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Clinical Trials Study

Association between acute pancreatitis and small intestinal bacterial overgrowth assessed by hydrogen breath test

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Abstract

AIM

To elucidate the effects of small intestinal bacterial overgrowth (SIBO) on the severity and complications of acute pancreatitis (AP).

METHODS

In total, 208 patients with AP as defined by the revised Atlanta classification were admitted to Xuanwu Hospital of Capital Medical University from 2013 to 2016. All patients were admitted within 72 h of AP onset. The hydrogen breath test was performed 7 d after AP onset to detect hydrogen production and evaluate the development of SIBO. The incidence of SIBO was analyzed in patients with AP of three different severity grades. The association between SIBO and complications of AP was also assessed.

RESULTS

Of the 27 patients with severe AP (SAP), seven (25.92%) developed SIBO. Of the 86 patients with moderately severe AP (MSAP), 22 (25.58%) developed SIBO. Of the 95 patients with mild AP (MAP), eight (8.42%) developed SIBO. There were significant differences in the rates of SIBO among patients with AP of different severities. Additionally, more severe AP

was associated with higher rates of SIBO positivity ($P < 0.05$). SIBO in patients with AP mainly occurred within 72 h of the onset of AP. The incidence of organ failure was significantly higher in patients with SIBO than in those without ($P < 0.05$).

CONCLUSION

SIBO occurs more frequently in patients with MSAP or SAP than in those with MAP, usually ≤ 72 h after AP onset. Additionally, SIBO is associated with organ failure.

Key words: Severe acute pancreatitis; Small intestinal bacterial overgrowth; Hydrogen breath test; Complication

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Core tip: The research on small intestinal bacterial overgrowth (SIBO) in acute pancreatitis is mostly confined to animal experiments. The traditional method of diagnosing SIBO is to take small intestinal fluid for bacterial culture, but it is difficult to achieve in clinical patients. In this study, a portable hydrogen expiratory detector was used to detect the patients' expired hydrogen concentration to diagnose SIBO. It was found that there were differences in the positive rates of SIBO in acute pancreatitis with different severity grades. Patients with more severe pancreatitis had a higher positive rate of SIBO. SIBO occurred mainly within 72 h of onset. Patients with SIBO were more prone to organ failure complications.

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INTRODUCTION

Previous metagenomic studies have shown that the gut microbiome comprises up to 3.3 million microbial genes, 10 bacterial genetic logic gates, and more than 1000 bacterial species^[1]. Maintenance of the dynamic equilibrium of the microbial ecosystem of the gut is crucial to human health, and abrupt and chaotic shifts in the gut microbiota can lead to many diseases. Small intestinal bacterial overgrowth (SIBO) is a type of dysbiosis and has no typical clinical presentation, and it is characterized by increasing numbers of intestinal bacteria and/or colonization of atypical microorganisms^[2]. SIBO is related to various disorders, including irritable bowel syndrome, non-alcoholic fatty liver disease, inflammatory bowel

disease, and pancreatitis^[3-5]. Many experimental animal studies have shown that SIBO can affect the severity and progression of AP^[6,7]. Paralytic ileus accompanied by bacterial overgrowth is an important mechanism of secondary pancreatic infection in patients with AP. Previous studies have shown that the pathogenic bacteria leading to pancreatic infection are similar to the opportunist species that overgrow in the small intestine, suggesting that SIBO plays a pivotal role in pancreatic infection^[7,8]. A recent study suggested that prophylactic total colectomy in patients with AP induces SIBO involving both Gram-negative bacilli (*Escherichia coli*, *Proteus* spp.) and anaerobic bacteria^[9]. We performed the present study to investigate the incidence of SIBO in AP with different severity grades and explore the correlation between SIBO and complications of AP.

MATERIALS AND METHODS

Patients

In total, 208 patients with AP admitted to the Department of Gastroenterology, Xuanwu Hospital, Capital Medical University from 2013 to 2016 were included in this study. The patients comprised 141 men and 67 women with an age range of 18 to 80 years and a mean age of 44.48 ± 0.26 years. There were no significant differences in sex or age among the three severity groups: severe AP (SAP), moderately severe AP (MSAP), and mild AP (MAP) ($P > 0.05$).

Diagnosis of AP

AP was diagnosed in accordance with the 2012 Atlanta Classification Criteria^[10], which state that clinically confirmed AP should meet at least two of the following three characteristics: (1) signs of abdominal pain consistent with AP; (2) serum amylase and/or lipase level at least three times higher than the upper limit of normal; and (3) abdominal imaging findings consistent with the imaging features of AP.

Classification of disease severity

AP was divided into three categories according to severity: MAP, MSAP, and SAP. Patients with MAP had no local or systemic complications or organ failure and usually recovered within 1 to 2 wk. Patients with MSAP had local or systemic complications with transient organ failure that recovered within 48 hours. Patients with SAP had persistent organ failure (*i.e.*, respiratory, cardiovascular, or renal failure for ≥ 48 h) that could not be restored without treatment and that may involve one or more organs.

Local complications of AP include acute fluid accumulation, acute necrosis, pancreatic pseudocyst formation, encapsulated necrosis, and pancreatic abscess formation. Systemic complications include organ failure (respiratory failure, circulatory failure, renal failure, *etc.*), systemic inflammatory response

syndrome, and systemic infection.

Inclusion criteria

The inclusion criteria for this study were as follows: age > 18 years; no colonoscopy or X-ray barium meal examination within the past 4 wk; and the presence of a clear consciousness, ability to communicate effectively with the physician, and ability to listen to instructions for completion of the breath-holding for 10 s.

Exclusion criteria

The exclusion criteria were postprandial hypoglycemia and a > 72-h duration from AP onset to hospitalization.

Study protocol

The hydrogen breath test was performed in all patients after admission using a lactulose hydrogen breath test instrument (Gastrolyzer 2; Bedfont Scientific Ltd., Maidstone, Kent, United Kingdom). The hydrogen concentration is expressed in ppm. The detection range was 0 to 500 ppm. The sensitivity was 1 ppm and the accuracy was $\pm 5\%$. The instrument was connected to the new D-type interface. The fasting expiratory hydrogen concentration was measured twice, and the highest value was used for analysis. The patients were instructed to quickly drink 10 g of lactulose in 100 mL of warm water, and the hydrogen concentration was then measured every 15 min for 3 h. The patients were asked to take a deep breath and hold it for 10 s, then breath. This was performed two consecutive times, and the maximum expiratory hydrogen concentration was recorded.

Result criteria

SIBO was defined as follows^[11]: a fasting expiratory hydrogen concentration of < 10 ppm or an elevated oral expiratory lactate concentration of ≥ 12 ppm after oral administration of lactulose. A fasting expiratory hydrogen concentration of > 20 ppm (with high defined as > 12 ppm) was more helpful for the diagnosis. The sum of the hydrogen breath values (lactulose hydrogen breath test set values) measured during the 90-min test was used as an index to evaluate intestinal bacterial growth.

Statistical analysis

Data are presented as mean \pm SD. Student's *t*-test, Mann-Whitney *U* test, and Spearman's test were performed using SPSS v.19.0 software (IBM Corp., Armonk, NY, United States). A *P*-value < 0.05 was considered statistically significant.

RESULTS

Incidence of SIBO in patients with AP of different severity grades

Of the 27 patients with SAP, seven (25.92%) had

SIBO. Of the 86 patients with MSAP, 22 (25.58%) had SIBO. Of the 95 patients with MAP, eight (8.42%) had SIBO. There were significant differences in these rates of SIBO positivity among patients with AP of different severities. Additionally, more severe AP was associated with higher rates of SIBO positivity ($P < 0.05$), as shown in Table 1.

Changes in small intestinal bacterial hydrogen production in early and late stages of AP

SIBO in patients with AP occurred mainly within 72 h of AP onset. The small intestinal bacterial hydrogen production (0-90 min) in patients with AP was 51.72 ± 1.63 ppm in the early stage (within 72 h) and 32.7 ± 0.69 ppm in the late stage (within 7 d). The intestinal bacterial hydrogen production was significantly lower in the late stage than in the early stage ($P < 0.05$), as shown in Table 2.

Correlation between SIBO and complications of AP

According to the results of the hydrogen breath test, the patients with AP were divided into an SIBO-positive group ($n = 37$) and an SIBO-negative group ($n = 171$), and the occurrence of complications was compared between the two groups. In the SIBO-positive group, 19 patients had respiratory failure, including two with acute renal failure and one with circulatory failure; the organ failure rate was 51.35%. In the SIBO-negative group, 44 patients had respiratory failure, including one with acute renal failure; the organ failure rate was 25.73%. The incidence of organ failure in the SIBO-positive group was significantly higher than that in the SIBO-negative group ($P < 0.05$). There was no significant difference in the other complications between the two groups, as shown in Table 3.

DISCUSSION

The effects of SIBO on the body mainly include the destruction of digestive enzymes and the decomposition of bile acids, causing indigestion of various nutrients^[12]. The production of large numbers of harmful metabolites leads to acute and chronic toxicities within the body, including small intestinal motor disorders and reduced intestinal clearance. SIBO can be caused by an abnormal anatomy of the intestinal tract, a decreased ability of the ileocecal valve to block reflux of the colonic contents, a shift of bacteria into the small intestine, gastric acid, the decrease or lack of bile acid and proteolytic enzyme, or reduced secretion of immunoglobulins, which leads to their bactericidal or antibacterial action to weaken and induces SIBO. In addition, certain liver diseases can damage the small intestinal villi and the immune defense mechanism, leading to bacterial migration and SIBO^[13-15]. The gold standard for the diagnosis of SIBO is culture of the small intestinal contents. Most

Table 1 Association between acute pancreatitis of different severity grades and small intestinal bacterial overgrowth

Disease classification	Total (n)	SIBO positive	SIBO negative	χ^2	P value
Mild	95	8	87	10.494	0.005
Moderate to severe	86	22	64		
Severe	27	7	20		

SIBO: Small intestinal bacterial overgrowth.

Table 2 Comparison of small intestinal bacterial hydrogen production in patients with acute pancreatitis in the early and late stages

Time	Hydrogen production (ppm)	T	P value
Early stage (within 72 h)	51.72 ± 1.63	4.734	0.000
Late stage (within 7 d)	32.7 ± 0.69		

Table 3 Correlation between small intestinal bacterial overgrowth and complications of acute pancreatitis

Complication	SIBO positive group (n = 37)	SIBO negative group (n = 171)	χ^2	P value
Organ failure			9.456	0.002
Yes	19	44		
No	18	127		
SIRS			0.586	0.444
Yes	22	113		
No	15	58		
Infection			0.001	0.976
Yes	9	42		
No	28	129		
Local complications			1.324	0.250
Yes	12	73		
No	25	98		

SIBO: Small intestinal bacterial overgrowth.

research has suggested that SIBO is present when the small intestinal bacterial count is $\geq 10^{10}$ CFU/mL or the proximal small intestinal fluid bacterial count is $> 10^5$ CFU/mL^[16,17]. However, this diagnostic method is complex, repetitive, and painful for the patient; it is thus difficult to apply in the clinical setting. The hydrogen expiratory test is one of the most widely used diagnostic techniques for SIBO because it is simple, rapid, and noninvasive^[18]. Animal studies have shown that SIBO is present in AP, even within 24 h of onset, and is related to AP disease progression^[19,20]. Because of the attenuation of intestinal peristalsis, especially inhibition of the movement of compound waves, normal digestive fluid secretion is lacking, and intestinal immune dysfunction occurs due to a rapid increase in large and small intestinal bacteria. Anaerobic bacteria and lactobacilli significantly decrease, and this is accompanied by excessive growth of pathogenic bacteria. Intestinal bacterial overgrowth is related to the severity of the disease^[21].

Klebsiella spp., which are resident bacteria of the colon, can reportedly be detected in the small intestine in cases of SIBO^[22]. Our findings are consistent with this. We used the hydrogen breath test to detect SIBO in patients with different severities of AP. We found a significant difference in the rates of SIBO positivity among patients with different severities of AP, and the rate of SIBO positivity increased with more severe AP ($P < 0.05$). SIBO in patients with AP mainly occurred within 72 h of AP onset, and the amount of hydrogen production in the small intestine was significantly lower in the late stage of AP ($P < 0.05$).

We found that the incidence of organ failure was significantly higher in patients with SIBO than in those without ($P < 0.05$). SIBO may be an important risk factor for the progression of SAP. At present, the course of AP is divided into two different stages: the acute inflammatory response period (within the first week after onset) and the infectious complication period (2–6 wk after onset). It is helpful to evaluate the prognosis of AP and its prevention measures by thoroughly evaluating the characteristics of these two stages. Intestinal bacterial changes can reportedly occur in patients with varying degrees of pancreatitis and are closely related to the inflammatory response of AP^[23]. Most of the bacteria in the intestinal tract are Gram-negative bacilli. SIBO results in the accumulation of large numbers of harmful metabolites, especially the release of large amounts of endotoxin^[24]. This increases the systemic inflammatory response and promotes the occurrence of multiple organ dysfunction syndrome through the immune amplification effect. A correlation between SIBO and endotoxemia has been reported in patients with SAP. Endotoxemia is considered to be related to the occurrence and mortality of systemic complications of AP^[25]. Endotoxin is a powerful immune system activator. It can act on neutrophils, macrophages, dendritic cells, and endothelial cells and result in the release of cytokines and inflammatory mediators, including interleukins (ILs) (e.g., IL-6, IL-1, and IL-10) and tumor necrosis factor- α (TNF- α), which may in turn induce a cascade of inflammatory reactions. Zhang *et al.*^[26] found that serum endotoxin and intestinal mucosal permeability were higher in patients with SAP than in normal controls. In recent years, researchers have studied the relationship between the intestinal microecology and development of AP at the molecular level, such as cellular signal transduction. Wu *et al.*^[27] constructed a rhesus monkey model of AP and found that Toll-like receptor (TLR) 2 and TLR4 were expressed in the ileal mucosa of rhesus monkeys with AP. The lipopolysaccharide of *E. coli*, in combination with intestinal epithelial cell receptors such as TLR, activates NF- κ B signal transduction and results in the release of excessive cytokines and inflammatory mediators, such as TNF- α , IL-6, and others. TNF- α level in the circulation is proportional to the degree of damage to the pancreas and lung tissue when AP occurs. IL-6

plays an important role in signal transduction during acute lung injury and is closely related to the severity of acute lung injury and organ failure.

SIBO may be an important cause of secondary infection in patients with AP. The mortality rate of patients with concurrent SAP and pancreatic infection ranges from 23% to 85%, which is higher than that in patients with SAP who do not have pancreatic infection^[28]. Patients with AP have intestinal motility disorders, slow intestinal peristalsis, and intestinal stagnation. The colonic bacteria proliferate and migrate to the small intestine to multiply, causing SIBO. Because of these two factors, the proximal small intestine plays an important role in pancreatic necrosis and infection. Many researchers believe that bacterial translocation occurs in the small intestine in patients with AP and that bacterial translocation is associated with the subsequent infectious complications of AP. However, no direct correlation between SIBO and secondary infection was found in the patients with AP in the present study, which may be related to the fact that the number of SIBO-positive patients was lower than that of SIBO-negative patients or that SIBO was not the main risk factor for infection in patients with SAP.

In the present study, patients with MSAP and SAP were more susceptible to SIBO than patients with MAP. SIBO occurred mainly in the early stage of AP and was related to organ failure. How to intervene in the presence of SIBO in patients with SAP in the early stage will be of guiding significance to reduce early organ failure and late infectious complications.

ARTICLE HIGHLIGHTS

Research background

Current clinical and animal studies have shown that gut bacterial overgrowth and translocation is the main reason of pancreatic secondary infection. Small intestinal bacterial overgrowth (SIBO) is related to various disorders, including irritable bowel syndrome, non-alcoholic fatty liver disease, inflammatory bowel disease, and pancreatitis. Many experimental animal studies have shown that SIBO can affect the severity and progression of AP. Previous studies have shown that the pathogenic bacteria leading to pancreatic infection are similar to the opportunist species that overgrow in the small intestine, suggesting that SIBO plays a pivotal role in pancreatic infection. A recent study suggested that prophylactic total colectomy in patients with AP induces SIBO involving both Gram-negative bacilli (*Escherichia coli*, *Proteus* spp.) and anaerobic bacteria. We performed the present study to investigate the incidence of SIBO in AP with different severity grades and explore the correlation between SIBO and complications of AP.

Research motivation

Clinical studies have revealed that in SAP patients with intestinal flora disorders, gut barrier dysfunction has a significant impact on the disease occurrence, development, and prognosis. The research on SIBO in AP is mostly confined to animal experiments. The traditional method of diagnosing SIBO is to take small intestinal fluid for bacterial culture, but it is difficult to achieve in clinical patients. In this study, a portable hydrogen expiratory detector was used to detect the patients' expired hydrogen concentration to diagnose SIBO. In the early stages of AP disease, monitoring gut microbiota and timely treatment can improve the prognosis.

Research objectives

How to protect the integrity of the intestinal mucosal barrier, maintain its function, adjust the intestinal flora disorders, and reduce and prevent bacterial translocation of the intestine has become the key to control the development of SAP and reduce complications. We performed the present study to investigate the incidence of SIBO in AP with different severity grades and explore the correlation between SIBO and complications of AP.

Research methods

Hydrogen breath test principle: After taking lactulose, it reaches the colon and is fermented and decomposed by bacteria to produce hydrogen, causing a peak of hydrogen content in the colon. If there is SIBO, lactulose is fermented by overgrowing bacteria to produce hydrogen before entering the colon. Thus, a peak of hydrogen concentration in the small intestine peak occurs. Expiratory changes in hydrogen concentration can reflect the growth of bacteria in the small intestine. Different from the traditional monitoring methods, in this study, a portable hydrogen expiratory detector was used to detect the patients' expired hydrogen concentration to diagnose SIBO.

Research results

It was found that there were differences in the positive rates of SIBO in AP with different severity grades. Of the 27 patients with SAP, seven (25.92%) had SIBO. Of the 86 patients with MSAP, 22 (25.58%) had SIBO. Of the 95 patients with MAP, eight (8.42%) had SIBO. There were significant differences in these rates of SIBO positivity among patients with AP of different severities. Patients with more severe pancreatitis had higher positive rate of SIBO. SIBO occurred mainly within 72 h of onset. Patients with SIBO are more prone to organ failure complications. How to take timely and effective measures to deal with SIBO is a problem to be solved.

Research conclusions

In the present study, patients with MSAP and SAP were more susceptible to SIBO than patients with MAP. SIBO occurred mainly in the early stage of AP and was related to organ failure. How to intervene in the presence of SIBO in patients with SAP in the early stage will be of guiding significance to reduce early organ failure and late infectious complications.

Research perspectives

Which method can be used to effectively prevent or treat small intestinal bacterial overgrowth in patients with AP, while monitoring the intestinal mucosal barrier, is the future research direction.

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