Predictive Value of Urinary Trypsinogen-2 Dipstick for Early Diagnosis of Acute Pancreatitis in Emergency Medicine

MOHAMED M. EL-SHEIKH, M.Sc.*; YASSER M. ABD EL-RAOUF, M.D.** and HESHAM A. EL-SOROGY, M.D.***

The Departments of Emergency Medicine & Traumatology*, Internal Medicine** and Clinical Pathology***, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

Background: Acute pancreatitis is a grave condition that requires fast and accurate diagnosis to save lives and prevent complications. In this study, we evaluated the fast and bedside urinary trypsinogen-2 dipstick test in the diagnosis of acute pancreatitis.

Aim of Work: This study was designed to evaluate the predictive value of the rapid urinary trypsinogen-2 test strip in acute pancreatitis, in comparison with serum amylase and serum lipase in Emergency Department at Tanta University Hospital.

Subjects and Methods: Thirty-five (35) patients with acute pancreatitis (Group I) and thirty-four (34) patients with other causes of acute abdomen (Group II) were included in the study.

Full history taking, clinical examination, and laboratory investigations including urine analysis and serum levels of creatinine, random glucose, lipid profile, total and direct bilirubin, albumin, liver enzymes, total calcium, amylase, and lipase were undertaken.

In addition, radiological examinations, using abdominal pelvic ultrasonography, computed tomography of the abdomen and conventional X-ray when appropriate were undertaken.

Urinary trypsinogen-2 was tested using dipstick.

Results: We found that the most common cause of acute pancreatitis was gall stone obstructive pancreatitis (76.47%), serum amylase and lipase were elevated in (91.18% and 88.24% respectively) in acute pancreatitis.

While urinary trypsinogen-2 dipstick test was positive in 100% of patients with acute pancreatitis.

The specificity of serum amylase, serum lipase and urinary trypsinogen-2 in diagnosis of acute pancreatitis was (76.47%, 88.24% and 100% respectively).

Conclusion: Urinary trypsinogen-2 dipstick test is a promising fast and easy test performed in the effort of diagnosis of acute pancreatitis. Further studies on large number of patients are mandatory to confirm the findings in this study.

Key Words: Acute pancreatitis – Acute abdomen – Serum lipase – Serum lipase.

Introduction

ACUTE pancreatitis is a medical emergency that can result from mechanical ampullary obstruction, penetrating peptic ulcers, mumps infection, abdominal trauma, post Endoscopic Retrograde Cholangiopancreatography (ERCP) and other causes [1].

It is an inflammatory condition that occurs due to activation of pancreatic proenzymes especially trypsinogen inside the pancreas while this activation occurs normally in the duodenum that lead to autodigestion of pancreas [2].

Acute pancreatitis may be mild or severe that is clinically diagnosed with severe epigastric pain radiating to the back, shock, respiratory distress, and multi-organ failure due to systemic inflammatory response that occurs in response to inflammatory mediators as TNF-alpha and IL-1 [3].

Differentiation of other causes of acute abdomen that may be mistaken with acute pancreatitis is essential due to different treatment [4].

Diagnosis of acute pancreatitis depends mainly on clinical diagnosis, elevated serum amylase and lipase, but characteristic abdominal imaging may be helpful in some cases following American College of Gastroenterology Guidelines [5].

However, traditional tests using amylase and lipase are time consuming and may be non-specific
which mandates finding another easy and fast laboratory test to diagnose acute pancreatitis [6,7].

It was found that large amounts of pancreatic enzyme trypsinogen-2 are excreted into urine within hours of onset of acute pancreatitis. This gives a hint about possible value of this enzyme in early diagnosis of acute pancreatitis to save time [8].

In this study, we evaluated the predictive value of urinary trypsinogen-2 in diagnosis of acute pancreatitis.

**Subjects and Methods**

This study was carried out in Tanta University Emergency Hospital from August 2016 till August 2017.

Thirty-five patients with acute pancreatitis (Group I) and thirty-four patients with other causes of acute abdomen (Group II) were included in the study.

The Faculty Ethical Committee approved the study and we obtained informed written consents from all patient after explanation of benefits and risks. We kept privacy of all patients' data secure. There was code number for every patient file that included all investigations.

Full history taking, clinical examination, and laboratory investigations including urine analysis and serum levels of creatinine, random glucose, lipid profile, total and direct bilirubin, albumin, liver enzymes, total calcium, amylase, and lipase were undertaken.

In addition, radiological examinations, using abdominopelvic ultrasonography, computed tomography of the abdomen and conventional X-ray when appropriate were undertaken.

Urinary trypsinogen-2 was tested using dipstick.

Urinary trypsinogen-2 dipstick test is an immunochromatographic test with a detection limit of 50 µg/L. The tip of the strip was immersed into a urine sample cup and was held for 20 seconds before being completely taken out of urine cup.

The strip was then kept at room temperature for 5 min to observe whether urine reacted with blue latex particles covered by monoclonal antitrypsinogen-2 antibodies.

Excess (more than 50 µg/L) urinary trypsinogen-2 caused the occurrence of 2 blue stripes (one for trypsinogen-2 & the other as control).

While only one strip (referred to as the control strip) was observed when urinary trypsinogen-2 concentration was within the normal range.

The appearance of the control strip confirmed the accuracy of the assay, while no blue stripes on the test strip suggested an erroneous test, in which case the test was repeated.

**Statistical analysis:**

Data was presented in terms of mean and Standard Deviation (SD) for quantitative variables and frequencies (number of cases) and percentages for qualitative ones.

Comparison of quantitative variables between the study groups was done using independent student t-test. For comparing categorical data, chi-square test ($\chi^2$) was used and Fischer's exact test was performed when appropriate.

A probability value ($p$-value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for Social Science; SPSS for IBM, USA) Version 23 for Microsoft Windows.

**Results**

Our study aimed at evaluation of role of urinary trypsinogen-2 excretion as a simple bedside and time saving modality in diagnosis of acute pancreatitis.

The study included 35 patients of acute pancreatitis (Group I) and 34 patients of acute abdomen other than acute pancreatitis (Group II). One of the patients in the group of acute pancreatitis was excluded as the possible acute pancreatitis diagnosed by elevated serum lipase and amylase couldn’t be confirmed on radiological basis as Computed Tomography (CT) of abdomen was declined by the patient and nature of patient's acute abdominal pain was confusing. In this patient urinary trypsinogen-2 dipstick test was negative.

We found no significant difference between the group of acute pancreatitis and the group of other causes of acute abdomen, regarding age, sex, BMI and smoking. $p>0.05$.

None of our patients in both groups was alcoholic.

The history of gall bladder stones was positive in the group of acute pancreatitis in 44.1% of cases, while it was positive in 5.9% of the group of other causes of acute abdominal pain. $p<0.001$. 
On the other hand, patients in Group I did not differ significantly than those in Group II regarding the medical history of DM, HTN, hepatic diseases, CKD, hypertriglyceridemia and stroke. \( p > 0.05 \).

Similarly, vital signs were not significantly different between both studied groups in relation to systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature. \( p > 0.05 \).

Table (1) shows that laboratory data didn't differ significantly as regards blood hemoglobin (HB), hematocrit (HCT) value, Platelet Count (PLT), Total Leucocytic Count (TLC), serum albumin, serum Triglycerides (TG), serum creatinine, and total serum calcium (Ca total). \( p > 0.05 \).

In addition, frequency of urine acetone positivity was higher in patients in the group of other causes of acute abdomen. \( p = 0.025 \).

Levels of serum amylase and lipase were higher in Group I compared with Group II (\( p < 0.001 \)). Similarly, urinary Trypsinogen-2 was positive in all of the patients in Group I and it was negative in all of the patients in Group II (\( p < 0.001 \)) (Table 2).

Ultrasound examination in Group I showed that 76.47% of patients had obstructive pancreatitis due to gall stones, while 8.82% had non-obstructive pancreatitis. The remaining (14.71%) of patients in Group I were diagnosed to have pancreatitis by Computed Tomography (CT) scan.

Final diagnosis of patients in the study showed that 76.47% of patients in Group I were diagnosed to have obstructive pancreatitis due to gall stone, while 23.53% of patients had non-obstructive pancreatitis.

On the other hand, in Group II the most common cause of acute abdomen was DKA with a percent of 17.65% followed by 14.71% of patients had acute cholecystitis with gall stones, and 5.88% of patients had acute cholecystitis without gall stones. Furthermore, 14.71% of Group II patients had acute appendicitis (Table 3).

This study found that the accuracy of urinary trypsinogen-2 compared with serum amylase and serum lipase, showed a sensitivity of 100% and specificity of 100%. Fig. (1).

### Table (1): Laboratory findings of studied patients.

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Group I (n=34) Mean ± SD</th>
<th>Group II (n=34) Mean ± SD</th>
<th>Statistic</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>12.28±1.80</td>
<td>11.77±0.97</td>
<td>( t = 1.444 )</td>
<td>0.155</td>
</tr>
<tr>
<td>HCT</td>
<td>36.15±3.94</td>
<td>35.12±4.37</td>
<td>( t = 0.201 )</td>
<td>0.156</td>
</tr>
<tr>
<td>PLT</td>
<td>247617.65±66415.14</td>
<td>242323.53±62589.43</td>
<td>( t = 0.338 )</td>
<td>0.736</td>
</tr>
<tr>
<td>TLC</td>
<td>16709.41±17047.24</td>
<td>13126.47±2927.95</td>
<td>( t = 0.210 )</td>
<td>0.231</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.76±0.41</td>
<td>3.84±0.36</td>
<td>( t = 0.850 )</td>
<td>0.199</td>
</tr>
<tr>
<td>TG</td>
<td>135.38±41.05</td>
<td>136.00±35.58</td>
<td>( t = 0.066 )</td>
<td>0.474</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.05±0.79</td>
<td>1.18±0.84</td>
<td>( t = 0.661 )</td>
<td>0.511</td>
</tr>
<tr>
<td>Ca total</td>
<td>8.95±0.53</td>
<td>9.13±0.492</td>
<td>( t = 1.460 )</td>
<td>0.075</td>
</tr>
<tr>
<td>ALT</td>
<td>68.91±13.41</td>
<td>29.82±15.42</td>
<td>( t = 2.859 )</td>
<td>0.007*</td>
</tr>
<tr>
<td>AST</td>
<td>87.61±21.98</td>
<td>35.05±17.54</td>
<td>( t = 2.369 )</td>
<td>0.024*</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>1.81±1.21</td>
<td>1.14±0.21</td>
<td>( t = 3.178 )</td>
<td>0.002*</td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td>1.16±0.89</td>
<td>0.64±0.16</td>
<td>( t = 3.372 )</td>
<td>0.001*</td>
</tr>
<tr>
<td>RBS</td>
<td>153.59±30.34</td>
<td>190.27±88.49</td>
<td>( t = 2.288 )</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

**Urinary Acetone:**

<table>
<thead>
<tr>
<th>Positive [n (%)]</th>
<th>0 (0)</th>
<th>6 (17.6)</th>
<th>Fischer exact test</th>
<th>0.025*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative [n (%)]</td>
<td>34 (100)</td>
<td>28 (82.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( t \) : Student \( t \)-test.
\( SD \) : Standard Deviation.
\* : Denotes statistically significance.
HB : Hemoglobin.
HCT : Hematocrit.
PLT : Platelet Count.
TLC : Total Leucocytic Count.
TG : Triglycerides.
Ca total : Total Calcium.
AST : Aspartate Transaminase.
ALT : Alanine Transaminase.
RBS : Random Blood Sugar.
Table (2): Laboratory finding suggesting diagnosis of pancreatitis in both groups.

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Group I (n=34) Mean ± SD*</th>
<th>Group II (n=34) Mean ± SD</th>
<th>Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Amylase</td>
<td>871.68±483.86</td>
<td>143.79±33.6</td>
<td>t=8.130</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Serum Lipase</td>
<td>931.2±99.58</td>
<td>89.15±21.6</td>
<td>t=8.264</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urinary Trypsinogen-2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive [n (%)]</td>
<td>34 (100)</td>
<td>0 (0)</td>
<td>χ²=68.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Negative [n (%)]</td>
<td>0 (0.0)</td>
<td>34 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

r : Student r-Test.          χ² : Chi Square Test. SD : Standard Deviation. Denotes statistically significance.

Table (3): Final diagnosis of studied patients.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I (acute pancreatitis):</strong></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Obstructive Pancreatitis due to gall stones</td>
<td>26</td>
<td>76.47</td>
</tr>
<tr>
<td>Non-obstructive pancreatitis</td>
<td>8</td>
<td>23.53</td>
</tr>
<tr>
<td><strong>Group II (other causes of acute abdomen):</strong></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>5</td>
<td>14.71</td>
</tr>
<tr>
<td>IO</td>
<td>2</td>
<td>5.88</td>
</tr>
<tr>
<td>Uremia</td>
<td>4</td>
<td>11.76</td>
</tr>
<tr>
<td>Cholecystitis with gall stones</td>
<td>5</td>
<td>14.71</td>
</tr>
<tr>
<td>Cholecystitis without gall stones</td>
<td>2</td>
<td>5.88</td>
</tr>
<tr>
<td>SBP</td>
<td>2</td>
<td>5.88</td>
</tr>
<tr>
<td>Perforated viscus</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>IBS</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>Ureretic colic</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>DKA</td>
<td>6</td>
<td>17.65</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>2</td>
<td>5.88</td>
</tr>
<tr>
<td>MI</td>
<td>2</td>
<td>5.88</td>
</tr>
<tr>
<td>UTI</td>
<td>1</td>
<td>2.94</td>
</tr>
</tbody>
</table>


Discussion

Acute pancreatitis is a grave medical emergency. Time factor and availability of diagnostic tools have a critical role in patient outcome. Simplifying the diagnosis of acute pancreatitis is of great importance to save patient's life.

The well-known enzymatic diagnosis of acute pancreatitis "serum amylase and serum lipase" is not readily available and it takes too long time to get the result. Furthermore, the cost of this enzymatic testing is high.

Beside the fact that acute pancreatitis is one of the common causes of acute abdomen presenting to Tanta University Emergency Hospital, that is why we tried to find an easy, low cost and fast method to diagnose acute pancreatitis.

Urinary trypsinogen-2 merged as a promising test in easy, fast and low cost diagnosis of acute pancreatitis in last few years.

Our study included 35 (34 of them completed the study) cases of acute pancreatitis and 34 cases of acute abdomen other than pancreatitis. The study showed that the most common cause of acute pancreatitis presented to our hospital was gall stone obstructive pancreatitis.

This result can be explained by the high rate of females presented with acute pancreatitis with high Body Mass Index [BMI (27.23±2.91)]. These two factors are important risk factors for the development of gallstones [9].

These findings agree with Laharwal, et al. [10], Cho, et al. [11] and Nesvaderani, et al. [12] who found that gall stone obstruction was the most common cause of acute pancreatitis in their localities (India, South Korea, and Western Sydney respectively) with incidence rate of (50%, 49.7%, 40.02% respectively).
While Hamada, et al. [13], Hofmeyr, et al. [14] and Pulkkinen, et al. [15] found that alcoholism was the main cause of acute pancreatitis in their patients in (Japan, South Africa, and Finland respectively) with incidence rate of (3.3%, 55.2%, 56% respectively). This might give an argument regarding other environmental factors which could be implicated in pathogenesis of acute pancreatitis in different regions.

Another factor that might have a role in the high rate of gall stone obstructive pancreatitis in our patients is the absent history of gall-stones in most of our patients (55.9%), which could delay the action to manage a gall bladder with small stones “the most likely to cause pancreatic obstruction” [16].

The studied patients with acute pancreatitis in this work had an elevated serum amylase and lipase levels in (88.24% and 91.18% of patients respectively), with a specificity of (76.47% and 88.24% respectively).

On comparing our results with those found in other localities we found that Salinas, et al. [17], Abraham [18] and Sáez, et al. [19] have reported results similar to our findings. The sensitivity and specificity of serum amylase ranged from (70-75% and 85-87% respectively), while Tseng, et al. [20] and Jang, et al. [21] demonstrated that the sensitivity of serum amylase was much lower (46.1% and 41% respectively).

On the other hand, Mayumi, et al. [22] and Tseng, et al. [20] showed that the specificity of serum amylase was much higher (96.4% and 94.2% respectively).

As regard serum lipase, results of our study were in line with Tseng, et al. [20], Sáez, et al. [19] and Smith, et al. [23] who reported in (Taiwan, Spain, and Sydney respectively) that the sensitivity and specificity of serum lipase ranged from (84-92.3% and 84.7-93% respectively).

On the other hand, Chang, et al. [24] and Çevik, et al. [25] found in (Hong Kong, and Turkey respectively) that the sensitivity and specificity of serum lipase were much higher (ranged from 95-100% and 96-99% respectively).

This variation in sensitivity and specificity of diagnostic value of serum amylase and lipase in acute pancreatitis might be due to ethnic background or the method of detection and the used kits.

Another explanation is the generation of lipase and amylase by different organs and mechanisms in the human body, this can contribute to the great variability in their sensitivity and specificity according to the clinical scenario, case by case.

The high sensitivity and specificity of urinary trypsinogen-2 as a marker of acute pancreatitis in our patients (100% for each) has no clear explanation.

One of our patients had probable acute pancreatitis diagnosed with increased levels of serum amylase and lipase, but had negative urinary trypsinogen-2 dipstick testing.

This patient had confusing clinical picture and negative ultrasongraphic data of acute pancreatitis.

With the possibility of acute pancreatitis on basis of increased levels of serum amylase and lipase, CT scan with pancreatic protocol was the only tool to confirm diagnosis of acute pancreatitis.

Unfortunately, patient declined this test because of fear of contrast media despite clear explanation to him. That is why we excluded this patient from statistical analysis.

The unconfirmed diagnosis of acute pancreatitis in this case could be a contributing factor leading to the high sensitivity and specificity of urinary trypsinogen-2 in diagnosis of acute pancreatitis in our study.

Andersen, et al. (2010) [26] showed results near to ours regarding specificity of urinary trypsinogen-2 in diagnosis of acute pancreatitis. The specificity in their study was 97%. Similarly, Nittala, et al. [27], Kamer, et al. [28], and Chen, et al. [29] reported that sensitivity of urinary trypsinogen-2 dipstick test in diagnosis of acute pancreatitis was (100%, 91%, 89.6% respectively).

In addition, Mayumi, et al. [22] have reported that specificity and sensitivity of urinary trypsinogen-2 dipstick test in diagnosis of acute pancreatitis mounted up to 92.2% and 97.63% respectively.

On the other hand, Lempinen, et al. [30] found that urinary trypsinogen-2 was less sensitive and specific in diagnosis of acute pancreatitis. The sensitivity and specificity in their study was 62% and 87% respectively.

The difference in sensitivity and specificity of urinary trypsinogen-2 dipstick test in diagnosis of acute pancreatitis has no clear explanation.
The studies showed high sensitivity and specificity of urinary trypsinogen-2 dipstick test demonstrated that obstructive pancreatitis was the most common cause of this condition like our study. This might raise the possibility that obstructive pancreatitis has the highest sensitivity and specificity for urinary trypsinogen-2 dipstick test. Furthermore, lack of standardization of urinary trypsinogen-2 dipstick test may add to the variability in the sensitivity and specificity in the different studies.

Our study had some limitations including the exclusion of one of the patients with possible acute pancreatitis before confirming or excluding the diagnosis. Another limitation was the limited number of patients in both groups which could have an impact on our findings.

Conclusion:
Urinary trypsinogen-2 dipstick test is a promising fast and easy test performed in the effort of diagnosis of acute pancreatitis. Further studies on large number of patients are mandatory to confirm the findings in this study.

References


القيمة التنبيؤية للتربيسينوجين 2 البولي في التشخيص المبكر

للإتهام البنكرياس الحاد لحالات الطوارئ

تم تنفيذ هذا العمل لتقييم دور مقياس التربيسينوجين-2 البولي في تشخيص إتهام البنكرياس الحاد وشملت الدراسة 25 مريضاً مصابين بإتهام البنكرياس الحاد (المجموعة الأولى) و24 مريضاً يعانون من أسباب أخرى لألم البطن الحاد (المجموعة الثانية)، واحض جميع المرضى لأخذ التاريخ المرضي وعمل الفحص السريري الكامل، والتحاليل المخبرية بالعمل بما في ذلك مستويات الكرياتينين، الجلوكوز، الكوليسترول، الصفراء الكلية، البشرة، إنزيمات الكبد، وإزمات الألبيز. تم عمل تحليل النتائج وحيدة مقياس التربيسينوجين-2 البولي وأيضاً تم إجراء الفحوص الإشعاعية باستخدام مجموعة فائق الصوتية على البطن واللوز والعصوش والأشعة المقطعة على البطن والأشعة السينية التقليدية كيماً إفتراضي.

وفي نهاية البحث وجدنا أن السبب الأكثر شيوعاً لإتهام البنكرياس الحاد هو إتهام البنكرياس الإسقاطي بواسطة حضور المرارة (77% - 89% على الترتيب) في مجموعة إتمام البنكرياس الحاد (المجموعة الأولى)، وكان مستوى الألبيز والإيبيز إيجابياً في (46% - 88%) على الترتيب. في حين كان إهلاك التربيسينوجين-2 البولي إيجابياً في (50%) من المرضى الذين يعانون من إتهام البنكرياس الحاد (المجموعة الأولى).

وقد كانت نسبة الخصوصية لكل من الألبيز والإيبيز والتربيسينوجين-2 البولي في إتهام البنكرياس الحاد (76% - 87% على الترتيب) وذلك إثباتاً للقيم الرئيسي لدراستنا وعلاقة الطريق بين مريضي إسقاطي وإغلاق واحد من المرضى على مجموعة إتهام البنكرياس الحاد قبل تأكيد أو استبعاد التشخيص.