MIGA-ORCZYKOWSKA, Nadia, SAJKIEWICZ, Ilona, LEMIESZEK, Paulina, JASIUK, Ilona, WÓJTOWICZ, Justyna, PUSTELNIAK, Martyna, KRUKAR, Katarzyna, ŁUKASZEWSKA, Ewa, RUDNICKA, Katarzyna and KISTER, Klaudia. The Role of Gut Microbiome in the Pathogenesis and Progression of Acute Pancreatitis: A Systematic Review. Journal of Education, Health and Sport. 2024;70:55262. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.70.55262
https://apcz.umk.pl/JEHS/article/view/55262

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.08.2024. Revised: 22.09.2024. Accepted: 23.09.2024. Published: 24.09.2024.

The Role of Gut Microbiome in the Pathogenesis and Progression of Acute Pancreatitis - A Systematic Review

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Abstract

Introduction and purpose

Acute pancreatitis (AP) is one of the most common abdominal conditions leading to hospital admissions worldwide. It is characterized by an inflammatory reaction triggered by the premature activation of trypsinogen and other enzymes, resulting in pancreatic autodigestion. While most cases of AP are mild and self-limiting, approximately 15-20% of patients develop severe AP with organ failure, which is associated with a mortality rate of up to 30%. In recent years, the impact of intestinal microbiome dysregulation on various diseases has been increasingly debated. This study aims to summarize the current knowledge regarding the role of intestinal microbiota dysbiosis in the pathogenesis and progression of acute pancreatitis.

Material and methods

This review is based on materials collected from the PubMed database. We conducted a search using the following keywords: "acute pancreatitis," "microbiome," and "dysbiosis," focusing on articles published between 2018 and 2024.

Results

Studies have demonstrated a relationship between gut dysbiosis and various disorders, including digestive, metabolic, and even cancer-related conditions. It is well-established that the pancreas is closely connected to the intestines, and its exocrine function can influence the composition of the gut microbiome. This interaction is often referred to as the "gut–pancreas axis."

Conclusion

The interaction between the pancreas and intestinal microbiota is believed to play a role in the pathophysiology of acute pancreatitis. Further research into this relationship could lead to the development of new diagnostic and therapeutic strategies.

Keywords: acute pancreatitis, microbiome, dysbiosis

Introduction

Acute pancreatitis is a common digestive system discorder, with an incidence of approximately 34 cases per 100,000 worldwide, and the number of cases has increased in recent years.[1] AP develops due to abnormal activation of pancreatic enzymes leading to autodigestion and widespread destruction of pancreatic tissue, accompanied by local or systemic inflammatory reactions. In recent years, the gut microbiome has become a frequent focus of scientific research. It has now been established that there is a bidirectional relationship between intestinal dysbiosis and the course of acute pancreatitis.[2] Pancreatic exocrine function can influence the composition of the gut microbiome, while intestinal dysbiosis can exacerbate the inflammatory response in AP.[3,4] Further investigation of this interplay could lead to new microbiome-targeted therapies for AP.[5]

The aim of the study

This study aims to summarize the current knowledge regarding the role of intestinal microbiota dysbiosis in the pathogenesis and progression of acute pancreatitis.

Materials and methods

This review is based on materials collected from the PubMed database. We conducted a search using the following keywords: "acute pancreatitis," "microbiome," and "dysbiosis," focusing on articles published between 2018 and 2024.

State of knowledge

Acute pancreatitis

Acute pancreatitis is an inflammatory reaction in which proteolytic enzymes such as trypsinogen are prematurely activated, which leads to auto-digestion of the gland, edema, vascular damage, haemorrhage, and necrosis.[6] Local inflammatory response involves cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β), that acting pro-inflammatorily initiate systemic inflammatory response syndrome (SIRS). After early phase of AP there is a second phase, during which it comes to anti-inflammatory response and risk of infection is increased. According to that, there are two peaks of mortality in AP - during early phase as a result of organ failure and in the second phase because of infectious complications.[7,8]

About 80% of AP cases develops due to alcohol abuse or obstruction of the common bile duct by stones. The exact mechanism underlying pathogenesis of AP is still not fully understood.[7] Studies described an occurrence of bacterial migration from gallbladder to pancreatic tissue through lymphatic system.[9]

Another possible explanation for relationship between acute pancreatitis and gallstone is that an obstruction of bile duct or pancreatic duct caused by gallstone leads to duct pressure increase and following enzymes activation.[6]

Other known causes of pancreatitis are pancreas divisum, endoscopic retrograde cholangiopancreatography, hypercalcaemia. In recent years an incidence of hypertriglyceridemia among acute pancreatitis etiological factor increases.[6,10]

The most frequently used to assess patients with acute pancreatitis is the Atlanta Classification, which distinguishes three degrees of disease severity: mild, moderate or

severe.[11] Atlatnta Classification establishes two morphological types of AP: interstitial oedematous pancreatitis which is the most common and necrotising pancreatitis, which accounts for 5% to 10% of cases.[12] Clinical outcomes of most cases of AP are mild and self-limiting, however, about 15-20% of patients may develop moderate or severe acute pancreatitis with their complications such as severe systemic inflammatory response syndrome (SIRS) and sepsis that require hospitalization in intensive care units. The severity of these complications is reflected in the mortality rate reaching 30%.[10,13] Infection of pancreatic necrosis occurs in about 20-40% of patients with severe acute pancreatitis and increases the risk of organ failure. Studies pointed out that infected necrosis concomitate organ failure is associated with mortality rate reaching over 35% in comparison to 19,8% for sterile necrosis with organ failure.[11]

Gut microbiome

Human intestinal tract contains more than 1500 species of bacteria and more bacterial cells than human body cells, which are beneficial as well as harmful or conditionally pathogenic bacteria. Stability between them is the basis for maintaining body homeostasis. [4] Composition of gut microflora is determined by many factors, such as age, diet, antibiotic use. Disturbances in the composition of microbiome may be reversible or permanent. Significant dysbiosis predisposes to the development of diseases, including digestive system diseases, obesity, diabetes, cardiovascular diseases or carcinoma.[15,16] Under normal conditions the most common phylum in human digestive tract are Firmicutes and Bacteroidetes. They constitute more than 80% of intestinal flora.[17] Gut microbiome plays an important role in maintaining epithelial barrier integrity. It participates in immunological reactions and metabolism.[2,5] Commensal bacteria transform many components coming from diet. Products of bacterial metabolism include bile acids, lactic acid, short-chain fatty acids. [2] Some beneficial bacteria can produce bacteriocins which are antibacterial molecules protecting host from pathogenic species. [18] Healthy pancreas harbors its own microbiome as well with a bacteria composition similar to those in duodenum with a predominance of Acidaminococcus, Escherichia, Bacteroides, and Shigella species. It is assumed that bacteria migrate to pancreatic tissue from the intestine through peripheral blood.[10] The pancreas remains in constant communication with intestinal tract due to pancreatic ducts.[14] Moreover, digestive enzymes and antibacterial substances secreted by pancreas to intestinal lumen can affect alteration of gut microbiome.[10] Abnormal pancreatic secretion which occurs in AP provokes imbalance of gut microflora. Strong

relationship between pancreatic exocrine function and gut microbiome is proved by a fact that considerably reduced diversity of microbiome and higher number of pathogenic bacteria has been observed among patients with chronic pancreatitis.[3] According to the described interactions between the pancreas and the intestinal microbiome, scientists suggest introducing the concept of "gut–pancreas axis".[8]

Scientists which induced an experimental pancreatitis in mice models observed that AP caused relevant differences in their microflora composition with predominance of facultative pathogenic bacteria, such as Escherichia/Shigella, Enterobacteriaceae diversa, Enterococcus or Staphylococcus. The most significant changes were observed in duodenal aspirates.[19]

In patients with AP increase of aerobic bacteria including Escherichia coli, Enterococcus, Enterobacter and Streptococcus and decrease of anaerobic such as Bifidobacterium, Bacteroidetes and Prevotella has been observed.[14]

Bacterial translocation in acute pancreatitis

Impaired homeostasis of intestinal microflora in AP can result in intestinal bacterial translocation. Microorganisms and their products enter the circulation or other organs. This phenomenon may be related to/ influences significantly patient clinical picture.[20] Bacterial translocation is closely correlated to infected necrotizing acute pancreatitis (NAP) and Multiple Organ Dysfunction Syndrome (MODS), which are characterized by high mortality rate. Infected pancreatic necrosis is charged by mortality rate of 20 to 50%.[21] Some studies suggest that infected pancreatic necrosis (IPN) is a risk factor for organ failure as well as severe acute pancreatitis. Patients with both IPN and organ failure had twice as high risk of death comparing to patients with only one of these complications.[22] Among mechanisms responsible for dysfunction of epithelial barrier integrity scientists mention microcirculation disorder, motility changes or abnormal immune response.[16] It is assumed that hypovolaemia and systemic inflammation lead to bacterial translocation as well.[23]

Authors of an experimental study investigated the role of regulatory T-cells in acute pancreatitis. Firstly, they observed increased number of Treg following AP induction. It is known that regulatory T-cells are responsible for anti-inflammatory reaction. During AP suppressive response mediated by T-cells may predispose to infectious complications. This study revealed that regulatory T-cells disrupt the protective functions of the intestinal barrier

through systemic immunosuppression. Impaired intestinal mucosal barrier enables bacterial translocation and pancreatic necrosis infection.[19]

Meta-analysis published in British Journal of Surgery showed that about 20% of patients with acute pancreatitis had dysfunction of gut barrier. However, authors did not find significant correlation between impaired epithelial barrier integrity and severity of the disease. This may lead to conclusion that gut barrier disfunction is a comorbid disorder rather than a risk factor of a severe onset of AP, but this occurrence needs further investigation.[24]

Intestinal dysbiosis in AP may be increased as the disease progresses. It has been documented that gut microflora composition differs according to acute pancreatitis severity. Researchers have named strains that may differentiate mild or moderate acute pancreatitis from severe pancreatitis. Acinetobacter, Stenotrophomonas and Geobacillus are increased whereas Bacteroides, Alloprevotella, Blautia and Gemella are decreased in microflora of SAP patients comparing to MAP.[5] Studies have shown reduced diversity of gut microbiome among patients with the severe outcome of AP, such as necrotizing AP. In prospective observational study faecal samples examinations revealed higher abundance of E. faecalis, Clostridium sporogenes and Klebsiella pneumoniae in patients with necrotizing AP in comparison to non-necrotizing AP. Further, some of those abnormalities in intestinal microflora were positively correlated to score in SOFA scale. These findings may implement predictive factor of severe AP.[1] Another study confirmed higher prevalence of severe AP complications among patients with altered gut flora composition.[25] Study in which researchers examined samples of rectal swabs of 450 patients with AP to investigate composition of gut microbiome revealed association between intestinal dysbiosis and course of acute pancreatitis including length of hospital stay, score in Atlanta Classification, morbidity. Finally, researchers identified 16 intestinal species, which could potentially differentiate severe- and non-severe acute pancreatitis. They found out that all of these species belong to families of short-chain fatty-acid bacteria. Although SCFAs are considered to have beneficial effect on human health, it has been proven that they play role in pathogenesis of some disorders too.[23]

Researchers have investigated differences in gut microbiome composition according to acute pancreatitis etiology. Thus, patients with chronic pancreatitis caused by alcohol had increased level of Proteobacteria and reduced level of Bacteroidetes, whereas patients with acute alcoholic pancreatitis presented increased Actinobacteria level and reduced Bacteroidetes level. Likewise, patients with HTGP had some differences in gut microbiome composition with

higher abundance of Escherichia-Shigella and decreased abundance of commensal bacteria including Bacteroides.[10]

On the other hand, there are also bacteria that can act protectively against inflammatory reaction in AP. Bifidobacterium spp. Are considered to alleviate AP. It has been proven in mice models that colonization of B. animalis resulted in milder course of AP, as well as exogenic supply of B. animalis metabolite lactate, that seem to have a crucial role in regulating local inflammation. Moreover, study has shown that patients with severe AP had decreased level of Bifidobacteria in faecal samples.[13]

Role of gut microbiome in diagnostics

The possibility of using knowledge about the relationship between the microbiome and pancreatitis in the diagnostic and therapeutic process is still a matter of debate. The observed differences in the microbiome between healthy people and patients with acute pancreatitis enable distinguishing new diagnostic markers. Zou et al. made research in order to find a predictive marker for acute necrotizing pancreatitis. They examined stool samples and rectal swabs of 20 healthy controls and 58 AP patients. Study pointed out that Finegoldia magna had the strongest correlation with APACHE II score. Enterococcus faecium was one of the most abundant species among patients with acute necrotizing pancreatitis and seem to be a promising biomarker distinguishing NP and non-NP.[3] Another research revealed differences in dominant species of gut microbiome according to AP severity. In patients with mild AP Bacteroides occurred in significant number, in moderate AP – Escherichia-Shigella, whereas in severe form of AP Enterococcus was predominant.[8] Intestinal dysbiosis and overgrowth of pathogenic bacteria transfers into elevated levels of inflammatory markers, such as IL-6, TNF-alfa, which may be responsible for AP aggraviation.[26] Moreover, it has been proven that elevated IL-6 serum level is associated with Enterobacteriaceae and Enterococcus and negatively correlated with Bifidobacterium.[25]

Potential treatment

Early oral feeding

In recent years, the approach to nutrition in acute pancreatitis has changed. Nowadays nutrition seems to be a crucial factor in managing and preventing many diseases. Latest research points out beneficial effect of early oral and enteral feeding in AP. Enteral feeding is a preferred method over parenteral nutrition because of lower number of complications and shortened length of stay at the hospital. [25] Time of introducing oral feeding in AP has been largely debated. Currently it is recommended to begin oral nutrition within 24 hours since admission to hospital in cases of mild AP. Studies demonstrated that following this time frame resulted in decreasing of AP complications, need of surgical intervention and mortality.[27] It has been pointed out that full solid diet shortened time of hospitalization among patients with mild AP in comparison to liquid diet.[28] Protective effect of enteral nutrition may come from specific substances such as glutamine, arginine, and n-3 fatty acids, that regulate gut microbiome.[10] Moreover, EN has a beneficial effect of intestinal barrier, thereby it may prevent bacterial translocation.[24]

Probiotics

Use of probiotics during AP is still a matter of debate. Several potential beneficial results of probiotics have been described. Firstly, lactobacilli and bifidobacteria seem to have antibacterial properties which help hosts defense mechanisms in eliminating pathogenic microorganisms.[29] Secondly, stimulating production of mucosa by some strains of bacteria strengthen gut barrier. Furthermore, probiotics are considered to regulate immune response for example by participating in cytokine production. Probiotics recommended in AP are Lactobacillus acidophilus, Lactobacillus bulgaricus and Bifidobacterium.[14] Study which investigated the effect of probiotics containing lactobacilli use in patients with severe acute pancreatitis receiving nasojejunal feeding showed that enteral nutrition with synbiotics resulted in lower number of multiorgan failure and septic complications.[30] On the other hand, use of probiotics may be controversial due to adverse effects such as antibiotic resistance, hypersensitivity reactions, probiotic-induced infections, and sepsis.[10] Role of probiotics in acute pancreatitis treatment needs further investigation. Despite positive effects, some potential risks must be considered and monitored.

Antibiotics

Currently, routine and preventive antibiotic therapy is not recommended in acute pancreatitis.[11] It is commonly known that unjustifiable antibiotic treatment, especially the overuse of broad-spectrum antibiotics is associated with the development of multidrug-resistant strains. [10] The use of antibiotics in the treatment of acute pancreatitis is approved in patients with infected necrosis or necrotizing pancreatitis. [15] In those cases, antibiotics with ability to penetrate pancreatic necrosis are used. It is recommended to choose antibiotics with activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria.[11]

FMT

Another potential microbiome targeting treatment is faecal microbial transplantation, which is based on implantation of healthy donors faecium into the recipient intestine. It is a proven therapeutic strategy in some gastrointestinal diseases, such as Clostridoides difficile infection.[31] However, its use in acute pancreatitis is controversial. According to study conducted on mice, FMT resulted in bacterial translocation and higher mortality.[32] Nevertheless, the research is inconclusive. Another study evidenced that FMT ameliorated intestinal dysbiosis and reduced inflammation through increasing serum NMN levels and pancreatic NAD+ expression.[4]

Conclusions

Gut microbiota plays a significant role in the etiology of acute pancreatitis (AP). Dysbiosis is associated with the severity and complications of AP, potentially contributing to the development of severe AP complications. Bacterial translocation exacerbates the disease course and is a known risk factor for organ failure. The composition of the microbiome correlates with both the etiology and severity of AP. Bacteria and their metabolites detected in stool samples show promise as biomarkers for AP. A deeper understanding of these relationships could lead to innovations in the diagnosis and treatment of acute pancreatitis. Given the observed differences in microbiota composition based on disease severity, bacteria and their metabolites identified in stool samples or rectal swabs could become promising markers for AP. Our review also discusses therapeutic strategies targeting the microbiome, such as probiotics, antibiotics, or fecal microbiota transplantation (FMT). However, further studies are needed to establish a stronger scientific foundation for targeted therapies in AP.

Declarations

Funding:

This Research received no external funding.

Author contributions:

All authors contributed to the article. Conceptualization: Nadia Miga-Orczykowska; methodology: Nadia Miga-Orczykowska, Ilona Sajkiewicz, software: Paulina Lemieszek, Justyna Wójtowicz, Ilona Jasiuk; check: Klaudia Kister; formal analysis: Katarzyna Rudnicka, Ewa Łukaszewska; investigation: Nadia Miga-Orczykowska, Paulina Lemieszek; resources: Katarzyna Krukar, Martyna Pustelniak; data curation: Katarzyna Rudnicka ; writing-rough preparation: Nadia Miga-Orczykowska; writing - review and editing: Ilona Sajkiewicz, Ilona Jasiuk

visualization: Paulina Lemieszek.; supervision: Paulina Wójtowicz; project administration: Nadia Miga-Orczykowska

All authors have read and agreed with the published version of the manuscript.

Conflict of Interest Statement:

The authors report no conflict of interest.

Financial Disclosure:

The study did not receive any funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable

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