

Metabolic Trifecta After Pancreatitis: Exocrine Pancreatic Dysfunction, Altered Gut Microbiota, and New-Onset Diabetes

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Abstract: Pancreatitis, a complex disease influenced by both genetic and environmental factors, often leads to metabolic sequelae (such as exocrine pancreatic dysfunction and new-onset diabetes). Several trillion micro-organisms inhabit the gastrointestinal tract, and this community plays an important role in the regulation of functions of not only the gut but also the pancreas. Studies to parse the underlying contributions of the gut microbiota to metabolic sequelae of pancreatitis will offer important translational insights with a view to preventing exocrine pancreatic dysfunction and new-onset diabetes after pancreatitis.

Clinical and Translational Gastroenterology ;10:e00086. <https://doi.org/10.14309/ctg.0000000000000086>

The human gut harbors arguably the highest density of micro-organisms on the planet. For example, it has been estimated that the colon of an average man has the same bacterial and archaeal density as the oceans and forest soils combined (1). The rich microbiota taking up residence in the human body has been actively investigated since 2007, in particular thanks to more than US\$1 billion funding by the National Institutes of Health to the Human Microbiome Project (2). The first phase of the project focused on cataloging species names that are part of “healthy” microbiota and characterizing ecological states of various niches, including the gut. The second phase aimed to explore the dynamics of host-microbiota interactions under specific disorders, including new-onset diabetes. It has become evident that one of the cardinal features of the human microbiota is its mutability, especially during development and in response to disorder. This is epitomized in the relationship between the gut microbiota and the exocrine function of the pancreas. At birth, the gastrointestinal tract of the infant is sterile, and the pancreatic juice contains virtually no amylase and lipase (hence, frequent occurrence of steatorrhea in infants). The formation of the microbiota is highly complex and not completely understood, but newborns definitely receive most of the early colonizers of the gut from their mothers. The oligosaccharides and fats in breast milk that infants cannot digest contribute to shaping the microbial community of the gut (3). By approximately 6 months of life, infants begin to have a gut microbial community that resembles the adult one, and the pancreas starts to secrete amylase and lipase. By approximately 2 years, the adult microbial community is established, and the exocrine pancreas functions adequately.

The relationship between the gut microbiota and the pancreas after pancreatitis is put on the center stage in the current issue of *Clinical and Translational Gastroenterology*. El Kurdi et al. (4) present a pooled analysis of 13 clinical studies of the gut microbiota in patients after pancreatitis. Let me make it clear upfront: the study is far from being perfect. A notoriously elusive and persistently ambiguous entity called “small intestinal bacterial overgrowth” was used to study the gut microbiota. Only 1 of the included studies used the gold standard—small bowel aspiration and quantitative culture. Criteria for diagnosing of pancreatitis varied greatly between the included studies. The designs of the primary studies did not allow for causal inferences. The degree of exocrine pancreatic dysfunction was not severe enough to cause steatorrhea in most patients. Moreover, the perennial questions of which patients after pancreatitis should be tested for small intestinal bacterial overgrowth, how it should be treated, whether any treatment improves gastrointestinal symptoms and response to pancreatic enzyme replacement therapy are all no closer to be answered compellingly now than they were before the publication of this study (5).

However, the study by El Kurdi et al. (4) is a welcome addition to the literature. It demonstrated that altered gut microbiota is 2.5 times more common in pancreatitis patients with exocrine pancreatic dysfunction than in those without it (the associated confidence interval is 1.2–4.8, and *P* value is 0.009). Similarly, altered gut microbiota is 2.5 times more common in pancreatitis patients with diabetes than in those without it (the associated confidence interval is 1.4–4.4, and *P* value is 0.002). Both estimates were

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Received August 8, 2019; accepted August 13, 2019; published online October 11, 2019

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derived from the subgroup analyses of studies that used glucose hydrogen breath test only, which is often considered the hydrogen breath test of choice nowadays. Notably, there was no statistical heterogeneity in the above analyses—a rare treat in meta-analytical studies and the one that strongly suggests that the associations are not spurious (6,7).

The above-mentioned associations are clinically important because metabolic sequelae develop after pancreatitis much more often than previously thought. Although the high frequency of exocrine pancreatic dysfunction and new-onset diabetes after advanced chronic pancreatitis or surgical resection of the pancreas has been known for decades, the large body of evidence that emerged in the past 5 years clearly indicates that both exocrine and endocrine functions of the pancreas are also impaired in a large fraction of patients after acute pancreatitis, and this is not affected materially by severity of acute pancreatitis (8–13). A 2014 meta-analysis by the COSMOS group found that newly diagnosed exocrine pancreatic dysfunction is present in 29% of patients after acute pancreatitis (14). Similar estimate was reported in a 2018 updated meta-analysis by others (15). The first meta-analysis on the topic also showed that the frequency of exocrine pancreatic dysfunction increased to 39% in the subgroup of new-onset diabetes after pancreatitis (14), which suggests that impairments of the exocrine and endocrine functions of the pancreas might be interconnected in many patients. Importantly, pancreatitis often represents a continuum, with 22% of patients with the first episode of acute pancreatitis developing a recurrent episode and 36% of patients with recurrent acute pancreatitis subsequently developing chronic pancreatitis (16). Early identification of pancreatitis patients who are at high risk of developing metabolic sequelae constitutes tertiary prevention of pancreatitis and is one of the cornerstones of the “holistic prevention of pancreatitis” framework (17).

Altered gut microbiota might be a link between exocrine pancreatic dysfunction and new-onset diabetes (Figure 1). A 2019 longitudinal study (as part of the Human Microbiome Project) revealed that the development of new-onset diabetes is accompanied by decreased gut microbiota Shannon diversity

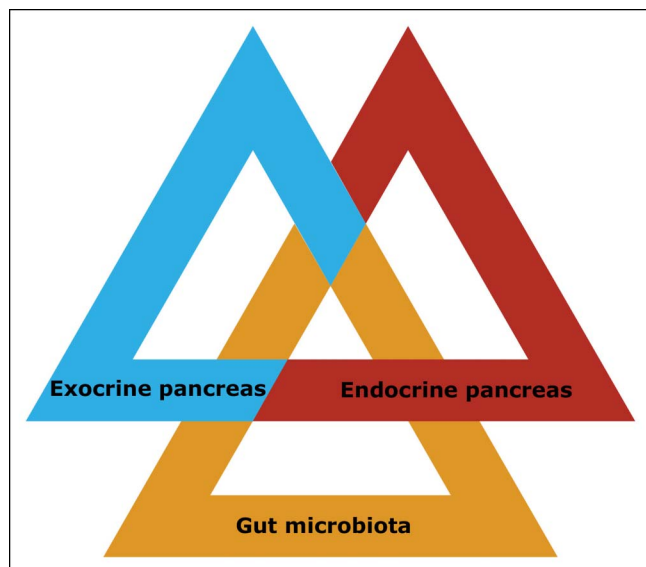


Figure 1. Components of the metabolic trifecta.

with time (18). Specifically, the phylum *Bacteroidetes* proportion was increased at the time point of lowest diversity to the detriment of beneficial bacteria, such as the genus *Faecalibacterium*. A 2019 cross-sectional study of 1795 volunteers (who had no history of diseases of the exocrine pancreas) demonstrated that exocrine pancreatic function (as measured by fecal pancreatic elastase) explains larger parts of variation in gut microbiota composition and diversity than age, sex, body composition, tobacco smoking, alcohol consumption, or diet (19). A 2019 longitudinal study observed a strong correlation between the microbiota composition and luminal pH, particularly in the duodenum (20). Significant positive correlations were found between pH and multiple *Streptococcus* operational taxonomic units, whereas significant negative correlations were found between pH and multiple *Prevotella* and *Pasteurellaceae* operational taxonomic units. Given that exocrine pancreatic dysfunction is often accompanied by the pH in the duodenum that is lower than normal (because of reduced secretion of bicarbonate by the pancreas), it is conceivable that exocrine pancreatic dysfunction may result in altered gut microbiota. Also, chronic inflammation of pancreatitis and immune system activation may promote changes in microbiota by altering the oxidative and metabolic environment of the gut, gut permeability, gut motility, and the gut-brain-pancreas axis (21–24). And, the microbial production of metabolites might affect the host in several ways that are relevant to the pathogenesis of metabolic sequelae of pancreatitis. This includes, but is not limited to, the effect on bile acid signaling through the nuclear farnesoid-activated X receptor and the production of short-chain fatty acids through the fermentation of undigestible carbohydrates (25).

The possibility that metabolic sequelae of pancreatitis might be linked to the gut microbiota opens up new opportunities for precision medicine in this category of patients. Precision medicine relies on the ability to assess disorder risk at an individual level, detect it early, and initiate preventive strategies (26). It becomes increasingly obvious that patients after pancreatitis develop metabolic sequelae through different pathways, and future studies will provide actionable insights into individual underlying mechanisms of new-onset diabetes and exocrine pancreatic dysfunction after pancreatitis. It is worth laying a wager on that.

CONFLICTS OF INTEREST

Guarantor of the article: Maxim S. Petrov, MD, MPH, PhD.

Specific author contributions: Concept and drafting of the manuscript: M.S.P.

Financial support: Rutherford Discovery Fellowship (Royal Society of New Zealand).

Potential competing interests: None.

ACKNOWLEDGEMENT

Associate Professor Max Petrov is the principal investigator of the COSMOS group.

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