Exocrine pancreas disfunction in severely traumatised patients and early enteral nutrition

Major trauma sonrası görülen pankreas salgı bozukluğu ve erken enteral beslenme

Metin SENKAL,1 Bülent CEYLAN,1 Thomas DESKA,1 Barbara MARPE,2 Bruno GEIER2

BACKGROUND
We investigated exocrine pancreatic insufficiency in severely traumatised patients with enteral nutrition using the fecal elastase-1 concentration.

METHODS
The fecal elastase-1 levels of critically ill patients after major trauma (n=18) were determined in a prospective study. Early enteral nutrition was started with a high molecular diet via a naso-duodenal tube, starting 24-36 hours after admission to the intensive care unit. Enteral feeding was administered continuously starting with 20 mL/h (1 kcal/mL) and advanced gradually to 80 mL/h in the next days. Stool samples from the first and second stool after beginning of the enteral nutrition were taken for determination of the fecal elastase-1. For elastase-1 analysis in a sandwich-type enzyme immunoassay (ELISA), a sample of approximately 1 g stool was taken from the first and second stool after beginning of the enteral nutrition. Elastase-1 concentration of >200 μg/g was considered as normal, whereas <100 μg/g elastase-1 was significantly low indicating a severe exocrine pancreas dysfunction.

RESULTS
All patients were fed enteraly without relevant feeding-association complications and no diarrhea occurred in any patient. In the initial stool pass age, 55.6% of the patients had moderately or severely decreased elastase-1 concentrations. In the second stool pass age, only 38.9% of the patients showed a decrease in the elastase-1 concentration (p<0.01). The average elastase-concentration in the first stool sample was 268.4 μg/g (median: 162.1 μg/g) and in the second sample 333.8 μg/g (median: 520.2 μg/g).

CONCLUSION
The data of this study suggests that initial exocrine pancreas insufficiency may occur in severely traumatised and critically ill patients, which improves under early enteral nutrition with polymeric enteral diets. The clinical consequences of exocrine pancreatic dysfunction in the early posttraumatic situation have to be defined.

Key Words: Enteral nutrition/adverse effects/methods; fecal elastase-1; pancreas, exocrine.

AMAÇ
Major trauma sonrasında yoğun bakım servisinde yatan ve enteral yoldan beslenen hastalarda, pankreas ekzozrin salgılardan görülen değişiklikleri saptamaktır.

GEREÇ VE YÖNTEM
Hastalar (n=18) yoğun bakım ünitesinde travma sonrası 24-36 saatlerde enteral yoldan beslenmeyi başlarlar, sonuçlar ileriye dönük olarak değerlendirildi. Başlangıçta yüksek moleküllü ağırlıklı diyetler 20 ml/sa’da (1 kcal/mL) verildi ve bu miktar aşamalı olarak 80 ml/sa’ya kadar yüksektildi. Sonrasında bu hastalardaki enteral beslenme sonrası birinci ve ikinci fakal elastaz-1 seviyelerine bakıldı. İlk defekasyondan bir gram grafi örneği alınarak ELISA yöntemiyle fakal elastaz-1 seviyesi belirlendi. Fakal elastaz-1 normal değeri >200 μg/g olan kabul edilirken, <100 μg/g olan değerler ciddi pankreas ekzozrin salgı bozukluğu olarak değerlendirildi.

BULGULAR
Tüm hastalar sadece enteral yoldan beslenmekte ve beslenmeye bağlı gastrointestinal komplikasyonlara rastlanmadı. İlk laboratuvar değerlerinde hastaların %55,6’sında fakal elastaz-1 seviyelerinde orta ve yüksek oranda düşüş gözlemdi. İkinci incelemlerde ise bu oranın %38,9 seviyelerine düşüşü görüldü (p<0,01). İlk incelemede ortalama fakal elastaz-1 seviyesi 268,4 μg/g (median 162,1 μg/g) iken, ikinci incelemede 333,8 μg/g (median 520,2 μg/g) olarak saptandı.

SONUÇ
Bu araştırmada, travma sonrası hastalarda ciddi oranda pankreas işlev bozukluğu olduğu, yüksek moleküllü ağırlıklı diyetle enteral yoldan beslenmenin ise kayda değer bir iyileşme sağladığı görüldü. Travma sonrası, hastalarda pankreas ekzozrin enzim seviyelerinin düşüşüğünün nedene yönelik araştırma larla ve bunun olumlu ya da olumsuz etkilerinin yapılabacak diğer çalışmalarla desteklenmesi gerektiğine kınanmak varıdı.

Anahtar Sözcükler: Enteral beslenme/yen etki/yöntemler, fakal elastaz-1; pankreas, ekzozrin.
Ischemia and reperfusion induced intestinal trauma not only attenuates the intestinal secretion but also changes the substrate adsorption of enterocytes. In sepsis and septic shock a secretory dysfunction of the exocrine pancreas occurs which correlates with the severity of illness. An impaired exocrine pancreas function could result in substantial reduction of the adsorption of high molecular food substrates. Patients with systemic inflammatory reaction or severe trauma the intestinal adsorption capacity was critically reduced as compared to physiologic conditions. In the current concept of nutrition of critically ill patients, early enteral nutrition is implemented to substitute the nutritional needs and to maintain gut mucosa integrity. Further, early posttraumatic administration of enteral feeds reduces the risk of bacterial translocation and the consecutive systemic inflammation. In the early nutrition concept, enteral feeding is started within 24 hours after trauma or surgery with high molecular diets. The increasing evidence favoring early enteral support of traumatized patients resulted in various examinations of the effects of the nutrition on different organ systems, but not of the exocrine pancreas function.

Pancreatic dysfunction may occur in various kinds of critical illness like sepsis, adult respiratory distress syndrome (ARDS) and after surgery with extracorporeal bypass. Severe impairment of exocrine pancreatic function has been described in critically ill patients with septic shock, which was not observed in nonseptic controls. These findings were consistent with animal studies where a substantial decrease of pancreatic perfusion early during the course of sepsis was observed. Also, cellular damage in the pancreas was significantly increased in a normotensive sepsis model of Pseudomonas aeruginosa-induced sepsis when compared with sham animals. Although the clinical consequences of exocrine pancreas dysfunction are still not clear, some of the complications of early enteral nutrition like abdominal distension and diarrhea could be related. Fecal elastase-1 was reported to be a highly sensitive and specific non-invasive test for exocrine function and a single analysis was claimed to be sufficient in most cases.

Since conventional pancreas tests are difficult to perform and since pancreas-independent parenteral nutrition was the preferred route of feeding trauma patients, little is known about the exocrine pancreas function in critically ill patients. However, in enteral nutrition, a normal exocrine pancreas function is mandatory for the adsorption of high molecular substrates, such as proteins and triglycerides.

The goal of the present study was to investigate the exocrine pancreas function of severely traumatized patients in need of intensive care and enteral nutrition using the fecal elastase-1.

**MATERIALS AND METHODS**

In an open prospective study, early enteral nutrition was started to severely traumatized patients (n=18) who needed intensive care (Table 1). Patients with torso trauma as well as patients with head injuries were included into the study. Exclusion criteria were known history of exocrine pancreas dysfunction and failure to administer enteral nutrition.

The Harris Benedict equation for basal energy expenditure and a designated multiplication factor of 1.4 to allow for trauma related increases in the basal energy expenditure was used to calculate the daily nutritional requirement.

All patients received an endoscopic guided naso-enteral multi-lumen tube (Freka-Trelumina, Fresenius-Kabi, Bad-Homburg, Germany) within 24 h of admission to the intensive care unit. The application of the enteral diet (Fresubin, Fresenius-Kabi, Bad Homburg, Germany) was started within 24 h after surgery using continuous infusion (20 mL/h) and was then increased every 6 hours until the volume required to meet caloric support was achieved. All patients received intravenous fluids (5% dextrose and normal saline solution) and elec-

<table>
<thead>
<tr>
<th>Table 1. Patients characteristics</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>Body height (cm)</td>
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<tr>
<td>APACHE II</td>
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<tr>
<td>GSC on admission</td>
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<tr>
<td>Head injury (n)</td>
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</tbody>
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APACHE II: Acute Physiology and Chronic Health Evaluation; GCS: Glasgow Coma Scale.
troltyes as clinically indicated. Intravenous ranitidine was given to all patients as the standard gut prophylaxis for stress ulceration.

Each patient’s age, sex, Acute Physiology and Chronic Health Evaluation scale (APACHE II), the presence or absence of major or moderate head injury defined as Glasgow Coma Scale score less than or equal to 12 and specific injury diagnoses were documented.

Clinical assessment was performed and recorded daily. Adverse gastrointestinal symptoms were recorded daily, i.e. any nausea or vomiting that required antiemetics, diarrhea of three loose bowel movements per 24 h or abdominal cramping. If any of these symptoms occurred in a moderate to severe fashion, infusion was discontinued for six to twelve hours and started again at the next lower infusion rate.

For elastase-1 analysis, a sample of approximately 1 g stool was taken from the first and second stool after beginning of the enteral nutrition. As recommended by the manufacturer, all stool samples were kept at -20°C until analysis. Samples of stool are stored at even room temperature for a period of one week. Watery unformed stools were excluded from the study.

Sample preparation

For the analysis of pancreatic elastase-1, we analyzed 100 mg stool using the dosing device from Boehringer Mannheim (Boehringer Mannheim, Germany). To 100 mg stool portion we added 10 ml of extraction buffer provided with the ELISA kit for pancreatic elastase-1 in stool from ScheBo-Tech Company (Wettenberg, Germany). The stool suspension was thoroughly homogenized for 5 minutes at room temperature using a vortex mixer. After centrifugation of the suspension a final 1:500 dilution of the supernatant was made with the sample-washing buffer provided with the test kit.

We determined pancreatic elastase-1 in stool using a sandwich-type enzyme immunoassay (ELISA). Two monoclonal antibodies binding to two distinct epitopes of the human pancreatic elastase-1 were employed (ScheBo-Tech, Germany). The performance of test is described elsewhere. Briefly, fifty microliters of the dilute (1:500) stool sample was micropipetted into the wells of the ELISA plate precoated with a monoclonal antibody to human pancreatic elastase-1 in duplicate. Five known standards of elastase at concentrations of 0.3, 1.0, 2.0, 4.0 and 10.0 ng/mL, a blank of the sample/washing buffer and a control of 3.8 ng/mL (±10%) elastase were also micropipetted into the wells in duplicate. After a 60-min incubation at room temperature, each well was washed with 200 µL of the sample/washing buffer three times, then 50 µL of a biotin-conjugated second monoclonal antibody to pancreatic elastase-1 were added to each well and incubated for 30 min. All wells were washed again. Then, 50 µL of the peroxidase-streptavidin solution was added and incubated for 30 min in the dark at room temperature. All wells were washed again and 100 µL of the substrate solution were added and incubated for 20 min in the dark. Then 100 µL of the stop solution were added and the plate was immediately analyzed. The substrate reaction was read at 405 nm using a reference wavelength at 492 nm. The measured elastase concentrations were multiplied by 50 (corresponding to the dilution 1:500) to yield results as micrograms per gram stool with a measuring range of the immunoassay between 15 and 500 microgram per gram stool.

Statistical analysis

Due to the small sample size, the results were evaluated mainly descriptively. Where appropriate the Mann-Whitney-U test was used. The incidence of elastase-1 reduction in the two stools was described in a cross-table and the significance was tested using the Exact-test. A p-value <0.01 was considered as significant.

RESULTS

In 18 patients (n=18) with severe blunt trauma admitted to the intensive care unit the fecal elastase-1 was determined. Eleven patients (n=11) had a head injury and the mean Glasgow Coma Scale was 7, the APACHE II Score 17±4 (Table 1). All patients received enteral nutrition within 24-36 h after admission. The enteral nutrition was well tolerated by all patients and no feeding associated complications, i.e. nausea, abdominal distension or diarrhea, occurred. No clinical or laboratory signs of pancreatitis were found.

The first stool was usually on the 4th day after admission to the intensive care unit and the second on the 5th day.
Table 2. Elastase-1 concentrations in the 1st and 2nd stool passage after trauma in enterally fed patients (n=18)

<table>
<thead>
<tr>
<th>Elastase-1 in stool 1</th>
<th>Elastase-1 in stool 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (&lt;200 µg/g)</td>
<td>Reduced (100-200 µg/g)</td>
</tr>
<tr>
<td>Normal (&lt;200 µg/g)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Reduced (100-200 µg/g)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Severely reduced (&lt;100 µg/g)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2 shows the incidence of normal, decreased and severely decreased elastase-1 concentrations in the first and second stool. There was a difference between the both measurements, demonstrating significantly more patients with reduced elastase-1 levels in the first stool as compared to their second stool (p<0.01).

Elastase-1 concentrations in the first stool passage varied between 27.4 µg/g and 756.6 µg/g interindividually. 16.6% of the patients (n=3) had elastase-1 concentrations lower than 100 µg/g stating a severe exocrine pancreas failure. As compared, in 33.3% of the patients (n=6) the elastase-1 levels in the stool was below 200 µg/g (mild pancreatic failure) whereas 50% of the patients (n=9) had a normal exocrine pancreas function with elastase-1 levels above 200 µg/g.

In the second stool passage the elastase-1 concentrations varied between 30.4 µg/g and 687.6 µg/g. Elastase-1 concentration in stool less than 100 µg/g was in 11.1% (n=2). A mild pancreatic failure (elastase-1 <200 µg/g) was found in 27.8% of the patients (n=5). 61.1% of the patients (n=11) had normal elastase-1 concentrations in the second stool.

The mean elastase-1 concentration in the first stool passage was 268.4 µg/g (median 162.1 µg/g) versus 333.8 µg/g (median 520 µg/g) in the second stool. This difference did not reach statistical difference (Fig. 1).

There were no clinical signs of intolerances of enteral nutrition or complications in patients with elastase-1 concentrations below normal levels (200 µg/g). Even patients with elastase-1 levels lower than 100 µg/g did not show any clinical symptoms of intolerance of the polymeric enteral diet.

**DISCUSSION**

Fecal concentration of pancreatic elastase-1 was reported to be highly sensitive and specific non-invasive test for exocrine pancreatic function. In comparison with the results of the secretin-pancreozymin or secretin-caerulein test, fecal elastase displayed - at a cut off of 200 µg/g stool- an excellent sensitivity (100%) in detecting moderate and severe pancreatic insufficiency and a sufficient sensitivity for mild pancreatic impairment (63%). However, large variations of fecal elastase-1 within one stool passage can occur intraindividually.

![Fig. 1. Pancreatic elastase-1 concentrations in stool samples of trauma patients (n=18) in the first and second stool passage after admission to the ICU and initiation of enteral nutrition.](image_url)
our knowledge, fecal elastase-1 has not been investigated in critically ill patients yet.

This study is the first to analyze the exocrine pancreatic function of enterally fed trauma patients using the fecal elastase test. The elastase-1 concentration in the stool, as an indicator for the exocrine pancreatic function, was significantly decreased in the first stool of the patients as compared to the second stool (p<0.01). However, although 16.6% of the patients had a severe and 33.3% a mild pancreatic insufficiency no clinical symptoms of intolerance of the administered polymeric enteral diet occurred. In the second stool passage only 11.1% had elastase-1 <100 µg/g stating a severe impairment of the exocrine pancreas function without any clinical symptoms of enteral intolerance. The data of our study suggest that exocrine pancreas insufficiency may occur in severely traumatized patients. However, there is a tendency that the initial insufficiency improves within a short period of 2-3 days. Further, it is unclear which clinical consequences exocrine pancreatic failure may have in critically ill trauma patients. The exocrine pancreatic insufficiency at this stage does not counteract the initiation of enteral feeding with polymeric enteral diets. Moreover, under early enteral nutrition the elastase-1 levels in stool improved slightly. Unfortunately, no valuable data about the absorptive activity of the gut in critically exist.

Also, our study demonstrates that transpyloric feeding using a multi-lumen tube does achieve full nutritional support with a standard enteral formula rapidly in severely traumatized patients. In contrast, significant risk of reflux associated with gastric feeding has been described, particularly in patients with head injuries.\(^{[19,20]}\)

Our data on trauma and critical illness are different from what has been found in animal studies and in septic patients. Application of LPS, which is well-established animal model of sepsis, reduced in vivo the protein content of pancreatic fluid in rats.\(^{[21]}\) Some studies in animal models of sepsis as well as in patients who died of sepsis and multiple organ failure focus on apoptosis in lymphocytes and parenchymal organs.\(^{[22]}\)

There is one study that reports the occurrence of apoptosis in the pancreas in human sepsis.\(^{[23]}\) Given the scarcity of data, the involvement of apoptosis in the development of exocrine pancreatic dysfunction in sepsis remains speculative and need to be further investigated.

This study indicates that the pancreatic elastase-1 in the stool is apparently at least to some extent impaired in patients with severe trauma. If the fecal elastase-1 is an indicator for the exocrine pancreatic function as it is described in the literature, then our study shows that in severely traumatized patients on intensive care exocrine pancreatic dysfunction may occur in 50% of the patients. In further investigations, the occurrence of the pancreas dysfunction has to be correlated to the other organ disturbances during critical illness as well as to the absorptive capacity of the gut. Current theory of nutrition in critical illness favours the enteral route to preserve gut integrity and meet nutritional requirements. It is current practice in intensive care units to administer polymeric enteral nutrition formulas in traumatized critically ill patients. Polymeric enteral nutrition formulas contain complete macronutrients and should be administered in patients with an unimpaired digestive and absorptive system. Our findings on mostly normal exocrine pancreatic function and absence of intolerance to polymeric enteral formula support the concept of early enteral nutrition in critically ill.

In contrast to our findings, studies in septic shock patients showed a dysfunction of the exocrine pancreas which correlated with the severity of the septic illness.\(^{[19]}\) Therefore, further studies evaluating potential pathophysiological mechanisms involved in the development of pancreatic dysfunction and thereby impaired digestive capacity in critically ill are necessary.

REFERENCES