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RAPID COMMUNICATION

Early diagnosis and prediction of severity in acute pancreatitis using the urine trypsinogen-2 dipstick test: A prospective study

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Abstract

AIM: To evaluate the use of the trypsinogen-2 dipstick (Actim Pancreatitis) test for early diagnosis and prediction of severity in acute pancreatitis (AP).

METHODS: Ninety-two patients with AP were included in this study. The control group was 25 patients who had acute abdominal pain from non-pancreatic causes. Urine trypsinogen-2 dipstick test (UTDT) and conventional diagnostic tests were performed in all patients. Patients were divided by the Atlanta classification into two groups as having mild or severe pancreatitis.

RESULTS: UTDT was positive in 87 (94.6%) of the AP patients and in two (8%) controls ($P < 0.05$). Positive UTDT was found in 61 (92.4%) of 66 (71.7%) patients with mild pancreatitis and in all (100%) of the 26 (28.3%) with severe pancreatitis ($P > 0.05$). UTDT positivity lasted longer in severe pancreatitis compared with that in mild pancreatitis (6.2 ± 2.5 d *vs* 2.0 ± 1.43 d, $P < 0.05$). The sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of UTDT were 91%, 72%, 96.6%, 70.4%, 3.4 and 0.1, respectively.

CONCLUSION: UTDT is a simple, rapid and reliable method for use on admission. It has high specificity and low NLR for early diagnosis and prediction of severity in AP. However, its relatively low NPV does not allow trypsinogen-2 dipstick test to be a stand-alone tool for diagnosis of acute pancreatitis; the use of other conventional diagnostic tools remains a requirement.

Key words: Acute pancreatitis; Urine trypsinogen-2 dipstick test; Early diagnosis; Disease severity

INTRODUCTION

Most patients with acute pancreatitis (AP) have a mild and self-limited form of the disease that resolves spontaneously, but approximately 20% of attacks are severe and represented by pancreatic necrosis, sepsis, and fulminant multiorgan/system failure with a life-threatening morbidity and a mortality rate of 20%-30%. Hence, early diagnosis and prediction of severity in AP has particular significance[1-6].

Early prediction of the severity of AP is difficult[3,7]. Multifactorial scoring systems like the Ranson prognostic signs and the Glasgow score can only be evaluated 48 h after admission. The acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) score has the invaluable advantage of being useful within a few hours after admission, and it can be assessed serially. However, it is cumbersome, which limits its use in clinical practice[7]. The current gold standard for staging AP combines clinical criteria with computed tomography (CT), but this has limited availability, high costs, exposes the patient to ionizing radiation, and lacks sensitivity and specificity in the early stage of the disease. Several laboratory markers have been evaluated as replacements for the multifactorial scoring systems, with CT being the most widely used[8,9]. Alternatively, magnetic resonance imaging can be used, e.g. in case of contraindications to intravenous CT contrast agents[10]. Various biochemical tests such as the urine trypsinogen-2 dipstick test (UTDT) have been developed over the past ten years for early diagnosis and prediction of severity in AP. Trypsinogen occurs as two major isoenzymes, trypsinogen-1 (cationic) and trypsinogen-2 (anionic), which are secreted at high concentrations into pancreatic fluid with a small proportion escaping into the circulation. Trypsinogen-1 and trypsinogen-2 are eliminated from the blood circulation by the kidneys. In AP, concentrations of trypsinogen-2 in serum and urine are higher than those of trypsinogen-1[11-13]. Although

UTDT has been evaluated in many studies, details of the clinical use of this test for early diagnosis and prediction of severity in AP remain obscure[3,13-15]. The aim of our prospective study was to evaluate the use of the trypsinogen-2 dipstick (Actim Pancreatitis) test in early diagnosis and prediction of severity in AP, and to compare the sensitivity, specificity and prognostic value of the this test with those of serum amylase, serum lipase and APACHE Ⅱ score.

MATERIALS AND METHODS

Materials

The prospective study population consisted of 92 consecutive patients with AP (study group: 69 males, 23 females; median age 58.9 year, range 36-80) and 25 consecutive patients with acute abdominal disease of extrapancreatic origin (control group: 15 males, 10 females; median age 59.2 year, range 34-78) admitted to the emergency unit at Izmir Ataturk Education and Research Hospital between January 2003 and July 2005. The study was approved by the Committee on Research Ethics at our hospital, and all patients gave their informed consent for inclusion in the study.

Study design

Diagnosis of AP was based on a history of prolonged upper abdominal pain, serum amylase at least three times the upper limit of normal and the presence of edema or necrosis on abdominal ultrasonography and/or contrast-enhanced CT. Patients who were admitted after the first 24 h after the onset of abdominal pain were not included in the study. APACHE Ⅱ score values were calculated on admission and at 48 h. Body mass index (BMI) of all patients was calculated. CT was performed selectively in patients with severe pancreatitis as predicted by either one of the two scoring systems (Ranson criteria > 2 or APACHE Ⅱ score > 7). Under the Atlanta classification, AP is predicted as severe if it is accompanied by single or multiorgan failure, local complications, 3 or more on the Ranson criteria, or an APACHE Ⅱ score of ⩾ 8 points[1].

Methods

Serum amylase and lipase concentrations were measured using enzymatic assay (Architect C 8000; Abbott, Abbott Park, IL, USA; reference interval, 26-100 U/L and 13-60 U/L, respectively). The Actim Pancreatitis test strip (Medix Biochemica, Kauniainen, Finland), an immunochromatographic test, was used for urine trypsinogen-2 determination (detection limit 50 μg/L). The tip of the strip was immersed into a urine-containing vial and was held for 20 s before being completely taken out of the vial. 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 (> 50 μg/L) urinary trypsinogen-2 caused the occurence of 2 blue stripes, while only one stripe (referred to as the control stripe) was observed when urinary trypsinogen-2 concentration was within the normal range. The appearance of the control stripe 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[16].

Table 1 Diagnosis and/or etiology of pancreatitis in the control and study groups

Control group	*n* (%)	Study group	*n* (%)
Familial Mediterranean fever	5 (20)	Gallstone	58 (63.0)
Acute appendicitis	5 (20)	Idiopatic	18 (19.6)
Acute cholecystitis	4 (16)	Post-ERCP	8 (8.7)
Perforated peptic ulcer	3 (12)	Alcohol	5 (5.4)
Acute cholangitis	2 (8)	Hypertriglyceridemia	3 (3.3)
Pelvic inflammatory disease	2 (8)		
Intestinal obstruction	2 (8)		
Gastric cancer	1 (4)		
Meckel diverticulitis	1 (4)		

ERCP: Endoscopic retrograde cholangiopancreaticography.

Statistical analysis

Data were expressed as the mean ± SE. The Mann-Whitney *U* and McNemar tests were used where appropriate for statistical analysis. All *P* values were two-tailed, and those with $P < 0.05$ were defined as statistically significant. For serum concentrations of amylase and lipase, a threefold increase in the reference values recommended by our laboratory were selected as cut-off values. Using these cut-off points, the sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and positive (PLR) and negative likelihood ratio (NLR) in establishing the diagnosis of AP were calculated. The SPSS/PC 10.0 (SPSS, Chicago, IL, USA) statistical package was used on a personal computer for the analysis of data.

RESULTS

The mean ages of patients in the study and control groups were 58.9 ± 14.2 year ($n = 92$, range, 36-80) and 59.2 ± 13.5 year ($n = 25$, range, 34-78), respectively ($P = 0.928$). No significant difference was found between the two groups in terms of gender (study group, M/F = 69/23; control group, M/F = 15/10; $P = 0.113$). Gallstones were the most common causes of AP ($n = 58$, 63%), while familial Mediterranean fever and acute appendicitis were the most common causes of acute abdominal pain in patients in the control group ($n = 5$, 20% and $n = 5$, 20%, respectively) (Table 1). Mean BMI of patients in the study and control groups were 24.0 ± 3.8 kg/m^2 (range, 16-33) and 23.5 ± 3.4 kg/m^2 (range, 16-30), respectively ($P = 0.902$). Both mean serum amylase concentrations and mean serum lipase concentrations were significantly higher in patients in the study group compared with those in the control [amylase, 600.8 ± 189.7 U/L (range, 376-1250) *vs* 67 ± 32.5 U/L (range, 18-176), and lipase, 96.2 ± 42.4 U/L (range, 58-230) *vs* 33.8 ± 15 U/L (range, 13-65); $P = 0.000$)].

UTDT on admission was positive in 87 (93.5%) of the 92 patients in the study group, and in two (8%) of the 25 patients in the control group ($P = 0.000$). In the control

Table 2 Demographics and results for control and study groups

	Control group (n = 25)	Study group (n = 92)	P
Age (yr)[1]	59.2 ± 13.5 (34-78)	58.9 ± 14.2 (36-80)	0.928
Gender (F/M)	15/10	69/23	0.113
BMI (kg/m^2)[1]	23.5 ± 3.4 (16-30)	24.0 ± 3.8 (16-33)	0.902
Amylase (> 100 U/L)[1]	67 ± 32.5 (18-176)	600.8 ± 189.7 (376-1250)	0.000
Lipase (> 60 U/L)[1]	33.8 ± 15 (13-65)	96.2 ± 42.4 (58-230)	0.000
UTDT +/- (on admission)	2/23	87/5	0.000
UTDT +/- (48 h later)	1/23	87/5	0.000
Duration of UTDT positivity (d)[1]	2.0 ± 1.4 (1-3)	3.6 ± 2.1 (2-13)	0.000
APACHE Ⅱ score (on admission)[1]	4.6 ± 1.5 (3-8)	6.1 ± 2.7 (3-13)	0.006

[1]Values expressed in mean ± SE (inter-quartile range).

Table 3 Demographics and results for control and study groups (Classified as mild and severe AP)

	Control (n = 25)	Mild AP (n = 66)	Severe AP (n = 26)	P^1	P^2	P^3
Age (yr)[4]	59.2 ± 13.5	58.7 ± 14.3	60.2 ± 14.9	0.883	0.796	0.655
Gender (F/M)	15/10	51/15	17/9	0.118	0.776	0.365
BMI (kg/m^2)[4]	23.5 ± 3.4	23.5 ± 3.9	24.2 ± 4.1	0.627	0.507	0.217
Amylase (> 100 U/L)[4]	67 ± 32.5	578.6 ± 171	658.2 ± 222	0.000	0.000	0.068
Lipase (> 60 U/L)[4]	33.8 ± 1	76.0 ± 23.9	110.4 ± 54.2	0.000	0.000	0.000
Positive UTDT (on admission)	2/23	61/5	26/0	0.000	0.000	0.351
Positive UTDT (48 h later)	1/24	61/5	26/0	0.000	0.003	0.351
Duration of UTDT positivity (d)[4]	2.0 ± 1.4	2.6 ± 0.6	6.2 ± 2.5	0.000	0.000	0.000
APACHE-Ⅱ score (on admission)[4]	4.6 ± 1.5	4.7 ± 1.4	9.7 ± 1.8	0.807	0.000	0.000
APACHE-Ⅱ score (after 48 h)[4]	-	4.24 ± 1.4	11.5 ± 2.9	-	-	0.000
Ranson score (on admission) > 2[4]	-	1.03 ± 0.8	3.73 ± 1	-	-	0.000

[1]Control group *vs* mild AP; [2]Control group *vs* severe AP; [3]Mild AP *vs* severe AP; [4]Values expressed as means ± SD.

group, false-positive UTDTs were normalized 1 d later in a patient with acute cholecystitis and 3 d later in a patient with gastric cancer. On the other hand, UTDT positivity lasted for an average of 3.6 ± 2.1 d (range, 2-13) in patients in the study group. APACHE Ⅱ score (cut-off > 8) was 6.1 ± 2.7 (range, 3-13) and 4.6 ± 1.5 (range, 3-8) in the study and control groups, respectively (P = 0.006) (Table 2).

Of the patients with AP, 66 (71.7%) had mild disease and 26 (28.3%) had severe disease according to the Atlanta classification[1]. Gallstones were the most common cause of both mild and severe AP (n = 45, 68.2% and n = 13, 50%, respectively). No significant difference was found between patients with mild and severe AP in terms of BMI (P = 0.217). However, both Ranson and APACHE Ⅱ scores on admission were significantly higher in patients with severe AP than in those with mild AP [Ranson, 3.73 ± 1.04 (range, 2-5) *vs* 1.03 ± 0.82 (range, 0-3), and APACHE Ⅱ, 9.73 ± 1.75 (range, 8-13) *vs* 4.68 ± 1.38 (range, 3-8), respectively; P = 0.000]. Likewise, APACHE Ⅱ score determined at 48 h later was significantly higher in patients with severe pancreatitis than in those with mild pancreatitis (4.24 ± 1.44 *vs* 11.5 ± 2.88, P = 0.000). Sensitivity and specificity of APACHE Ⅱ score on admission were 56.0% and 89.4%, respectively.

Table 4 Sensitivity, specificity, PPV, NPV, PLR and NLR of serum amylase, serum lipase, UTDT and APACHE Ⅱ scoring systems in AP

	Sensitivity %	Specificity %	PPV %	NPV %	PLR	NLR
On admission						
Serum amylase (> 100 U/L)	78.0	87.3	94.8	61.5	6.1	0.3
Serum lipase (> 60 U/L)	86.2	89.4	96.6	76.0	8.1	0.2
UTDT, positive	91.0	72.0	96.6	70.4	3.4	0.1
APACHE Ⅱ > 8	56.0	89.4	61.0	84.2	5.3	0.5

Table 5 Comparisons of sensitivity and specificity of UTDT in AP in present study with those reported previously

Reference	Sensitivity (%)	Specificity (%)
Kemppainen *et al* 1997[29]	94	95
Kylanpaa-Back *et al* 2000[28]	96	92
Lempinen *et al* 2001[5]	62	87
Pezzilli *et al* 2001[27]	53.3	-
Lempinen *et al* 2003[7]	72	81
Chen *et al* 2005[16]	89.6	85.7
Saes *et al* 2005[30]	68	86.4
Present study	91	72

Mean serum amylase concentrations were not significantly different in patients with severe and mild AP (658.2 ± 222.5 U/L *vs* 578.6 ± 171.3 U/L, respectively, P = 0.068), while serum lipase concentrations in patients with severe AP were significantly higher than those in patients with mild AP (76.0 ± 23.9 U/L *vs* 110.4 ± 54.2 U/L, respectively, P = 0.000). UTDT was positive in 61 of the 66 (92.4%) patients with mild AP and in all 26 (100%) patients with severe AP (P = 0.351). No significant difference was found between patients with severe AP and those with mild AP in terms of UTDT positivity at 48 h after admission (P = 0.351). Positive UTDT continuation averaged 2.6 ± 0.6 d (range, 2-4) and 6.2 ± 2.5 d (range, 3-13) in patients with mild and severe AP, respectively (P = 0.000) (Table 3).

In AP, the sensitivity, specificity, PPV, NPV and PLR of serum amylase and lipase were 78%, 87.3%, 94.8%, 61.5% and 6.1, and 86.2%, 89.4%, 96.6%, 76.0% and 8.1 respectively, while UTDT sensitivity was 91%; specificity was 72%; PPV was 96.6%; NPV was 70.4% and PLR was 3.4 (Table 4). Sensitivity and specificity rates of UTDT obtained in our study were compared with those reported in the literature and are listed in Table 5.

DISCUSSION

AP presents in various clinical forms ranging from

mild abdominal discomfort to multiple organ failure. After a mild pancreatitis attack, 80% of patients recover completely, while the disease worsens in 20% and has a mortality rate of 30%[1,17-19]. Thus, early diagnosis and determination of severity of AP are of great importance in terms of mortality and morbidity.

Several methods have been used to diagnose AP and determine its prognosis and severity; these include scoring systems (such as Ranson, Glasgow, and APACHE), biochemical parameters [e.g. serum amylase, lipase, C-reactive protein (CRP), trypsinogen-activation peptide (TAP), interleukins 6 and 8, carboxypeptidase B activation peptide, tumor necrosis factor-α, platelet-activating factor, polymorphonuclear elastase, and serum procalcitonin], and imaging techniques (such as CT)[5,20-22]. The methods that can be used to compare the predictive value of different tests have been summarized in a paper by Jaeschke[23]. What is needed is an immediate test with high specificity and low NLR[24].

In the mid 1990s, urine trypsinogen concentration and TAP were reported to be of high sensitivity and specificity in diagnosing and predicting severity of AP. Since then, determinations of urine trypsinogen concentration and TAP have been considered as good alternative biochemical tests[25,26]. Lempinen et al have compared urinary trypsinogen-2 with urinary TAP and serum CRP for early differentiation between severe and mild AP and concluded that urinary trypsinogen-2 is superior to serum CRP, and is as good as or even better than urinary TAP for the early prediction of disease severity in the first 24 h of admission for AP[7].They have also noted that the result of a trypsinogen-2 dipstick test is available within 5 min, whereas TAP requires a laborious ELISA method, which takes several hours and requires skilled laboratory personnel; the rapid urinary trypsinogen-2 test does not require the use of laboratory equipment[7].

Sensitivity and specificity of UTDT in AP has been reported in the literature as 53.3%-96% and 85.7%-95%, respectively[22,25-31]. We calculated a sensitivity of 91% and specificity of 72% for UTDT. Consistent with a previous report, we found higher sensitivity for UTDT compared with that for serum amylase and lipase concentrations (91% *vs* 78% and 86%, respectively)[4]. However, Pezzilli *et al* reported a low sensitivity for UTDT in their study in which 30 patients with AP were investigated, 11 of whom were included at 2-3 d after onset of the attack[27]. We believe that this late inclusion of a considerable number of patients in the aforementioned study might have affected urinary trypsinogen-2 concentrations and, thus might have decreased the sensitivity and specificity of UTDT for AP diagnosis. In agreement with this view, Chen et al have recently reported a gradually decreasing sensitivity for UTDT in diagnosis of AP from the first to the fourth day of admission (i.e. 90.6%, 81.2%, 59.4% and 50% on the first, second, third and fourth days of admission, respectively)[16]. Considering the effect of late admission (which resulted in delayed UTDT), we did not include patients who were admitted 24 h after the onset of abdominal pain. Thus, we obtained a homogeneous study group in terms of timing of UTDT. We found a positive UTDT in 93.5% and 8% of patients with AP and those with acute abdominal pain due to non-pancreatic causes, respectively. This statistically significant difference supports the use of UTDT in AP diagnosis within the first 24 h of acute abdominal pain.

Chen *et al* have concluded that UTDT can be used in the differential diagnosis of AP due to its high NPV[16]. Lempinen *et al* and Kylanpaa-Back *et al* have reported NPV rates for UTDT of 85% and 99%, respectively[5,28]. We found that the NPV for UTDT was 70.4%, which is higher than the NPV of serum amylase and close to that of serum lipase. We believe that AP diagnosis must be confirmed by other biochemical tests and imaging techniques in patients with a positive UTDT. This is because urinary trypsinogen-2 concentrations may also be increased in other diseases such as hepatobiliary and pancreatic malignancies, colon cancers, and chronic pancreatitis[13]. On the other hand, we found that the PPV (96.6%) for UTDT was higher than that of serum amylase and was equal to that of serum lipase. Thus, we believe that the use of UTDT is advantageous for an early diagnosis of AP because of its rapid action, high sensitivity and high PPV.

UTDT has been reported to have a direct correlation with the severity of AP, as its sensitivity increases with increased severity of AP[4,16]. We have been unable to confirm this conclusion, because in our study we found the sensitivity of UTDT was 87.2% in severe AP and 82.8% in mild AP. However, these rates were not significantly different. On the other hand, a longer duration of UTDT positivity in severe AP compared with that in mild AP was detected. These data suggest that repeating UTDT every day may allow a clinician to predict the severity of AP that varies with time. Thus, such patients will probably benefit from admission to a medical center, prophylactic antibiotic administration, early enteral nutrition, and early endoscopic retrograde cholangiopancreatography in pancreatitis of suspected biliary origin[25].

In conclusion, while there are a few studies on the value of the trypsinogen-2 dipstick test as a predictive test for the severity of AP, its relatively low NPV does not allow UTDT to be a stand-alone tool for diagnosis of AP. Thus, the use of other conventional diagnostic tools becomes an additional requirement. However, UTDT is a simple, rapid and a reliable method that can be used on admission with high specificity and low NLR for early diagnosis and prediction of severity in AP.

COMMENTS

Background

Urine trypsinogen-2 dipstick test (UTDT) is simple, rapid and a reliable method that can be used on admission with high specificity and low negative likelihood ratio (NLR) for early diagnosis and prediction of severity in acute pancreatitis (AP).

Research frontiers

Early diagnosis and prediction of severity in AP is of particular significance.

Innovations and breakthroughs

Although UTDT has been evaluated in many studies, clinical use of this test for early diagnosis and prediction of severity in AP is obscure. The aim of our

prospective study was to evaluate the use of a trypsinogen-2 dipstick (Actim Pancreatitis) test in early diagnosis and prediction of severity in AP and to compare the sensitivity, specificity and prognostic value of this test with those of serum amylase, serum lipase and APACHE Ⅱ score.

Applications

UTDT is a simple, rapid and reliable method that can be used on admission for early diagnosis and prediction of severity in AP.

Terminology

Various biochemical tests, one of which is the UTDT, have been developed over the past ten years for early diagnosis and prediction of severity in AP. Trypsinogen occurs as two major isoenzymes, trypsinogen-1 (cationic) and trypsinogen-2 (anionic), which are secreted at high concentrations into pancreatic fluid with a small proportion escaping into the circulation. Trypsinogen-1 and trypsinogen-2 are eliminated from the blood circulation by the kidneys. In AP, concentrations of trypsinogen-2 in serum and urine are higher than those of trypsinogen-1.

Peer review

The authors evaluated the use of a trypsinogen-2 dipstick (Actim Pancreatitis) test in early diagnosis and prediction of severity in AP. UTDT is a simple, rapid and a reliable method that can be used on admission with high specificity and low NLR for early diagnosis and prediction of severity in AP.

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