

Review Article

Biochemical markers in differentiating gallstones pancreatitis from non-gallstone pancreatitis

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ABSTRACT

Acute pancreatitis has many causes; however, the most common cause of pancreatitis is gallstones globally. We have searched for relevant studies in this field aiming at establishing a short review about the usefulness of biomarkers in the diagnosis of acute pancreatitis and the relevant biomarkers and tests that can differentiate acute gallstone pancreatitis from other etiologies. It is worth mentioning that for the diagnosis and prognosis of biliary pancreatitis, radiological and laboratory diagnosis plays a major role in this field. Three biomarkers including serum amylase, lipase, and trypsinogen are the most important and most frequently noticed biomarkers in association with acute pancreatitis. Serum amylase has a specificity rate of 95% and a sensitivity of 61% when it measures more than 1000 IU/l which is three times as high as the normal level. However, it can be also found in other intrabdominal inflammatory conditions, and therefore, it cannot be used alone in the diagnosis. It has been reported that the specificity and sensitivity were 95% and 94%, respectively, for detecting high trypsinogen-2 levels in the patients' urinary samples, which were indicative of acute pancreatitis. For the diagnosis of biliary pancreatitis, liver function tests should be assessed. Although they might be specific, they are not always diagnostic in some cases, and therefore, other approaches for detecting gallstones as ultrasonography and MRCP should be considered together with the liver enzymes for an appropriate diagnosis.

Keywords: Pancreatitis, Gallstone, Biomarker; Trypsinogen, Liver functions

INTRODUCTION

Acute pancreatitis has many causes; however, the most common cause of pancreatitis is gallstones globally. This

etiology has been found to occur in 50% of the patients that suffer from acute pancreatitis in the western nations while acute pancreatitis itself accounts for 4.8-24.2 per 100,000 cases in these countries.¹⁻³ In the United States,

acute pancreatitis affects around 80,000 patients, which are equal to 17 per 100,000.⁴ A yearly incidence that ranges between 5-80 per 100,000 has also been estimated in the Japanese population.^{5,6} In patients with acute biliary pancreatitis, spontaneous recovery usually occurs in 15-30% of the patients, however, in some cases, patients develop severe sequelae of pancreatitis that requires special attention for appropriate management.⁷ Moreover, if left untreated, many complications following acute biliary pancreatitis as necrosis, hemorrhage, abscess, and pseudocyst formation, in addition to other disorders of systemic involvement as pleural effusion, renal impairment, adult respiratory distress syndrome, and other complications that usually require intensive care unit admission for management.^{7,8}

Many risk factors as, gender and the size of the stone may be associated with the development of biliary pancreatitis, and therefore, the identification of such risk factors might be important for the early detection and management of acute pancreatitis. Interestingly, acute pancreatitis is more common in male patients while it has been noticed that the development of gallstones is more common in female patients.⁹ The pathophysiology of acute pancreatitis has not been fully comprehended, yet, however, many theories have been proposed. Moreover, many etiologies have been reportedly associated with the development of acute pancreatitis. Premature activation of trypsinogen to trypsin within the pancreas is thought to play a major role in the inflammation of the pancreatic tissue.^{10,11} Additionally, looking at its unique function of activating other pancreatic enzymes, activated trypsinogen also plays a major role in the process of autodigestion found in acute pancreatitis.¹² For the diagnosis of pancreatitis, many serum biomarkers might be helpful. These include serum amylase, serum lipase, and serum and urinary trypsinogen. These biomarkers are of great value in the management and diagnosis of acute pancreatitis and all of them have variable efficacies that should be considered when initiating the diagnosis.

Acute pancreatitis is considered a fatal disease although many interventional approaches have been proposed. The estimated mortality rate for acute pancreatitis has been estimated to be 2-7%.¹³⁻¹⁶ Two major factors are considered as the determinant of the prognosis and severity of the diseases like organ failure and the presence of pancreatic necrosis. It has also been estimated that around 50% of the patients with acute pancreatitis usually die within the first one to two weeks, which may be induced by the presence of an underlying organ failure. In addition to the multiple complications that may occur following biliary pancreatitis, an estimated risk ratio of 32-61% was found for acute biliary pancreatitis recurrence.^{14,15} Therefore, it might be crucial in identifying the proper etiology of acute pancreatitis for proper management which may be dependent on the etiology. We have searched for relevant studies in this field aiming at establishing a short review about the usefulness of biomarkers in the diagnosis of acute

pancreatitis and the relevant biomarkers and tests that can differentiate acute gallstone pancreatitis from other etiologies.

Extensive literature search of the Medline, Cochrane, and EMBASE databases was performed on 18 December 2020 using the medical subject headings (MeSH) or a combination of all possible related terms. Studies discussing the usefulness of biomarkers in the diagnosis of acute pancreatitis and the relevant biomarkers and tests that can differentiate acute gallstone pancreatitis from other etiologies; were screened for relevant information. We did not pose any limits on date, language, or publication type.

Differentiating gallstones from non-gallstones acute pancreatitis

Studies suggest that acute biliary pancreatitis diagnosis should be established if the patient has a history that mimics the pain of biliary colic.^{17,18} Although acute biliary pancreatitis is deemed the commonest type of pancreatitis, when initiating the diagnosis and management, other causes of acute pancreatitis should be considered. For instance, prolonged alcohol consumption is also another common cause of acute pancreatitis. Other etiologies include the consumption of certain medications that can cause pancreatic toxicity, infectious diseases, genetic disorders, postoperative cause, and other causes as surgical operations involving the pancreas, or the bile duct which can cause pancreatitis from an underlying injury.¹⁸⁻²⁰ Although pancreatic biomarkers play an important role in initiating the appropriate diagnosis, carefully approaching the patient by obtaining a proper history and physical examination would be the key-role for a rightful diagnosis. For the diagnosis and prognosis of biliary pancreatitis, radiological and laboratory diagnosis also play a major role in this field.^{21,22}

DIAGNOSTIC BIOMARKERS OF ACUTE PANCREATITIS

Serum amylase

Elevated levels of the serum amylase is an indicator of acute pancreatitis on the condition that the rise would be three times higher than the normal limits. It is considered as the fastest marker to rise in the patient's serum as it rises 12 hours within the onset of acute pancreatitis symptoms then it rapidly falls in the next four to five days.²³ However, in 19-32% of patients with acute pancreatitis that are admitted to the hospital, serum amylase may show normal levels which may be attributable to delayed admission by the patient or the presence of an underlying exocrine insufficiency which may be attributable to chronic alcohol consumption.^{24,25} Additionally, the presence of other conditions as hypertriglyceridemia in the affected patient's serum may interfere with the appropriate interpretation of abnormal serum amylase levels masking these high levels, and

therefore, this should be considered by administration of lipid-lowering drugs by the patient before measuring the amylase levels to obtain the right results.²⁶ Although serum amylase levels are good indicators of acute pancreatitis, it can also be found elevated in other conditions as in other intra-abdominal inflammatory disorders, salivary gland diseases, and renal impairment because the kidneys cannot tolerate the excretion of the excess amounts of serum amylase leading to macroamylasaemia as serum amylase has been found conjugated with circulating compounds as polysaccharides and immunoglobulins leading to the formation of larger molecular weight compounds that are hard to excrete.²⁶ Serum amylase sensitivity and specificity of detection of acute pancreatitis are hugely dependant on the specified threshold. A review by Yadav et al showed that a specificity rate of 95% and a sensitivity one of 61% for serum amylase can be found when it measures more than 1000 IU/l which is three times as high as the normal level.²⁶ Therefore, other adjuvant approaches should be used when approaching the diagnosis of acute pancreatitis.

Serum lipase

The advantage of serum lipase over amylase is that it remains in the patient's serum for a longer period (8-14 days), therefore, it can be used for the diagnosis of acute pancreatitis in patients with delayed hospital admission. Because serum lipase activities are four times as high as these of serum amylase, it is less likely to be affected by the presence of chronic pancreatic insufficiency.²⁷ A review by Werner et al suggests that serum lipase, whenever available, should be preferred to serum amylase according to recent United Kingdom guidelines for managing pancreatitis.²⁸ Despite these advantages, elevated serum lipase levels are not always specific to acute pancreatitis. Similar to amylase, it can also be detected in other intraabdominal inflammatory conditions and renal impairment. Although hypertriglyceridemia does not interfere with the high levels of serum lipase, high levels can be found after the administration of certain drugs as frusemide. Besides, previous reports show that serum lipase has a better predictive value for acute pancreatitis. The estimated specificity for a 600 IU/l elevation in the serum lipase levels is equal to or more than 95% while the estimated sensitivity ranges between 55-100%.^{26,29}

Serum and urinary trypsinogen

Trypsinogen is a pro-enzyme that is cleaved in the presence of duodenal enterokinase or by the presence of inadequate amounts of trypsin, which results in the conversion of trypsinogen into trypsin, by positive feedback. This process results in the formation of trypsinogen activation peptide (TAP), and active 24 kDa protease trypsin. There are two major isoenzymes of trypsinogen; 1 and 2. Trypsinogen-2 exists in acute pancreatitis in high serum levels.³⁰ Genetic predisposition

plays a major role in trypsinogen dysfunction and can lead to the formation of pancreatitis.¹² Moreover, high serum calcium levels may also predispose to the development of pancreatitis as calcium intervenes against the autolysis of trypsin.³¹ Within a few hours to three days from the initiation of acute pancreatitis, high levels of serum and urinary trypsinogen-2 can be detected in the affected patient. In patients with acute pancreatitis following endoscopic retrograde cholangiopancreatography, high levels of this iso-enzyme could be detected in the serum within one hour.³² Kempainen et al conducted a retrospective study of 500 patients presenting with symptoms of acute pancreatitis to determine the positive predictive value of trypsinogen-2.³³ The authors reported that the estimated specificity and sensitivity were 95% and 94%, respectively, for detecting high trypsinogen-2 levels in the patients' urinary samples which were indicative of acute pancreatitis. The sensitivity and specificity of urinary trypsinogen-2 were higher than the serum levels of amylase and lipase in the determination of acute pancreatitis. Moreover, a negative predictive value of 99% has been previously estimated for urinary trypsinogen-2 in diagnosing acute pancreatitis.²⁹ Therefore, it has been estimated that trypsinogen-2 levels might be more efficacious than serum levels of amylase and lipase in detecting acute pancreatitis.

Diagnosis and identification of acute gallstone pancreatitis

The first step for initiating the diagnosis of acute biliary pancreatitis is an abdominal ultrasound for the detection of stones blocking the biliary ducts and canaliculi starting from the gall bladder to the common bile duct. Ultrasound imaging has been reported to have a sensitivity of 95% of any underlying gallstones on the condition that the case was not complicated. However, this rate begins to decrease reaching up to 67-87% when the case is complicated with acute pancreatitis as a result of bowel and/or biliary distensions.³⁴ Although the sensitivity of ultrasound might be high, previous studies also showed that the sensitivity for detection of gallstones in the common bile duct is hugely variable ranging between 25-90%. In addition to the aforementioned biomarkers, other tests and markers help to differentiate between biliary and non-biliary pancreatitis. Liver function tests and enzymes, for instance, are hugely useful in the diagnosis of gallstones pancreatitis. A previous meta-analysis showed that a triple time increase in the levels of serum alanine transaminase, which is nearly equal to or more than 60 IU/l within 48 hours from the initiation of symptoms, is a good indicator of the presence of gall stones and biliary obstruction, in addition to the presence of acute pancreatitis with an estimated positive predictive value of 95%.³⁵ The same results were also confirmed by a previous study which supports the hypothesis.³⁶ On the other hand, another study showed that normal liver enzymes were detected in 10-15% of the patients with acute gallstones pancreatitis.³⁷ Therefore, liver enzymes should not be always used for the diagnosis

of biliary pancreatitis. Other imaging procedures as magnetic resonance cholangiography (MRCP) has also shown favourable outcomes regarding the diagnosis of gallstones presence and biliary obstruction with an estimated specificity, sensitivity, positive predictive value, and a negative predictive value of 96-100%, 84-95%, 91-100%, and 92-98%, respectively.³⁸⁻⁴¹ However, previous studies said that this role has not been evidenced, yet, in the diagnosis of associated pancreatitis. This tool might be highly favorable for confirmation of the diagnosis of severely ill patients with acute pancreatitis that has been previously diagnosed with biomarkers and abdominal ultrasonography. Endoluminal ultrasonography has also been used as a useful technique for the detection of gallstones that is similar to the MRCP.⁴²

CONCLUSION

In this review, we have discussed the relevant biomarkers that can be used in the diagnosis of actual pancreatitis. Three biomarkers including serum amylase, lipase, and trypsinogen are the most important and most frequently noticed biomarkers in association with acute pancreatitis. Although serum and urinary trypsinogen levels might be the best markers for establishing the diagnosis of acute pancreatitis, it is estimated that all of these biomarkers should be investigated together with other diagnostic approaches. For the diagnosis of biliary pancreatitis, liver function tests should be assessed. Although they might be specific, they are not always diagnostic in some cases, and therefore, other approaches for detecting gallstones as ultrasonography and MRCP should be also considered together with the liver enzymes for an appropriate diagnosis.

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