

## Review Article

# Diagnostic role of rapid urinary trypsinogen-2 strip test in acute pancreatitis

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## ABSTRACT

Acute pancreatitis is one of the most common surgical conditions that present with acute abdomen. Serum amylase and lipase are one of the most important and widely used laboratory methods to diagnosis acute pancreatitis. However, these tests have had unsatisfactory results in terms of their sensitivity and specificity. Urinary trypsinogen-2 strip test has been developed for the detection of increased levels of trypsinogen-2 in urine and has been suggested to play an important role in the screening of acute pancreatitis on the basis of its rapid results. In this review, we aimed to assess the diagnostic role of the same existing articles using databases like pubmed, google scholar, medline, pubmed central. We analysed about 50 articles all of which were in English and 15 were excluded on the basis of our subject criteria.

**Keywords:** Acute pancreatitis, Urinary trypsinogen, Amylase, Lipase

## INTRODUCTION

Acute pancreatitis (AP) is an aggressive, evolving and a serious condition with a variable severity.<sup>1</sup> It is one of the most frequently encountered surgical cases seen in the emergency department. Most patients develop a mild and self-limited course which resolves spontaneously; while 10%-20% have a rapidly progressive inflammatory response associated.<sup>2,3</sup> Early diagnosis of acute pancreatitis is crucial to ensure rapid and appropriate treatment.

Clinically, it could be difficult to differentiate from other causes of pain abdomen. Determination of amylase in serum or urine is one of the primary laboratory methods for diagnosing acute pancreatitis but hyperamylasemia is absent in 19% of cases.<sup>4</sup>

Proteolytic enzymes play an essential role in the pathophysiology of AP and the serum concentration of trypsinogen reflect pancreatic damage. Pancreatic fluid contain high concentrations of both trypsinogen-1 and

trypsinogen-2.<sup>5</sup> Intrapaneatic activation of trypsinogen to trypsin plays a pivotal role in the development of acute pancreatitis.<sup>6</sup> Therefore, assessing the severity of the disease remains one of the most important aspects when a patient presents to the hospital.

This topic has been widely studied by various investigators and inconclusive results have been reported.

## METHODOLOGY

In this review, we aim to assess the diagnostic role of the rapid urinary trypsinogen 2 strip in acute pancreatitis by interpreting existing articles using databases like pubmed, google scholar, medline, pubmed central with the help of keywords like Acute Pancreatitis, urinary trypsinogen, amylase and lipase. All the articles were in English and the oldest article dated to 1932. The articles were prospective, retrospective and case control. A total of 50 articles were analysed and 15 were excluded since they didn't meet the criteria of the subject of the discussion.

## DISCUSSION

### *Epidemiology*

Worldwide, the incidence ranges from 5-80 per 100,000 population with the maximum in United States and Finland. It shows significant variation which is related to the prevalence of the etiological factors and ethnicity.<sup>1</sup> It has an overall mortality of about 10%-15% and increases up to 40% in severe cases.<sup>7</sup> Men have a higher incidence than women about 10%-30% and is probably attributed to the higher incidence of alcoholic pancreatitis.<sup>8</sup> 80% of the cases are associated with gallstone disease or alcohol consumption. The rest 10% are related to other miscellaneous causes like drugs, metabolic causes and other causes and 10% are idiopathic.<sup>9</sup>

### *Etiology*

There are many factors that are associated with the onset of acute pancreatitis, commonest of which are gallstones and alcohol comprising of about 80% of the cases.<sup>1</sup> The prevalence of alcoholism in a population that has been studied and the population determines the relative frequency. In the UK, gallstone disease contributes to 50% of the cases, 25% are attributed to alcohol and 25% to other factors. In the United States alcohol abuse has been reported to be the most predominant cause of acute pancreatitis.<sup>9</sup> Studies show that females are more prone to have gallstone pancreatitis whereas alcohol induced is the predominant cause among the males.<sup>10</sup>

### *Diagnostic work up*

The diagnosis of acute pancreatitis requires at least the presence of two of the three following criteria: (i) abdominal pain in congruous with the disease (sudden onset of a continuous, severe, epigastric pain radiating to the back), (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and (iii) characteristic features on abdominal imaging.<sup>11</sup>

The pancreatic origin of blood amylase was first proclaimed by Schlesinger following the disappearance of the enzyme post pancreatectomy in dogs and cats.<sup>12</sup> In 1919, it was used as a diagnostic marker for the first time for diseases of pancreas. Stratification of severity and prognosis of acute pancreatitis goes back to the later half of the last century and are driven by prime advances in new laboratory tests and imaging procedures. Elman et al. first used amylase levels to make a diagnosis of acute pancreatitis in the 1920s.<sup>13</sup> On the other hand, Cherry and Candall for the first time used lipase for the diagnosis of AP.<sup>14</sup>

Evaluation of pancreatic enzymes especially serum amylase and lipase is a crucial aspect of managing acute pancreatitis but there's no gold standard test at present for the same. Serum amylase levels usually increase within 24 hours of the onset of acute pancreatitis but this is transient

as it slowly reverts back to normal within 3-5 days.<sup>4</sup> It has a low sensitivity, ranging between 55-84% and a specificity of 85-98%. Serum lipase levels rise within 4-8 hours after the onset of the symptoms, peaks at 24 hours and returns to normal levels within 7-14 days.<sup>15</sup>

### *Serum amylase and lipase in acute pancreatitis*

Amylase is a glycoside hydrolase enzyme which is mainly produced by the pancreas and in small quantities in other tissues including the salivary glands. Its levels usually rise within 24 hours of the onset of acute pancreatitis but this elevation is transient as it slowly reverts back to normal within 3-5 days.<sup>4</sup> It has been stated that levels of hyperamylasemia does not show compelling correlation with the severity of the disease and at the same time is also seen in other cause of acute abdominal pain of non-pancreatic origin. Whether serum amylase levels can be used to confirm or refute a diagnosis of acute pancreatitis is still not very well defined.

Cochrane review on laboratory diagnosis of acute pancreatitis recommend that on presentation even if the patients have normal levels of enzymatic tests, they should be admitted and treated as having acute pancreatitis on suspicion as about 1 in 10 patients without AP maybe misdiagnosed.<sup>16</sup>

Clavien et al., in his prospective study aimed to see if patients with acute pancreatitis who had normal levels of amylase behaved differently than those who had elevated levels. In his series he concluded that AP did not behave differently in terms of statistical significance whether amylase on admission was normal or elevated, although there was a tendency for normoamylasemic attacks to follow milder course in the hospital. Spechler et al., reported a higher incidence (32%) of normal amylase levels in acute pancreatitis.<sup>17</sup> He suggested that could be because the diseased parenchyma is no longer able to produce adequate amounts of enzymes especially in acute alcoholic pancreatitis.

In the expertise of Albo et al., one third of their really unwell patients with hemorrhagic pancreatitis had normal levels of amylase suggesting that the enzyme levels can be reciprocally associated with the severity of the disease.<sup>18</sup>

Several studies have been done to compare serum amylase with serum lipase assays and have shown that serum lipase level is a more accurate diagnostic biomarker in diagnosing acute pancreatitis.<sup>19-21</sup>

The proportion of patients with isolated hyperlipasemia has been reported to up to 32% in AP in literature.<sup>4,17,22</sup> Frank et al., in his retrospective study aimed to identify clinical scenarios in which the lipase is significantly elevated but the amylase is normal. He reported in his case series this was either related to renal insufficiency, non-pancreatic sources of lipolytic enzymes due to malignant tumors, to acute cholecystitis or esophagitis, to

hypertriglyceridemia, or to subclinical pancreatitis in patients without abdominal pain. Therefore concluded that increased levels of lipase should not be equated with evidence for pancreatitis if the amylase is normal and both should be determined for the evaluation of patients with abdominal pain.<sup>23</sup>

The JPN guidelines after their metaanalysis in 2015 recommended that measurement of serum lipase is more important in the diagnosis of acute pancreatitis but serum amylase is suggested if measurement of lipase levels cannot be carried out.<sup>24</sup>

From the above mentioned studies, it is therefore interesting to note that at present there is still no biochemical test that can be considered the “Gold standard” for the diagnosis and evaluation of the cause of acute pancreatitis. Several other pancreatic enzymes and inflammatory biomarkers like trypsinogen, phospholipase A2, elastase, urinary trypsinogen activated protein and carboxypeptidase have been evaluated in the past for their diagnostic value in acute pancreatitis. Among these, the best studied was trypsinogen as their levels in both serum and urine rise within a few hours of onset of acute pancreatitis.<sup>25</sup>

#### ***Role of trypsinogen as a biomarker for the diagnosis of acute pancreatitis***

Proteolytic enzymes play an important role in the pathophysiology of acute pancreatitis. Of utmost importance is the role of trypsinogen whose premature activation is a crucial event in the early phase of the disease. Trypsinogen-1 (cationic) and trypsinogen-2 (anionic) enter the bloodstream and are excreted in the urine.<sup>26</sup> Measurement of urine trypsinogen levels and TAP carried out for the first time in the mid 1990s showed more sensitivity and specificity and since then has been suggested as a good alternative biochemical test in diagnosing acute pancreatitis.<sup>27</sup>

Itkonen et al., in 1990 developed an immunofluorometric assay which used monoclonal antibodies produced by immunization for measurement of both trypsinogen 1 and 2. He reported that in acute pancreatitis the concentration of trypsinogen-2 is 50-fold higher than in controls, whereas the difference in trypsinogen-1 concentrations is only 15-fold.<sup>5</sup>

Mero et al, in his study aimed to study the correlation between serum immunoreactive trypsin, phospholipase A2 along with trypsin inhibitory capacity of serum in patients with acute hemorrhagic pancreatitis and concluded that there was no correlation between them and the severity, however markedly decreased values of alpha<sub>2</sub>-macroglobulin indicated a fulminant course of the disease.<sup>28</sup>

Hedstrom et al., developed a sensitive time-resolved immunofluorometric assay (IFMA) where he assessed the

clinical utility of the trypsin-2-AAT assay with that of free trypsinogen-2 and amylase in serum in patients with acute pancreatitis and acute abdominal pain of extrapancreatic origin and concluded that assays of free trypsinogen-2 and amylase, assay of trypsin-2-AAT improved the clinical specificity for acute pancreatitis. However, there was a drawback to this as increased concentration of trypsin-2-AAT and trypsinogen-2 were also observed in patients with chronic renal failure undergoing dialysis.<sup>29</sup>

Hedstrom et al., in 1996 conducted a study where he compared results of urinary trypsinogen and trypsinogen concentrations in the serum of patients with acute pancreatitis and found that the sensitivity of the urinary strip was close to that of the quantitative test for trypsinogen in serum (91%) and a specificity of 90%. He concluded that this test should be prospectively tested in a consecutive series of patients who are suspected to have acute pancreatitis.<sup>30</sup>

According to Saino et al., who studied the accuracy of serum trypsinogen-2 in predicting the severity of acute necrotizing pancreatitis concluded that there was a significant difference in serum trypsinogen-2 values between patients with uncomplicated and complicated disease ( $p=0.002$ ) and hence can be used as a useful method to predict the severity of acute necrotizing pancreatitis.<sup>31</sup>

The above mentioned studies have shown varying results regarding the definitive role of the urinary trypsinogen 2 strip in acute pancreatitis.

In another prospective study carried out by Kemppainen et al., the clinical utility of urinary trypsinogen-2 strip was evaluated in cases of image proven acute pancreatitis and showed a sensitivity of 94% and specificity of 95%.<sup>2</sup> However, it was only compared to serum lipase levels which served as a major limitation of this study.

The timing on when the urinary trypsinogen test should be carried has been debated for a long time and various observations have been made.

Saez et al. in his prospective study found UT to have a clinical value similar to amylase and lipase with a sensitivity of 68%, 13.6% in extrapancreatic controls ( $P<0.01$ ), but when performed within 48 hours of symptom onset. He concluded that, urinary CAPAP was the most reliable test for the diagnosis of acute pancreatitis (sensitivity 66.7%, specificity 95.5%, positive and negative predictive values 96.6% and 56.7%, respectively), with a 14.6 positive likelihood ratio.<sup>32</sup>

Chen et al., in his study stated that UT when performed immediately in patients who presented within 24 hours of onset of symptoms was comparable to amylase/lipase and found the sensitivity, specificity, and accuracy of the

urinary trypsinogen-2 test strip for were 89.6%, 85.7%, and 87.3% and diagnostic accuracy rates of serum amylase and serum lipase were 88.5% and 93.3%.<sup>33</sup> He concluded that there was no significant difference in the sensitivity between urinary trypsinogen-2 and serum lipase. Chandra et al., from Karnataka, India assessed the role of urinary trypsinogen-2 strip test in comparison to amylase and lipase as a screening test in acute pancreatitis and showed that it had a 100% sensitivity & specificity with the ROC being 1. He suggested that it could replace the conventional method of measuring amylase and lipase.<sup>34</sup>

According to Anandh et al., who evaluated the efficacy of urinary trypsinogen 2 strip test in the patients of acute pancreatitis in SRMC, Chennai found that urinary trypsinogen-2 dipstick test sensitivity was 90%, specificity was 84.5%, its positive predictive value was 80.0% and negative predictive value was 92.5% and to serum amylase and serum lipase. He concluded that urinary Trypsinogen-2 Dipstick Test results interpreted in background of lipase provide a fairly accurate early diagnosis of AP; however, larger series will validate these findings.<sup>35</sup>

## CONCLUSION

Previous studies conducted on this subject have shown controversial results regarding the diagnostic role of the rapid trypsinogen-2 strip test in acute pancreatitis. The major drawbacks of these studies were that the sample size in some of them was limited, there was no well-defined time frame of carrying out the test and the enzyme variants used were different in most of the studies.

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