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Observational Study

Urinary trypsinogens and trypsinogen activation peptide as biomarkers in pediatric acute pancreatitis: A prospective observational study

Urinary biomarkers in pediatric pancreatitis

Kamila A Kwiatek-Średzińska, Kinga Trochimczyk, Jacek Jamiołkowski, Dariusz M Lebensztejn

Abstract

BACKGROUND

The natural history of acute pancreatitis (AP) in children remains poorly understood, and no reliable noninvasive biomarkers are available to predict progression to severe disease. Studies in adults suggest the usefulness of trypsinogens and trypsinogen activation peptide (TAP) as biomarkers in AP.

AIM

To evaluate the predictive value of urinary trypsinogen-1, trypsinogen-2, and TAP in paediatric AP.

METHODS

This prospective study included 61 children with AP hospitalized at the Department of Gastroenterology over a 5-year period and 29 controls with functional abdominal pain. In patients with AP, urinary trypsinogen-1, trypsinogen-2, and TAP were measured at three time points: at admission or within 24 h, after 48 h, and after 72 h of hospitalization. Their predictive value for disease severity was compared with that of serum C-reactive protein (CRP), using receiver operating characteristic (ROC) analysis and univariate logistic regression.

RESULTS

AP was classified as mild in 49 and moderately severe in 12 patients. Urinary trypsinogen-2 after 48 h was higher in AP than controls (P = 0.022). Moderately severe AP was associated with higher urinary TAP after 48 (P = 0.043) and 72 h (P = 0.001), and higher serum CRP after 48 (P = 0.002) and 72 h (P < 0.001). ROC analysis showed moderate to good diagnostic performance for TAP and CRP after 48 and 72 h, with area under the curve values ranging from 0.692 to 0.857 (95%CI: 0.542 –0.998). Logistic regression revealed that TAP after 72 h (odds ratio = 1.034, 95%CI: 1.009–1.059) and CRP after 48 and 72 h predicted AP severity.

CONCLUSION

Urinary trypsinogen-2 may serve as a noninvasive biomarker of AP, whereas TAP may be a useful indicator of disease severity in children.

Key Words: Trypsinogen-1; Trypsinogen-2; Trypsinogen activation peptide; Urinary biomarkers; Acute pancreatitis; Paediatric pancreatitis; Children

Core Tip: This is the first prospective study in children evaluating the usefulness of urinary trypsinogens and trypsinogen activation peptide (TAP) as biomarkers in paediatric acute pancreatitis (AP). Urinary trypsinogen-2 may serve as a noninvasive biomarker of AP, whereas urinary TAP may reflect disease severity in children, although with certain time-dependent limitations. Assessment of urinary parameters offers a simple, noninvasive, and painless approach with potential clinical utility.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process involving the pancreatic parenchyma and is associated with premature activation of pancreatic proenzymes (mainly trypsin). The most common causes of AP in children are structural anomalies, trauma, infections, biliary disease, medications, systemic diseases, and genetic etiologies[1-4]. A diagnosis of AP is established by meeting at least two of the following three criteria: Acute-onset abdominal pain, especially in the epigastric region; serum amylase and/or lipase activity at least three times greater than the upper limit of normal; and characteristic imaging findings of AP[1,5].

In the course of AP, the inflammatory process may remain localized in the pancreas, spread to regional tissues, or involve distant organ systems[6]. According to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Pancreas Committee, the severity of pediatric AP is classified as mild, moderately severe, or severe. Mild AP is the most common form in children. It is not

associated with organ failure or local or systemic complications, and usually resolves within the first week after presentation. Moderately severe AP is diagnosed when transient organ dysfunction or local (fluid collection, necrosis) or systemic (exacerbation of preexisting comorbid disease) complications occur. Severe AP is defined as the development of organ failure persisting beyond 48 h[7].

The incidence of AP is increasing in the pediatric population worldwide[8]. Despite this more frequent presentation, the natural history of AP remains poorly understood, and no reliable predictors of progression to severe disease in children have been established[7]. In recent years, increasing focus has been given to identification of noninvasive biomarkers that could improve early diagnosis and risk stratification in AP[9-11]. In particular, urinary biomarkers have drawn interest due to their ease of collection and potential application in clinical practice[10]. Studies in adults suggest the usefulness of trypsinogens and trypsinogen activation peptide (TAP) as biomarkers in AP[11-13]. Therefore, the aim of this study was to evaluate the predictive value of urinary concentrations of cationic and anionic trypsinogen (trypsinogen-1 and trypsinogen-2), and TAP in pediatric patients with AP.

MATERIALS AND METHODS

This prospective study included children with AP hospitalized at the Department of Gastroenterology of a university hospital over a 5-year period (2020-2024). The patients with AP were followed until August 2025 for the occurrence of subsequent episodes of the disease. A diagnosis of AP was established on the basis of the revised Atlanta criteria, approved by the International Study Group of Pediatric Pancreatitis: In Search for a Cure[5]. Only children during their first episode of AP were included. The study sample comprised all consecutive pediatric patients meeting the inclusion criteria who were hospitalized during the study period. Due to the relatively low incidence of AP in children, no formal sample size calculation was performed. The disease was classified as mild, moderately severe, or severe in accordance with the NASPGHAN consensus statement[7]. The control group consisted of pediatric patients with functional

abdominal pain. The study was approved by the Bioethics Committee of the Medical University of Bialystok (approval no. R-I-002/299/2019, dated 30 May 2019). The research was conducted in accordance with the ethical standards established in the Declaration of Helsinki. Written informed consent was obtained from the legal guardian of each patient and from children over 16 years of age.

The demographic data and information about possible etiologic factors were recorded. Urine samples from children with AP were collected at three time points: at admission or within 24 h, after 48 h and after 72 h of hospital admission. For the control group, urine samples were obtained once, after a diagnosis of functional abdominal pain had been established. These samples were frozen at -80°C and stored until the performance of analysis. Urinary concentrations of trypsinogen-1, trypsinogen-2, and TAP were measured using an enzyme-linked immunosorbent assay (Cloud-Clone, USA). In patients with AP, the concentrations of these urinary parameters were analyzed in relation to disease severity. The predictive value of the urinary parameters for disease severity was compared with the predictive value of serum C-reactive protein (CRP). Blood samples for CRP were obtained at the same three time points: at admission, after 48 h, and after 72 h. Serum CRP was determined by immunoturbidimetry (Cobas 6000-c501). All laboratory analyses were conducted in accordance with the manufacturer's instructions.

The statistical analyses were performed using Statistica software (Statsoft, Krakow, Poland, version 14.1.0.4). Categorical variables were summarized as numbers and percentages. Continuous data were presented as means with standard deviations (SD) and compared between the groups using the Student's *t*-test or the Mann–Whitney U test, depending on normality of the distribution, as assessed by the Shapiro–Wilk test. The variables showing statistically significant associations with AP were further analyzed using the receiver operating characteristic (ROC) curves to establish optimal cut-off values based on the area under the curve (AUC). The diagnostic value of these variables was further assessed using univariate logistic regression. In order to compare parameters at three time points, the Friedman test was applied. The P value < 0.05 was

considered statistically significant. The statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 90 pediatric patients were enrolled in the study (median age 12 years), including 61 patients diagnosed with AP and 29 with functional abdominal pain (control group). AP was classified as mild in 49 children (80%) and as moderately severe in 12 patients (20%). No child developed persistent organ failure. In 13 patients with AP (21%), recurrent episodes occurred during the follow-up period. The etiology of the disease is shown in Figure 1.

Children with AP had higher urinary concentrations of trypsinogen-2 48 h after admission than patients in the control group (P = 0.022). There were no statistically significant differences in urinary concentrations of trypsinogen-2 at other time points or in trypsinogen-1 or TAP levels at any time point between patients with AP and controls (Table 1).

Table 2 shows the performance of urinary trypsinogen-2 after 48 h for AP diagnosis in children. The concentration of trypsinogen-2 after 48 h ≥ 0.381 ng/mL predicted AP with 48.3% sensitivity and 82.8% specificity (AUC = 0.651, 95% confidence interval (CI): 0.535–0.767; P = 0.010).

The urinary concentrations of trypsinogen-1, trypsinogen-2, and TAP in patients with AP did not differ significantly among the three time points (Table 3).

Compared with patients with mild AP, those with moderately severe AP had higher urinary TAP concentrations after 48 h (P = 0.043) and 72 h (P = 0.001) of hospitalization, as well as higher serum CRP concentrations after 48 h (P = 0.002) and 72 h (P < 0.001). There were no statistically significant differences between disease severity and urinary trypsinogen-1 or trypsinogen-2 Levels at any time point, urinary TAP levels within 24 h, or the serum CRP concentrations at admission (Table 4).

Table 5 and Figure 2 present the assessment of urinary TAP after 48 and 72 h as biomarkers of AP severity compared with serum CRP. The concentration of TAP after

48 h ≥ 25.412 pg/mL predicted moderately severe AP with 83.3% sensitivity and 54.3% specificity (AUC = 0.692, 95%CI: 0.542–0.842; *P* = 0.012), while after 72 h, a cut-off ≥ 43.844 pg/mL yielded 83.3% sensitivity and 73.9% specificity (AUC = 0.810, 95%CI: 0.692–0.928; *P* < 0.001).

In the univariate logistic regression analysis, urinary TAP concentrations after 72 h (odds ratio (OR) = 1.034, 95%CI: 1.009–1.059; *P* = 0.007) and serum CRP concentrations after 48 (OR = 1.031, 95%CI: 1.012–1.050; *P* = 0.001) and 72 h (OR = 1.039, 95%CI: 1.017–1.061; *P* = 0.001) were identified as predictors of AP severity.

DISCUSSION

Pancreatitis is a disease entity that requires identification of the etiologic factors, early recognition, accurate diagnostic testing, appropriate risk stratification, timely intervention with optimal management during the initial presentation, and efforts to prevent the recurrence of AP or its progression to a more severe or chronic state[9]. Most cases of AP in children are mild and single-episode, with up to 30% of patients experiencing severe courses or recurrence[14-18]. The results of this study revealed that 20% of the children had moderately severe AP and that 21% experienced a subsequent episode of the disease, and this corresponds with the published data. In the present study, idiopathic pancreatitis, infections and biliary disease were among the most common etiologic factors, which is consistent with the findings of other studies[9,14,16].

Trypsinogen, a proenzyme synthesized in the pancreas, is activated to trypsin in the duodenum by intestinal enterokinase. During pancreatitis, both trypsinogen-1 (cationic) and trypsinogen-2 (anionic) are released into the bloodstream and subsequently filtered into the urine, with trypsinogen-2 usually reaching higher concentrations[10,19]. The urine trypsinogen-2 dipstick test has been presented as a useful diagnostic tool for AP in both children and adults[10,13]. In the study conducted by Yasuda *et al*[12], urinary trypsinogen-2 was shown to be a marker of extrapancreatic inflammation in AP in adults. The present study demonstrated that pediatric patients with AP had higher

urinary trypsinogen-2 concentrations after 48 h than children in the control group. However, its diagnostic performance was only moderate (AUC = 0.651, 95%CI: 0.535–0.767; diagnostic odds ratio (DOR) = 4.48), suggesting that urinary trypsinogen-2 may support the diagnosis of pediatric AP, particularly as a noninvasive biomarker, although it should be interpreted in conjunction with clinical findings and standard biochemical parameters.

Predicting the severity of AP in children is challenging because there is no universally accepted pediatric-specific scoring system[20]. The Pediatric Acute Pancreatitis Severity Score, proposed by the Midwest Multicenter Pancreatic Study Group in 2002, was the first predictive tool designed specifically for children. It included eight parameters: Age, weight, white blood cell count, lactate dehydrogenase, calcium, albumin, fluid sequestration, and rise in blood urea nitrogen[17,18]. However, its sensitivity and negative predictive values have varied among studies[16,17,20,21]. Therefore, numerous laboratory parameters have been assessed as potential indicators of AP severity[22-26].

Urinary TAP has been evaluated as a marker of AP severity in adults[13, 27-30]. The measurement of TAP for severity assessment is appealing, as the activation of trypsinogen to trypsin, resulting in TAP release, occurs prior to all other systemic and clinical manifestations of severe AP[27,28]. In the present study, urinary TAP measured after 48 and 72 h was demonstrated to be a predictor of AP severity in pediatric patients, with TAP after 72 h showing good discriminatory ability (AUC = 0.810, 95%CI: 0.692–0.928; DOR = 14.196). In the study conducted by Neoptolemos *et al*[27], the TAP concentrations differed significantly between patients with AP and controls after symptom onset and between mild and severe pancreatitis over time. The differences between mild and severe pancreatitis were significant at 24 and 48 h, but not between mild pancreatitis and the control[27]. Lempinen *et al*[13] reported that during the early phase of AP, TAP correlated with disease severity in both plasma and urine, but there was no difference between controls and patients with mild AP. In this study, there was no statistically significant difference in urinary TAP concentrations between children

with AP and those in the control group, most likely because the number of patients with mild pancreatitis was much greater than that with moderately severe or severe AP. Moreover, there was no significant difference between disease severity and urinary TAP concentrations within 24 h, perhaps due to the fact that parents are more likely to bring their children to the emergency department soon after symptom onset, whereas adults often delay presentation.

Additionally, in the present study, the predictive value of urinary TAP for disease severity was compared with that of serum CRP. For a disorder such as AP, a useful prognostic assay should have high negative predictive value for severe disease, enabling most patients with mild disease to be managed in low-cost wards[27]. This study demonstrated better diagnostic performance of TAP after 72 h than after 48 h, similar to CRP. Generally, the performance of TAP was slightly worse than that of CRP (AUC after 48 h = 0.692 versus 0.794; AUC after 72 h = 0.810 *vs* 0.857; with TAP after 48 h failing to reach significance as a predictor of AP severity in univariate logistic regression). On the other hand, in the study conducted by Neoptolemos *et al*[27], the AUC values for urinary TAP were greater than those for CRP. Notably, in this study the highest negative predictive value (94.4%) was observed for urinary TAP after 72 h, suggesting that this biomarker may help identify children at low risk of developing severe disease. Information like this could potentially support clinical decision-making and assist in the appropriate allocation of healthcare resources.

To the best of our knowledge, this study is the first to evaluate the predictive value of urinary trypsinogen-1, trypsinogen-2, and TAP concentrations in pediatric patients with AP. Another strength of the present research is the use of AP classification on the basis of the NASPGHAN consensus statement[7] and its prospective design. In addition, the analysis of urinary parameters represents a noninvasive and painless method. This may be particularly relevant in pediatric populations, where repeated blood sampling can be challenging. Moreover, various biomarkers may be more reliable in children because, unlike adults, they typically do not have multiple comorbidities. There are several limitations to this study. First, owing to its single-center design and the relatively rare

occurrence of pancreatic complications and organ failure in children with AP, the study group was relatively small, particularly for severe cases. There were only patients with moderately severe disease, and no child with severe AP. Therefore, the generalizability of the results is limited, and assessment of the biomarkers in the most severe forms of the disease was restricted. Additionally, no formal sample size calculation was performed. Furthermore, the urinary parameters assessed in this study cannot be utilized upon hospital admission, and their performance in predicting AP severity was slightly worse than that of CRP.

The present prospective study contributes additional evidence regarding the potential role of urinary biomarkers in children with AP. The use of noninvasive biomarkers may shorten diagnostic time and reduce healthcare costs. Further multicenter research with larger populations is needed to determine the precise roles of urinary trypsinogen-1, trypsinogen-2, and TAP in pediatric AP, and to establish whether urinary biomarkers could be incorporated into clinical prediction models for the disease.

CONCLUSION

Urinary trypsinogen-2 may serve as a noninvasive biomarker of AP, whereas urinary TAP may indicate disease severity in children, although within certain time limitations. Determination of these urinary parameters is promising and may facilitate diagnosis and prediction of AP severity; therefore, further studies are warranted. Future research should focus on integrating urinary biomarkers with clinical and laboratory parameters to develop predictive models for severity assessment in pediatric AP.