylase.

CONCLUSION



The following points can be made about serum lipase and amylase as diagnostic tests for AP from the review of current literature. Either one or both could be elevated in patients with AP. The ACG practice guidelines

recommend that either lipase and /or amylase elevation greater than 3 times ULN in patients with abdominal pain consistent with AP is diagnostic of AP. Lipase has slightly better specificity than amylase for AP. Also it is elevated earlier than serum amylase and stays elevated longer than amylase in patients with AP. In patients with hypertriglyceridemia AP, amylase is not significantly elevated. Lipase elevation, previously thought to be very specific for AP, is now increasingly seen with IBD, DKA and a host of other conditions. The extent of elevation in these non-pancreatitis causes of abdominal pain could be as high as 3 times ULN. Neither lipase nor amylase can be used to predict the severity or etiology of AP. Continuous elevation of lipase or amylase does not necessarily predict the occurrence of complications following an attack of AP[2]. Studies have shown that there is no diagnostic advantage of using lipase and amylase together routinely. In view of the slightly superior specificity of lipase over amylase and the lack of benefit from routinely performing both tests together, some Emergency Departments are checking only serum lipase in patients presenting with abdominal pain consistent with AP.[8] This approach seems justifiable based on the current review of literature. Routine use of both together adds to cost and is not recommended. Conditions under which the diagnosis of AP can be missed by just using lipase or amylase include; Very early in the course of the disease, example - a patient already admitted to the hospital develops abdominal pain since one hour; history of abdominal pain is not available, example - demented patients, critically ill patients and severe necrotizing AP. There is no definite correlation between cut off values and specificity.[5] Using a higher cut off values does not necessarily result in improved specificity, and similarly using lower cut off values does not necessarily result in diminished specificity.[7] One possible explanation for this could be the fact that the level of elevation of serum lipase or amylase is not related to the severity of the disease. Although the correlation is not absolutely linear from various ROC studies, increasing cut off may lead to diminished sensitivity. Further studies to quantify this decrease in sensitivity by using 3 times ULN as cut off as compared to using 2 times ULN or ULN as cut off are needed. If the clinical suspicion of AP is high, a low degree of enzyme elevation cannot rule out the diagnosis of AP, a recommendation endorsed by the ACG practice guidelines.

Table: 1 Levels of amylase and lipase

Acute pancreatitis (*n* = 50)	Raised lipase and amylase	Raised lipase with normal amylase levels	Total raised lipase levels
	42 (84 %)	08 (16 %)	50 (100 %)

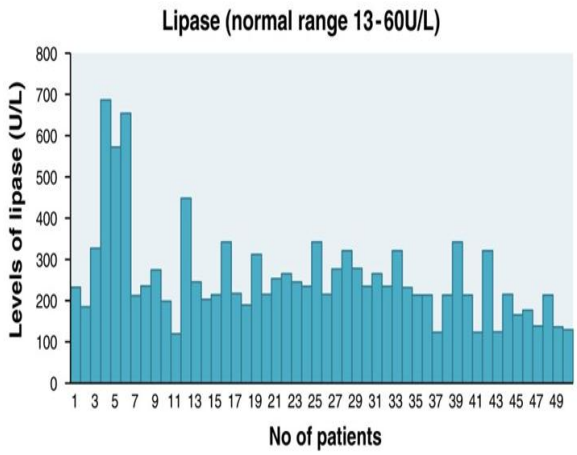


Figure: 2

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