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## Urinary trypsinogen-2 test a boon in diagnosing acute pancreatitis

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### A B S T R A C T

Urine Trypsinogen-2 dip stick test is a simple, rapid, easy, and non-invasive test which can diagnose or rule out, most of the cases of acute pancreatitis. The urinary trypsinogen-2 test could be used as a screening test for acute pancreatitis. It has been shown to be a reliable and useful screening test for acute pancreatitis in daily practice, particularly in healthcare units lacking laboratory facilities.

## Introduction

Acute pancreatitis (AP) is an inflammatory disease, and it manifest with broad clinical spectrum varying from mild self-limiting form to severe form such as pancreatic necrosis, multi-organ failure and death.<sup>1,2</sup>Early diagnosis and treatment of acute pancreatitis is critical in reducing the morbidity and the mortality of the patients.<sup>3,4</sup>Unfortunately, to date there is no "gold standard biomarker" for the diagnosis of AP. Measurement of serum amylase or lipase is the principal laboratory method used to diagnose acute pancreatitis, but unsatisfactory sensitivity and specificity of these assays warrants better investigation.<sup>5</sup>The goal of this prospective study is to evaluate the accuracy of urinary trypsinogen-2 relative to serum amylase and lipase for the early diagnosis of acute

pancreatitis in healthcare units lacking laboratory facilities.

## Materials and Methods

### Patients

Patients between 20 and 60 years with features suggestive of acute pancreatitis were enrolled in the study prospectively in the emergency department of our institution from January 2013 to November 2013. Written consent from the patient and Institutional Ethical Committee approval was obtained. Exclusion criteria includes age above 60 years, proven cases of chronic pancreatitis, pancreatic cancer, hereditary pancreatitis and cystic fibrosis.

## **Study design**

Blood and urine samples were obtained from all study participants. A qualitative assay for the detection of Urine trypsinogen-2 were measured using a dipstick test (Actim Pancreatitis, Medix BiochemicaOy AB, Kauniainen, Finland) based on an immunochromatography assay. The detection limit of the test was approximately 50 ng/mL. After the test strip has been dipped into the urine sample, trypsinogen-2 bound to monoclonal antibody-labeled blue latex particles migrate across a nitrocellulose membrane with a zone containing another antibody. At trypsinogen-2 concentrations higher than 50 µg/L, a blue line develops in this zone. The test was considered positive when a clear blue line along with a control line has been detected within 5 min. If the control line is undetectable the assay is repeated. Serum amylase and lipase were measured immediately using a standard automated analyser. Patients were also evaluated with ultrasound (USG) abdomen and contrast enhanced computed tomography (CECT) abdomen in conditions where serum parameters were within normal limits.

Acute pancreatitis is diagnosed using the diagnostic criteria of acute pancreatitis established by the Japanese Ministry of Health, Labour and Welfare (JMHLW) (2008).<sup>5</sup> These criteria are composed of 3 items: (1) acute abdominal pain and tenderness in the upper abdomen, (2) elevated levels of pancreatic enzymes in the blood or urine, and (3) findings of acute pancreatitis detected by ultrasonography (US), computed tomography (CT), or magnetic resonance imaging. Patients who presented with at least 2 of the above 3 manifestations and in whom other pancreatic diseases and acute abdomen had been ruled out were diagnosed as having acute pancreatitis. Elevation of serum amylase or

lipase was defined as more than 3 times the upper normal value. Endoscopic retrograde cholangiopancreatography (ERCP) related acute pancreatitis were diagnosed using the diagnostic criteria of post-ERCP pancreatitis.

The results were analysed using Microsoft Excel for tabular transformation and graphical representation. For comparing the parameters, Chi Square test or Fischer's exact test were used. SPSS software was used for statistical analysis. The primary outcome of this study was the relative accuracy of the urine trypsinogen test for the diagnosis of acute pancreatitis when compared with serum amylase and lipase.

## **Results and Discussion**

A total of 100 consecutive patients (84 men and 16 women) with acute abdominal pain who were seen in the emergency department were included in this study. There were 61 patients with acute pancreatitis and 39 patients with other diseases.

### **Sensitivity and specificity of diagnostic tests for acute pancreatitis**

The results of the urinary trypsinogen-2 dipstick test were positive in 48 of 61 patients with acute pancreatitis (sensitivity, 78.69%). Results were also positive in 3 of 39 patients with abdominal pain but no evidence of acute pancreatitis (specificity, 92.31%). False positive results is seen in 3 of the 39 non-pancreatitis cases, namely 2 cases of Gallstones and 1 case of renal failure.

When urine trypsinogen-2 assay greater than 50ng/mL was defined as positive, the sensitivity and specificity of the assay for acute pancreatitis were 78.69% and 92.31%, respectively. When serum amylase greater than 3 times the upper normal value was

defined as positive, the sensitivity and specificity of the assay for acute pancreatitis were 73.77% and 89.74%, respectively. When serum lipase greater than 3 times the upper normal value was defined as positive, then the sensitivity and specificity of the assay for acute pancreatitis were 59.02% and 89.74%, respectively.

Acute pancreatitis (AP) is an inflammatory disease, and it manifest with broad clinical spectrum varying from mild self-limiting form to severe form such as pancreatic necrosis, multi-organ failure and death.<sup>1,2</sup> Since 1974, several scoring systems have been developed clinically and radiologically assessing the prognosis of the disease. The rationale behind the assessment of severity is mainly for practical purpose, where mild pancreatitis needs supportive care but severe pancreatitis needs intensive care. The key to reduce the mortality and morbidity of the disease is early detection and appropriate management.

An ideal diagnostic method should differentiate patients with mild and severe disease, have easy usability, wide availability and high accuracy, and with low inter-observer variability. Serum amylase and serum lipase which are used for the diagnosis of acute pancreatitis are relatively less sensitive and specific. Various scoring systems are being used in acute pancreatitis to predict the severity and outcome of the disease. There is no single comprehensive test to aid in early and accurate detection of acute pancreatitis. The urinary trypsinogen-2 dipstick test is proposed to be a rapid method for the diagnosis of acute pancreatitis at the earliest, based on the immunochromatographic method.

Under normal conditions, trypsinogen is secreted into pancreatic fluid by acinar cells. Intrapancreatic activation of trypsinogen to

trypsin is a central pathophysiologic event in the development of acute pancreatitis.<sup>6</sup> Human pancreatic juice has three isoforms of trypsinogen (TPS) namely, cationic (TPS-1) and anionic TPS (TPS-2), and a minor isoenzyme (TPS).<sup>7</sup> During acute pancreatitis, trypsinogen 2 has been observed to be excreted in significant amount, making this proenzyme a potential diagnostic marker for acute pancreatitis.<sup>6-8</sup> In 1990, Itkonen et al<sup>9</sup> developed an immunofluorometric technique to detect serum TPS-1 and TPS-2, and subsequently commercial urinary TPS-2 (UT-2) dipstick (Actim Pancreatitis®) based on the same technique was introduced.<sup>10</sup>

The diagnosis of acute pancreatitis relies on clinical symptoms and is supported by elevation of standard biochemical blood markers, such as amylase or lipase, and diagnostic imaging.<sup>3,5</sup> With regard to the diagnosis of acute pancreatitis, both blood lipase and blood amylase exhibit similar sensitivity, but lipase being more specific.<sup>3,5</sup> UT-2 estimation doesn't require laboratory facilities and is undertaken almost instantaneously (within 5 minutes) as opposed to serum amylase and lipase, results for which may require an hour to get back to the physician.

Four studies from the affiliated Finnish group and 3 studies from other geographic areas and ethnic populations demonstrated high sensitivity (89.6%-100%) and specificity (85.7%-100%) for this assay,<sup>6,7,11-15</sup> but these findings were not reproduced in 5 other studies (range of sensitivity 53.3%-77.3%; range of specificity 86.4%-100%).<sup>8,16-19</sup> In our study, the sensitivity and specificity of the urine trypsinogen-2 dipstick test for the diagnosis of acute pancreatitis was superior to that of serum amylase and lipase. Therefore, the urinary trypsinogen-2 test can be used as

screening test for acute pancreatitis, as a negative result would exclude most cases of acute pancreatitis. Mero et al<sup>20</sup> also reported that the total TPS immunoreactivity in serum lasts for more than 9 days. High specificity of UT-2 could potentially be useful in its application in emergency department to improve accuracy of diagnosing AP.

One of the limitation of this study is that the enrolment to this study was performed by the surgeons. In emergency department, resident physicians and emergency medical staff initially examine and treat the patients visiting the emergency department. If the patients need to be admitted, they were referred to the staff of the surgical departments. Therefore, the ratio of acute pancreatitis in this study was very high and was disproportionate to the number of cases of acute pancreatitis among patients who visit the emergency department with acute abdominal pain. Second, the patient population in the present study is composed of a high proportion of patients with mild acute pancreatitis, which, for reasons stated earlier, may not be representative of the patient population in other countries. Thus, the sensitivity and specificity of these diagnostic tests for acute pancreatitis may be different in other countries.

### **Conclusion**

Urine Trypsinogen-2 dip stick test is a simple, rapid, easy, and non-invasive test which can diagnose or rule out, most of the cases of acute pancreatitis. Its estimation doesn't require laboratory facilities. It is undertaken almost instantaneously (within 5 minutes) as opposed to serum amylase and lipase, results for which may require an hour to get back to the physician. The urinary trypsinogen-2 test could be used as a screening test for acute pancreatitis.

Modification of the cutoff point of this assay increases the specificity to the point where it can be used for diagnosis. And hence it has been shown to be a reliable and useful screening test for acute pancreatitis in daily practice, particularly in healthcare units lacking laboratory facilities.

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