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Changes In The Intestinal Microbiota In Patients With Chronic Pancreatitis: Systematizing Literature Data

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The purpose of the review. To systematize literature data on changes in the structure of the intestinal microbiota in patients with chronic pancreatitis (CP).
Key findings. The human intestinal microbiota is a dynamically changing system that is constantly undergoing qualitative and quantitative changes, especially in several pathological conditions of the digestive system. At present, the differences in the intestinal microbiota in pancreatic diseases are poorly understood. The severe CP is associated with impaired synthesis of antimicrobial peptides, bicarbonates, and digestive enzymes by the pancreas, which is a risk factor for dysbiotic changes in the intestinal microbiota, consisting in the development of small intestinal bacterial overgrowth (SIBO) and gut dysbiosis. The results of two large meta-analyses show that about a third of CP patients have SIBO. The colonic microbiota in patients with CP is also characterized by dysbiotic disorders, primarily in the reduction of alpha-diversity. Some studies have shown that these patients have an increase in *Firmicutes*, while *Bacteroides* and *Faecalibacterium* are reduced. In addition, as a rule, in patients with CP, the growth of *Escherichia*, *Shigella* and *Streptococcus* is recorded.
Conclusion. In general, scientific papers have revealed significant heterogeneity in the profiles of the intestinal microbiota in patients with CP. Thus, several questions remain open, prioritizing the further study of the intestinal microbiota in patients with CP for identifying the specifics of its structure that can personalize the selection of enzyme replacement therapy and restrict the unreasonable prescription of additional pharmacotherapy (the use of proton pump inhibitors and / or antibacterial drugs).
Keywords: chronic pancreatitis, exocrine pancreatic insufficiency, intestinal microbiota, microbiome, bacterial overgrowth syndrome, 16S rRNA gene sequencing, whole genome sequencing
Conflict of interest: the authors declare no conflict of interest.

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Изменения кишечной микробиоты у пациентов с хроническим панкреатитом: систематизация литературных данных

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Цель исследования: систематизировать литературные данные об изменениях структуры кишечной микробиоты у пациентов с хроническим панкреатитом (ХП).
Основные положения. Микробиота кишечника человека является динамически изменяющейся системой, которая постоянно претерпевает качественные и количественные изменения, в особенности при ряде патологических состояний органов пищеварения. В настоящее время различия профилей кишечной микробиоты при заболеваниях поджелудочной железы, в частности при ХП, малоизучены. Прогрессирующее течение ХП, ассоциированное с экзокринной недостаточностью поджелудочной железы, приводит к нарушению синтеза антимикробных пептидов, бикарбонатов и пищеварительных ферментов поджелудочной железой, что является фактором риска изменений кишечной микробиоты, заключающихся в формировании синдрома избыточного бактериального роста в тонкой кишке (СИБР) и нарушении микробиоценоза толстой кишки. Результаты двух крупных метаанализов демонстрируют, что около трети пациентов с ХП имеют СИБР. Толстокишечная микробиота у пациентов с ХП также характеризуется нарушениями, заключающимися в первую очередь в снижении альфа-разнообразия. В некоторых исследованиях было показано, что на уровне типов у пациентов отмечается увеличение количества *Firmicutes*, тогда как *Bacteroides* и *Faecalibacterium* снижены. Помимо этого, как правило, у пациентов с ХП регистрируется рост *Esherichia*, *Shigella* и *Streptococcus*.

Заключение. В целом кишечная микробиота у пациентов с ХП характеризуются значительной неоднородностью профилей. Остается открытым ряд вопросов, что делает приоритетным необходимость дальнейшего глубокого изучения кишечной микробиоты у пациентов с ХП. Выявление специфики ее структуры и состава может быть ключевым фактором для персонифицированного подбора заместительной ферментной терапии и отказа от необоснованного назначения дополнительной фармакотерапии, в частности, ингибиторов протонной помпы и/или антибактериальных препаратов
Ключевые слова: хронический панкреатит, экзокринная недостаточность поджелудочной железы, кишечная микробиота, микробиом, синдром избыточного бактериального роста, секвенирование гена 16S рРНК, полногеномное секвенирование.
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Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas in persons with genetic, environmental and/or other risk factors [1, 2]. Continuous and progressive inflammation involves all structures of the pancreas: acini, insular apparatus, ductal system, blood vessels, nervous apparatus, and interstitial tissue [3–5]. According to one of the latest meta-analyses, the overall incidence of CP is 9.62 cases (95 % confidence interval (CI): 7.86–12.00) per 100,000 population per year [6]. The median prevalence of CP, according to various data, varies from 40 to 50 cases per 100,000 population per year [7, 8]. In a long-term model, CP progressively leads to the formation of exocrine and endocrine pancreatic insufficiency, increasing the risk of complications of this disease, as well as significantly reducing the quality of life of patients [9–11].

Exocrine pancreatic insufficiency (EPI) is the most common complication of CP in the adult patient population [9, 12]. This pathological condition is defined as insufficient secretion of pancreatic enzymes (acinar cell function) and/or sodium bicarbonate (ductal function) [9, 10]. Clinically significant EPI in CP develops with a decrease in the production of about 90 % of pancreatic enzymes and is observed in 60–90 % of patients with CP within 10–12 years from the time of diagnosis [13]. Digestive enzyme deficiency in EPI mediates the development of maldigestion and nutrient malabsorption syndromes, inducing clinical symptoms such as steatorrhea, abdominal discomfort, flatulence, and unmotivated weight loss [9, 14, 15]. In patients with chronic pancreatitis and associated EPI, there are disorders of the absorption of alimentary fats and fat-soluble compounds (vitamins A, D, E and K), an increased risk of developing osteoporosis, sarcopenia and complications associated with these pathological conditions [16–21]. In addition, impaired synthesis of antibacterial peptides, bicarbonates, and digestive enzymes by the pancreas in patients with EPI can lead to negative changes in the intestinal microbiota (Fig. 1) [22–24].

The intestinal microbiota is a highly organized system that responds with qualitative and quantitative shifts to various conditions of the macroorganism, has an extremely high metabolic potential and plays a significant role in the development of the pathology of the digestive system [25, 26]. In eubiosis, the intestinal microbiota plays an important role in the mechanisms of immune homeostasis of the gastrointestinal mucosa, colonization resistance, nutrient metabolism, and the

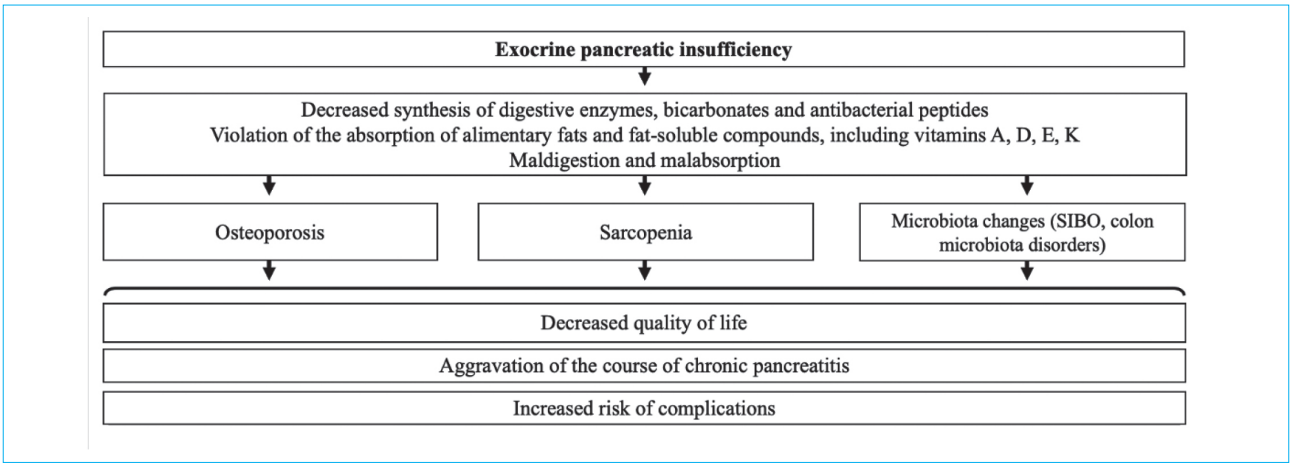

Fig. 1. Complications of EPI in CP patients

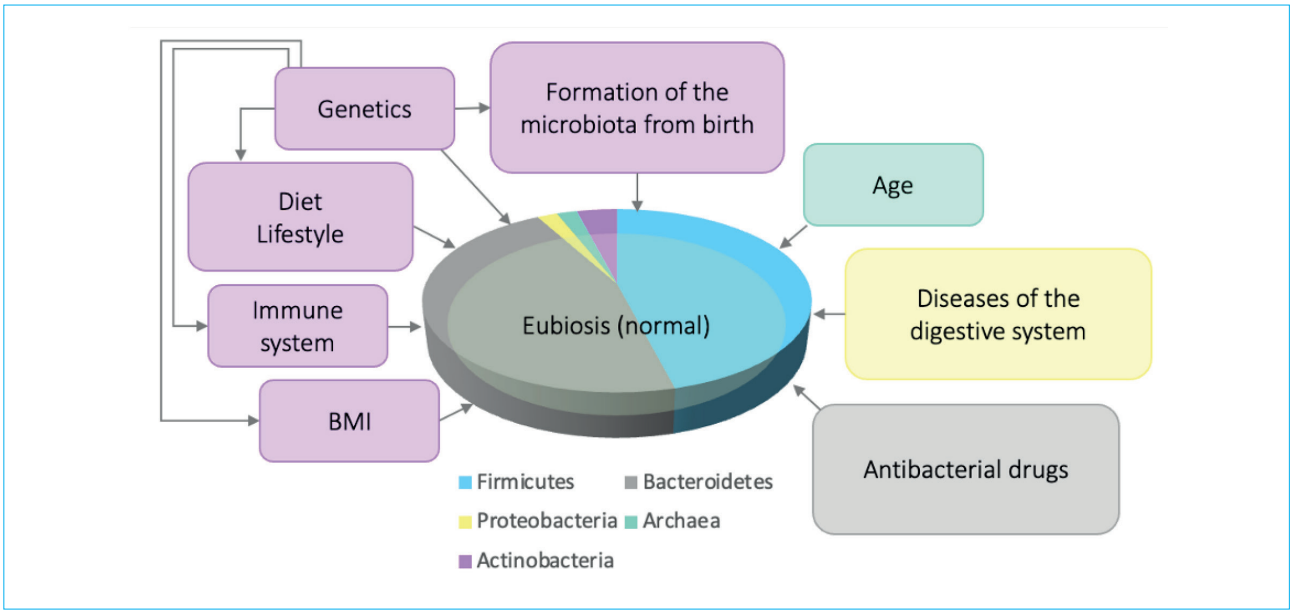

Fig. 2. Factors that modulate the gut microbiota

production of a few vitamins [26–28]. In healthy people, the intestinal microbiome is characterized by high species diversity, and *Firmicutes* and *Bacteroidetes* prevail in the general pool of microorganisms (up to 85–90 %) [29]. At the same time, a whole range of factors capable of modulating the composition of the intestinal microbiota is known to date, among which the role of pathological conditions of the digestive organs is being actively studied (Fig. 2) [24, 30, 31].

The progressive course of CP associated with EPI leads to disruption of the synthesis of antimicrobial peptides, bicarbonates, and digestive enzymes by the pancreas, which is a risk factor for dysbiotic changes in the intestinal microbiota, consisting in the formation of small intestinal bacterial overgrowth syndrome (SIBO) and colon dysbiosis [22–24, 32, 33]. Such disorders can provoke the development of an inflammatory process in the pancreas itself, be inducers of the formation of persistent clinical symptoms, and initiate the development of comorbid pathology [23, 33, 34]. Currently, the basis for the treatment of EPI is enzyme replacement therapy (ERT), the effectiveness of which is assessed by an increase in the fat absorption ratio and leveling of the malabsorption syndrome in patients with CP [35–37]. Some authors suggest that the correction of EPI during the use of PRT also contributes to positive changes in the qualitative and quantitative composition of the intestinal microbiome and the maintenance of eubiosis, which is confirmed in experimental works [23, 38].

Small bacterial overgrowth syndrome in patients with chronic pancreatitis

SIBO is a clinical syndrome characterized by a significant increase in the number of bacteria in the small intestine and is manifested by bloating, flatulence, nausea, abdominal pain, and diarrhea [39, 40]. Culturing of the bacteria of aspirate of the small intestine is considered the most accurate diagnostic method for verifying SIBO, which makes it possible to determine the composition of dominant bacteria and their sensitivity to antibiotics; however, this technique is not currently used in routine clinical practice due to a few limiting reasons (labor intensity and invasiveness) [40, 41]. According to the latest recommendations of the American College of Gastroenterology (ACG), the basis for diagnosing SIBO is hydrogen breath tests (HBT) using glucose or lactulose, and treatment should include antibiotic therapy using nonabsorbable or systemic antibiotics [39].

According to epidemiological data, the frequency of SIBO in patients with CP is significantly higher than in healthy individuals [42–44]. In a meta-analysis by G. Capurso et al. (2016), who summarized the results of nine studies, the prevalence of SIBO in patients with CP ranged from 14 % to 92 % (mean, 36 %; 95 % CI: 17–60). Six studies using glucose HBT showed a pooled prevalence of 21.7 % (95 % CI: 12.7–34.5), while three studies with lactulose HBT showed a cumulative prevalence of 73.3 % (95 % CI: 67.4–90.6). The risk of SIBO in patients with CP was significantly higher than in the control group (OR 4.1; 95 % CI: 1.6–10.4) [43]. In 2019 B.E. Kurdi et al. published an updated meta-analysis on the combination of SIBO and CP included 13 studies. The main criteria for inclusion in the work were: diagnosed CP, presence of EPI, clinical and laboratory data indicating the presence of SIBO. According to the results of a meta-analysis, the cumulative prevalence of SIBO in patients with CP was 38.6 % (95 % CI: 25.5–53.5) compared with 9.9 % (95 % CI: 4.9–19.0) in the control groups. It was shown that CP is a significant risk factor for SIBO

(OR 5.58; 95 % CI: 2.26–13.75), while the presence of EPI multiplies this risk (OR 2.5; 95 % CI: 1.3–4.8). Regression of clinical manifestations of CP was noted in 76 % of patients after SIBO treatment [44].

Thus, the results of the conducted meta-analyses show that about a third of patients with CP have SIBO. Patients with CP should be screened for SIBO, regardless of symptoms and response to ERT, to avoid inappropriate prescribing of microbiota-correcting drugs, particularly antibiotics, in the absence of bacterial overgrowth, and essentially pointless dose escalation of enzyme preparations when present [40, 45]. Priority in the treatment of SIBO should be given to antibacterial drugs designed to eliminate an excess amount of bacteria. Undoubtedly, the choice of antibiotic should depend on the severity of SIBO, the identified abnormalities in the intestinal microbiota, and the sensitivity of the dominant bacteria to antibacterial drugs. Successful implementation of this task requires high-precision and high-performance methods for diagnosing SIBO [45].

Colon dysbiosis in patients with chronic pancreatitis

Colon dysbiosis is negative qualitative and quantitative changes in the intestinal microbiome (a decrease in bacterial diversity, a decrease in the absolute number of individual taxa), leading to a violation of immune homeostasis and metabolic activity of the microbiota, as well as a decrease in colonization resistance [30, 31, 46]. Currently, the most promising methods for assessing changes in the composition of the intestinal microbiota and its functional potential are genetic methods – sequencing of the highly specific 16S rRNA gene and whole genome sequencing [47–50]. Sequencing of the bacterial 16S rRNA gene is the most common method for analyzing bacterial species diversity. Some regions of the gene are highly conserved, which makes it possible to select universal primers, while other regions are characterized by variability, which makes it possible to identify diverse taxonomic units. Sequencing uses PCR to amplify portions of the hypervariable regions (V1–V9) of the bacterial 16S rRNA gene. The study makes it possible to compare the microbiota of healthy individuals and patients with various diseases, to evaluate the dynamics of changes in the composition during treatment [48, 49, 51]. A more accurate answer, especially for previously unexplored types, is given by whole genome sequencing (WGS) or shotgun sequencing. WGS reads fragments of total DNA isolated from a sample. The study makes it possible to learn not only data on the complete composition of the community, having a higher accuracy of species identification than 16S rRNA, but also to carry out functional profiling of the metagenome – to obtain quantitative information on the relative representation of individual genes and their groups, on the diversity of metabolic pathways, to evaluate the variation of gene sequences between species and communities [48, 50, 52].

The results obtained in the study of the intestinal microbiota of the colon, both among the healthy population and among individuals with various diseases of the gastrointestinal tract, in particular in patients with CP, provide convincing data on the difference in the profiles of the intestinal microbiota, which indicates its potential participation in the pathological cascade, exacerbations, as well as resistance to therapeutic measures [30, 33, 51, 52]. Over the past 5 years, several studies have been published in which high-throughput sequencing methods have studied changes in the intestinal microbiome in patients with CP, including those with EPI (Table) [54–59].

S.M. Jandhyala et al. (2017) analyzed the taxonomic and functional changes in the intestinal microbiota of 40 individuals, which were divided into groups: 1) 14 CP patients with pancreatogenic diabetes mellitus (PDM); 2) 16 patients with CP without PDM; 3) 10 healthy individuals who were closely related to the patients of the first two groups, which, in particular, made it possible to exclude the hereditary risk factor for the development of CP and control other factors (nutrition and environment). Analysis of the taxonomic profile of the intestinal microbiota was obtained by sequencing the 16S rRNA gene from stool samples. According to the study, the key finding was the detection of a decrease in the number of *Faecalibacterium prausnitzii* in patients with CP without PDM compared with healthy individuals, and this decrease was more prominent in patients with CP and PDM. *Faecalibacterium prausnitzii* is one of the most abundant bacterial communities in the colon and has a number of positive properties. Being a butyrate producer, *Faecalibacterium prausnitzii* provides colonocytes with nutrients; increases mitochondrial activity, providing energy; has anti-inflammatory properties, inducing the production of IL-10 and regulating the T-cell response in the intestine. Also, *Faecalibacterium prausnitzii*, by stimulating the synthesis of mucin, increases the intestinal barrier function. Another finding of this study was a decrease in the number of *Ruminococcus bromii* in both CP patients with DM and without DM. It is known that the amylolytic bacteria *Ruminococcus bromii* have the ability to degrade starch resistant to digestion. It is not difficult to assume that the depletion of such bacterial representatives as *Faecalibacterium prausnitzii* and *Ruminococcus bromii* contributes to the disruption of the barrier function of the colon mucosa [54].

In a prospective study by D. Ciocan et al. (2018) compared the profiles of the intestinal microbiota of patients with chronic alcoholic pancreatitis (CAP) (n = 24), alcohol dependence with alcoholic hepatitis (AH) (n = 13) and patients with alcohol dependence (AD) without CAP and AH (n = 45). The composition of the gut microbiota was analyzed by sequencing targeting the V3-V4 regions of the 16S rRNA. Patients with CAP were characterized by lower alpha-diversity compared to AD. At the phylum level, it was found that in patients with CAP, in comparison with the AD

Table. Overview of studies on the intestinal microbiota in patients with CP [54–59]

Author, year	Study Type	Study group, *n*	Control group, *n*	Analysis material, method	Main result, at the phylum level	Main result, at the level of genera and species
S.M. Jandhyala, 2017	Observational	*n* = 14, CP + PDM; *n* = 16, CP without PDM	*n* = 10, healthy controls (patients' family members)	Fecal sample, 16S rRNA sequencing (V3–V4 regions)	Increased *Firmicutes* and *Actinobacteria*; reduced *Bacteroides*	Decreased *Ruminococcus bromii*, *Faecalibacterium prausnitzii*
D. Ciocan, 2018	Observational	*n* = 24, chronic alcoholic pancreatitis (CAP); *n* = 13, alcoholic hepatitis (AH)	*n* = 45, alcohol dependent (AD) patients without AH	Fecal sample, 16S rRNA sequencing (V3–V4 regions)	In the CAP group increased *Proteobacteria*, reduced *Bacteroidetes* and *Fusobacteria*	In the AD group, the most represented *Klebsiella*, *Enterococcus* and *Sphingomonas*; in the AH group increased *Haemophilus*, *Sutterella*, *Campylobacter*, *Lactobacillus*, *Faecalibacterium*, *Prevotella*, *Paraprevotella* and *Fusobacterium*; in the CAP group increased *Serratia*, *Acinetobacter*, *Pseudomonas* and *Enterococcus*
S. Hamada, 2018	Observational	*n* = 8, chronic pancreatitis (CP)	*n* = 12, autoimmune pancreatitis (AIP)	Fecal sample, 16S rRNA sequencing (V4–V5 regions)	There are no differences between groups	In the CP group enlarged *Bacteroides ovatus*, *Streptococcus australis*, *Streptococcus gordonii*, *Clostridium lavalense*, *Clostridium lactatifermentans*
C.-H. Zhou, 2019	Observational	*n* = 71, chronic pancreatitis (CP): 1) CP with EPI (*n* = 42); 2) CP without EPI (*n* = 28)	*n* = 69, group of healthy controls (HC)	Fecal sample, 16S rRNA sequencing (V4–V5 regions)	In the CP group reduced *Firmicutes* and *Actinobacteria*, *Proteobacteria* most were represented	In the CP group enlarged *Escherichia-Shigella*, *Dialister*, *Parabacteroides*, *Prevotella_7*; significantly reduced *Faecalibacterium*, *Subdoligranulum*, *Prevotella_9*, *Megamonas*, *unclassified_f_Lachnospiraceae*, *unclassified_f_Peptostreptococcaceae*, *Collinsella*, *Erysipelotrichaceae_UCG-003*, *Butyricicoccus* and *Dorea*
F. Frost, 2020	Observational	*n* = 51, chronic pancreatitis (CP)	*n* = 102, nonpancras diseases	Fecal sample, 16S rRNA sequencing (V1 – V2 regions)	In the CP group and the control group, the genus Bacteroides is most represented, with prevalence in the CP group; significantly reduced in the CP group *Faecalibacterium* and *Prevotella*	In the CP group, Escherichia were increased (significantly), *Streptococcus*, *Esherichia*, *Shigella*

group, Proteobacteria dominated. No differences were found between the groups of patients with CAP and AH at the phylum level. It was found that 17 genera differ in number between CAP and AD groups. In the group of patients with AD, *Klebsiella*, *Enterococcus* and *Sphingomonas* are the most represented. No differences were found at the level of phylum between the groups of patients with CAP and severe AH. The abundance of *Haemophilus*, *Sutterella*, *Campylobacter*, *Lactobacillus*, *Faecalibacterium*, *Prevotella*, *Paraprevotella*, and *Fusobacterium* was higher in patients with severe AH, but the abundance of *Serratia*, *Acinetobacter*, *Pseudomonas*, and *Enterococcus* was higher in patients with CAP. The relative abundance of *Haemophilus* was 100 times higher in patients with severe AH than in patients with CAP. In 85 % of cases, the genus *Haemophilus* is represented by one species: *Haemophilus parainfluenzae*. Differences in the structure of the intestinal microbiota between AD and patients with AH were revealed. Decreased gut microbiota diversity was directly correlated with low levels of antimicrobial peptides and EPI in CP patients [55].

According to the analysis carried out by S. Hamadaet al. (2018), the intestinal microbiota of patients with autoimmune pancreatitis (AIP) (n = 12) and CP of other etiologies (n = 8) showed no differences at the phylum level. Several bacterial species were more prevalent in the gut microbiota of CP patients compared to AIP patients: *Bacteroides ovatus*, *Streptococcus australis*, *Streptococcus gordonii*, *Clostridium lavalense*, *Clostridium lactatifermentans*. Possible reasons for the increase in the proportion of these bacteria may be malabsorption in the small intestine and a decrease in the production of pancreatic enzymes in EPI. Thus, the differences found emphasize that the profiles of the intestinal microbiota can be useful for the differential diagnosis of pancreatic diseases [56].

C.-H. Zhou et al. (2019) conducted a comparative study of the composition of the fecal microbiota of patients with CP (n = 71) and a group of healthy individuals (n = 69). The group of patients with CP was additionally divided into two subgroups: 1) patients with EPI (n = 42); 2) patients without EPI (n = 28). According to the results obtained at the phylum level, the number of *Firmicutes* and *Actinobacteria* was lower in comparison with the control group, and the number of Proteobacteria was higher. In the CP patient group, the following genera of bacteria significantly predominated: *Escherichia-Shigella*, *Dialister*, *Parabacteroides*, *Prevotella_7*, while *Faecalibacterium*, *Subdoligranulum*, *Prevotella_9*, *Megamonas*, *unclassified_f_Lachnospiraceae*, *unclassified_f_Peptostreptococcaceae*, *Collinsella*, *Erysipelotrichaceae_UCG-003*, *Butyricicoccus* and *Dorea* were significantly reduced. The dominant genera in the group of patients with CP were *Escherichia-Shigella*, *Prevotella_7*, *Parabacteroides*, *Eubacterium_hallii_group*, and *Sutterella*. E*ubacterium_rectale_group*, *Coprococcus*, *Sutterell*a, and *Eubacterium_ruminantium_group* were identified as the prevalent genera in the CP with EPI group. *Pseudomonas*, *Fusobacterium*, and *Ruminococcus_gnavus_group* dominated the CP group without EPI. Thus, the number of beneficial bacteria is progressively reduced in patients with CP and EPI. This study showed that *Lachnoclostridium* and *Bifidobacterium* positively correlate with the presence of EPI, being directly involved in the development and maintenance of dysbiosis [57].

F. Frost et al. (2019) conducted a large population-based study to assess the impact of pancreatic exocrine function on the composition and diversity of the gut microbiota. The taxonomic composition was obtained by sequencing the 16S rRNA gene from fecal samples of 1795 volunteers who did not have a history of pancreatic diseases. Patients with EPI that was established by fecal elastase-1 and secretin-stimulated secretion of the pancreas tests formed an experimental group (n = 171). A marked decrease in *Bacteroides* and an increase in *Prevotella* was observed in the EPI group compared to the control group. The results obtained indicate that changes in the level of pancreatic elastase-1 are more associated with the variability in the composition and structure of the intestinal microbiota than with the biological, anthropometric, and clinical characteristics of the subjects. Thus, the state of pancreatic acinar cells can be considered as the most significant factor associated with changes in the composition of the intestinal microbiota in these patients [58].

In 2020 F. Frost et al. in an observational study proved that the intestinal microbiota in patients with CP is characterized by a significant predominance of opportunistic bacteria and dysbiosis. For the study, two groups were formed prospectively: 1) patients with CP (n = 51); 2) a group of patients with non-pancreatogenic diseases (n = 102). Etiological factors in the development of CP: alcohol (n = 35), mutation SPINK 1 (serine protease inhibitor Kazal type-1) (n = 3), and idiopathic CP (n = 13). For taxonomic analysis of the microbial community, a stool sample was taken from each of the subjects. DNA was extracted from each sample and the composition of the gut microbiota was determined by bacterial 16S rRNA sequencing. According to the results of the study, *Bacteroides* was the most represented genus, both in cases with CP and in the control group; however their larger number was in the group of people with CP (27.3 % vs. 16.7 %). In the CP group, the largest reduction was in *Faecalibacterium* (3.8 % vs. 6.8 %) and *Prevotella* (7.0 % vs. 11.7 %). A positive correlation between age and the number of facultative pathogens was found in patients with CP. Other factors (gender, BMI, smoking, PDM, stool pancreatic elastase level) did not show a significant correlation with the number of facultative pathogenic bacteria. In addition, a pronounced increase in the opportunistic bacteria *Enterococcus* was found in patients with CP in comparison with the control group. It is known that the growth of *Enterococcus* can provoke the risk of developing systemic infections.

Other findings were the detection *Streptococcus*, *Esherichia*, *Shigella* in infected tissues of pancreatic cysts and necrotic tissues of the pancreas. Thus, the researchers made the following conclusions: CP correlates with a high degree of intestinal dysbiosis, which does not depend on the severity of EPI; the abundance of producers of short-chain fatty acids and lactate is reduced in CP; the number of opportunistic pathogens, in particular *Enterococcus*, is significantly increased in patients with CP [59].

Conclusion

Analysis of the studies presented in this review demonstrates a significant heterogeneity of the results both at the level of phyla and at the level of genera. The intestinal microbiota of patients with CP, in comparison with control groups represented by healthy individuals or patients with other diseases, has its own special structure and taxonomic composition. Attention is drawn to the fact of lower alpha-diversity in patients with CP, in particular in the presence of EPI. Some authors suggest that the decrease in the level of antimicrobial peptides in EPI is a predictor of the low diversity of the intestinal microbiota in patients with CP. In general, there is an increase in the number of potential pathogens with a simultaneous depletion of potentially protective taxa in patients with CP. It is likely that the detected changes in the intestinal microbiota in patients with CP may contribute to the progression of CP, the development of its complications and reducing the therapeutic response.

The heterogeneity of results in published papers raises a number of questions:

- Are disorders of the intestinal microbiota a cause or consequence of CP?
- To what extent does the ERT regimen affect the structure of the intestinal microbiota?
- Is it possible to normalize the structure of the intestinal microbiota in EPI with an individual selection of the ERT regimen?

It seems extremely relevant to further comprehensive study of qualitative and quantitative changes in the intestinal microbiota in patients with CP, which will update the concept of the pathogenesis of the disease and improve the tactics of diagnosis, prognosis and treatment of these patients in the future.

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