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The gastrointestinal tract and cardiovascular diseases - do they have anything in common?

Prebavna cev in srčno-žilne bolezni – ali imajo kaj skupnega?

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Abstract

Human gut microbiota is a collection of bacteria, archaea, fungi, viruses and parasites that inhabit the gastrointestinal tract and produce a diverse ecosystem of about 10^{14} microorganisms. Microbiota diversity is caused by differences in the host genome and by environmental factors such as hygiene, lifestyle, nutrition and various drugs. The results of research over the last decade have confirmed that altered gut microbiota, dysbiosis, contributes to the development of various diseases, including cardiovascular diseases, type 2 diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD), chronic inflammatory bowel disease and even some cancers. In the article, the authors present some recent findings on the diversity of gut microbiota, diagnostic methods and some of the pathophysiological mechanisms that influence the development of cardiovascular diseases.

Izvleček

Človeška črevesna mikrobiota je združba bakterij, arhej, gliv, virusov in parazitov, ki v prebavni cevi tvorijo ekosistem, sestavljen iz približno 10^{14} mikroorganizmov. Raznolikost te združbe je posledica razlik v genomu gostitelja in vplivu okoljskih dejavnikov, med katere sodijo higiena, prehrana, življenjski slog in uporaba različnih zdravil. Rezultati raziskovalnega dela v zadnjem desetletju so potrdili, da spremenjena sestava mikrobiote (disbioza) prispeva k razvoju različnih bolezni, vključno s srčno-žilnimi, sladkorno boleznijo tipa 2, kronično boleznijo ledvic, nealkoholno zamaščenostjo jeter (NASH), kronično vnetno črevesno boleznijo in celo nekaterimi vrstami raka. V prispevku avtorja predstavita nekaj sodobnih spoznanj o raznoliki sestavi človeške črevesne mikrobiote, diagnostičnih postopkih in nekaterih patofizioloških mehanizmih, ki vplivajo na razvoj srčno-žilnih bolezni.

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1 Introduction

In the last decade, understanding the human gut microbiota and its role in var-

ious diseases has advanced significantly (1). The gut microbiota is a collection of bacteria, archaea, fungi, viruses, and parasites in the gastrointestinal tract that produce a diverse ecosystem of about 10^{14} microorganisms. It is crucial for maintaining the homeostatic functions of the gastrointestinal tract, as it participates in the processes of the host's digestion, metabolism and regulation of the intestinal immune system (2). At birth, the gastrointestinal tract of the newborn is not populated with microorganisms, in the following hours it is colonized by the mother's microorganisms, initially coliform bacteria and streptococci, later lactobacilli and enterococci. Of course, this colonization of microorganisms also depends on the method of delivery (vaginal or by caesarean section). In adulthood, most of the gut microbiota is composed of five phyla, namely: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria*, and *Cerrucomicrobia*, in which the relative abundance of *Bacteroidetes* and *Firmicutes phyla* are >90% (3-5). The *Firmicutes/Bacteroidetes* ratio is not the same in all individuals, the differences are due to differences in host genomes, environmental factors such as hygiene, diet, lifestyle and the use of antibiotics (4).

The gut microbiota is much more diverse than researchers have predicted in the past. Modern molecular diagnostic methods, compared to isolation and *in vitro* cultivation, have provided a more detailed insight into the diversity of the microbiota and the intensity of colonization in the gastrointestinal tract. Due to the acidic environment and intense peristalsis (rapid passage of intestinal contents), fewer microorganisms (10^{1}-10^{3}/ml) are present in the stomach and duodenum, most of which are Gram-positive bacteria. Lactobacilli and enterococci are also present in the duodenum, and the number of bacteria in this area is usually 10^{4}/ml (5). The richest in number and diversity of types is the large intestine (10^{12}/ml), which is mostly populated with Gram-negative and anaerobic bacteria.

Gut microbiota homeostasis is crucial for maintaining human health, while dysbiosis contributes to the development of a variety of diseases, including cardiovascular diseases, chronic kidney disease, type 2 diabetes, non-alcoholic fatty liver disease, and even some cancers

Table 1: Summary of the effects of possible forms of cardiovascular disease treatment aiming at changing the composition of the gut microbiota (Adapted from 1).

Treatment / measure	Prebiotics	Probiotics
Definition	Nutritional ingredients that promote a "healthy" (appropriate) composition of the gut microbiota.	Beneficial living microorganisms that can colonize the human gut, establish and/or restore a healthy gut microbiota.
Examples and effects	• plant polyphenols, • fruits and vegetables (e.g., apples): reduce inflammation and total cholesterol levels and promote the growth of bifidobacteria, • dietary fructans, • foods rich in inulin and/or oligofructose, stimulate the growth of bifidobacteria, the restoration of the population of bacteria that form butyrates.	*Lactobaccillus* strains, *L. reuteri* (microencapsulated in yogurt): reduces LDL cholesterol, total cholesterol, and non-HDL cholesterol. *L. plantarum* (capsules): reduce total cholesterol.

(1,6,7). Some effects of possible forms of cardiovascular disease treatment that aim at changing the composition of the gut microbiota are shown in Table 1. Gut dysbiosis is a change in the composition of the gut microbiota that can result from exposure to various factors such as diet, increased stress levels, local and systemic inflammation, and the use of antibiotics. Gut dysbiosis may explain why some individuals are more prone to developing certain diseases. The change in the composition of the microbiota has recently been identified as an important factor contributing to the development of atherosclerosis and hypertension, which are the two main risk factors for the development of cardiovascular diseases (1,7,8). In recent years, the influence of microbiota composition on various chronic and autoimmune diseases has been studied, especially in animal studies (3,8). They found statistically significant differences between the composition of the microbiota in lean and obese mice and animals with different chronic diseases. These results point to the importance of the microbiota in relation to health and immunity and offer new, as yet undiscovered possibilities for applying this knowledge in the treatment of other diseases, such as metabolic syndrome, insulin resistance, some cancers, chronic inflammatory bowel disease and other (1,6,9).

The paper presents some modern diagnostic methods that have provided a more accurate insight into the diversity of the gut microbiota, and certain pathophysiological mechanisms that influence the development of certain cardiovascular diseases.

2 Diagnostic procedures for determining the composition of the gut microbiota

The composition of the microbiota, its diversity and potential role in maintaining epithelial cell homeostasis, in inhibiting the growth of pathogenic microorganisms and the formation of various components, can be defined by a

Table 2: A brief summary of possible methods for the analysis of the gut microbiota (the first part summarized from Durack J and Lynch SV (53)).

Area	Name	Principle	Method	Positive	Negative
Composition	Profiling of biological markers	DNA	NGS	Cost effective; semi-quantitative.	No functional information.
	Metagenomics	DNA	NGS	Strain level resolution.	Expensive. Compute-intensive.
Metabolic production	Metabolomics	Metabolites	LG/GC - MS	Semi-quantitative. Targeted or non-targeted.	The origin of the metabolite is unclear.
Function	Metatranscriptomics	RNA	NGS	Gene transcription of the host or of microorganisms.	Samples require RNA preservation; host genes may predominate.
	Metaproteomics	Proteins	LG/GC - MS	Semi-quantitative.	The origin of the protein is unclear.

Legend: NGS - new generation sequencing, LG/GC - liquid/gas chromatography, MS - mass spectrometry.

number of methods that differ in resolution (2,5,8). With different methods we can compare the composition of the microbiota between different samples, determine the microbiota composition and what the interrelationships are, determine the metabolic potential of microbes with their sets of genes, their interdependence and their metabolic role (10). Accurately determining the composition of the gut microbiota is a key goal of the "Human Microbiome" and "MetaHit" (Metagenomics of the Human Intestinal tract) projects, which were launched in the recent past (11,12). Methods for determining the composition of the microbiota include traditional ones, such as cultivation, and molecular methods. Traditional methods include "counting colonies on selective medium" and "the method of the most probable number of cells" (10). Cultivation methods are associated with some important limitations: testing being time-consuming and the difficulty of culturing most of the gut microbiota (10). It should be noted that only 0.01-10% of all cells present in the microbial sample can grow on the media. In most molecular methods, 16S- and 18S-ribosomal RNA (rRNA), which are preserved in all bacteria, archaea and eukaryotes, are used as a phylogenetic marker for the taxonomic classification of organisms. An overview of the different techniques is shown in Table 2.

3 Mechanisms of microbiota activity in the etiopathogenesis of cardiovascular diseases

Atherosclerosis is a major risk factor for cardiovascular disease. This process is characterized by the accumulation of cholesterol and macrophages (inflammatory cells) in the vascular walls, which contributes to the formation of atherosclerotic plaques (1,8,9). Recent studies have shown that intestinal dysbiosis can contribute to the development of atherosclerosis by modulating inflammatory processes and the formation of certain microbial metabolites (13-15).

3.1 Gut dysbiosis and atherosclerosis

The integrity of the gut mucosa is the first barrier that protects the host from the intrusion of pathogens, the passage of intestinal contents and bacterial components into the blood vessels. Reduced concentration of proteins that ensure close contact between cells and their impermeability, including ZO-1 (TJP1), claudin-1 and occludin, allows increased permeability of the gastrointestinal wall with an imbalance between mucosal cell death and regeneration (1,13,14). If the mucous barrier is damaged, the intrusion of microbes with their products, i.e., with pathogens associated with molecular patterns (PAMPs) in the blood vessels triggers an immune response, tissue and systemic inflammation. Lipopolysaccharides (LPS) and peptidoglycans (PG) are components of bacteria associated with the development of cardiovascular disease. LPS is a component of the cell wall of Gram-negative bacteria. The association between plasma LPS levels and the risk of heart disease was first studied in 1999 by Niebauer et al. (15). The results of the study confirmed that the level of endotoxemia was highest in patients with most severe cardiovascular diseases. Cani and colleagues confirmed in their study that gut dysbiosis prevented the formation of "close-contact proteins," resulting in increased permeability of the gut mucosa and thus the passage of LPS into the blood (16). LPS, which are produced in increased amounts in gut

dysbiosis, may play an important role in the modulation of "Toll-like receptors" that recognize bacterial products and regulate the immune system of the host. Clinical studies have shown that the upregulation of "Toll-like receptors" is associated with anti-inflammatory activity and promotes the development of atherosclerosis in humans. PG, a minor component of the cell wall of Gram-negative bacteria and an important component of Gram-positive bacteria, has also been found to be associated with a risk of cardiovascular disease because it damages the epithelial barrier (8,9). It was also shown that patients with atherosclerosis had an increased number of genes encoding the synthesis of pro-inflammatory bacterial peptidoglycans (8,17). PAMPs that can promote inflammatory processes include CpG-oligodeoxinucleotides and flagellin, lipopeptides, and others. The results of research in recent years confirm the role and importance of gut microbiota and dysbiosis in the risk of atherosclerosis (1,3,8).

3.2 Gut microbial metabolites in atherosclerosis

In the metabolism of gut bacteria, various metabolites are formed that participate in the development of atherosclerosis. Among the most important are various amines, methylamines, polyamines, short-chain fatty acids, trimethylamine, and secondary bile acids. In particular, short-chain fatty acids are a group of gut microbial metabolites that are important in metabolic diseases. Studies have shown that the gut microbiota is involved in the formation of trimethylamine N-oxide (TMAO) (8,14). Trimethylamine (TMA) is a by-product of bacterial metabolism that is absorbed into the bloodstream and converted to TMAO in the liver by specific liver enzymes, flavin-containing monooxygenases. Different bacterial compositions naturally have different abilities to produce TMAO. Studies have confirmed that TMAO promotes the development of atherosclerosis by stimulating cholesterol influx, inhibiting cholesterol excretion, inhibiting secondary bile acid metabolic pathways, and/or by increasing platelet activation (1,8). According to the researchers, TMAO, in addition to the role of a biological marker for atherosclerosis and cardiovascular diseases, could also represent a possible therapeutic goal in the future (18).

3.3 Gut microbiota and hypertension

As early as 1982, Honor and colleagues demonstrated that antibiotic treatment could cause higher blood pressure (15). A 2015 Yang et al. study in rats with hypertension confirmed that altering the gut microbiota by significantly reducing microbial diversity and increasing the ratio of bacteria from *Firmicutes/Bacteroidetes* phyla can affect blood pressure regulation (8). Although the relationship and mechanism of the gut microbiota and hypertension activity have not yet been fully elucidated, existing evidence highlights the important role of short-chain fatty acids and oxidized low-density lipoproteins (LDL) in hypertension. The microbiota of an individual is very specific and relatively stable throughout the adult life, despite the fact that 90% of it is represented by only two phyla of the bacteria *Firmicutes* and *Bacteriodetes*. Bacteria of these phyla (e.g., *Lactobacillus sp., Bacteriodes sp., Prevotella sp.*, etc.) form structural polysaccharides and short-chain fatty acids (acetate, propionate and butyrate) that are crucial for intestinal microbiome homeostasis, immune system and host response (1,5,8).

Interestingly, different bacteria form different types of short-chain fatty acids. Clinical studies have shown that an increased abundance of butyrate-forming bacteria (families *Lachnospiraceae, Ruminococcaceae* and *Acidaminococcaceae*) is associated with lower blood pressure in overweight pregnant women (14). Short-chain fatty acids can stimulate the regulation of G-protein Coupled Receptors, which affect renin secretion and thus blood pressure (19). The regulation of blood pressure also depends on the control of vasoconstriction and vasodilation of blood vessels. Gut dysbiosis contributes to hypertension with vasoconstriction that is regulated by LDL oxidation. Dysbiosis may promote the expression of inflammatory cytokines. Inflammation can cause oxidative stress, which can promote LDL oxidation (1,14). Higher levels of oxidized LDL can lead to insufficient production of vasodilator substances and excessive production of vasoconstrictor substances. A disturbed balance, however, leads to hypertension.

3.4 Gut microbiota and heart failure

There is growing evidence of an association between the gut and the pathogenesis of heart failure. In the English literature, the term "gut hypothesis of heart failure" (20-23) is used to define this connection. This hypothesis explains that decreased cardiac output (DCO) and increased systemic congestion can lead to intestinal ischemia and/or edema of the intestinal wall, leading to increased bacterial passage into the blood vessels, thereby increasing the circulating endotoxin level. This can trigger inflammation in patients with heart failure. Niebauer and colleagues found that patients with heart failure with peripheral edema had higher levels of endotoxin and inflammatory cytokines in plasma compared to patients without edema (15). Following short-term diuretic therapy, serum concentrations of endotoxin, but not cytokines, decreased. In another study, the same researchers confirmed that patients with heart failure with reduced intestinal blood flow had higher serum concentrations of immunoglobulin A - anti-lipopolysaccharide. Compared with the control group, patients had a different microbiota composition (24). Studies have also confirmed that circulating TMAO levels are higher in patients with heart failure compared to the control group without heart failure (20-23).

3.5 Gut microbiota in myocardial infarction

Atherosclerotic plaques contain bacterial DNA. Bacterial species found in atherosclerotic plaques, however, are also present in the intestines of the same individuals (18,20). From this, it can be concluded that intestinal microbial communities may be a source of bacteria in plaque, which may affect plaque stability and the development of cardiovascular disease. A recent study in rats reported an association between the gut microbiota and the extent of myocardial infarction (21,22). The study looked at Dahl S rats that drank drinking water to which the vancomycin antibiotic was added, which reduced circulating leptin levels by 38%, caused a smaller myocardial infarction (27% reduction of the area) and improved restoration of post-ischemic myocardial contractility (35%) compared to control specimens that did not receive it. Vancomycin altered the abundance of gut bacteria and fungi as measured by the amount of 16S and 18S rRNA. In rodent studies, administration

of *Lactobacillus plantarum* as a probiotic (Goodbelly contains leptin-inhibiting bacteria, *Lactobacillus plantarum 299v*) resulted in a 41% reduction in circulating leptin, a 29% reduction in myocardial infarction and a better recovery of shrinkage functions by 23% (21). However, if rodents received leptin at a dose of 0.12 μg/kg i.v. prior to the study, it nullified the protective effect of the probiotic on the heart. This study was the first to confirm a direct link between changes in the gut microbiota and myocardial infarction. It demonstrates that probiotic supplementation can reduce the extent of myocardial infarction (21). Another animal study using *Lactobacillus rhamnosus GR-1* similarly showed a beneficial effect on cardiac function after artificially induced myocardial infarction (23).

3.6 Gut microbiota and chronic kidney disease

Cardiovascular diseases and kidney diseases are closely related, the so-called "cardiorenal syndrome" is associated with poor clinical outcome. Patients with chronic kidney disease (CKD) are at greater risk of accelerated atherosclerosis and increased mortality. Studies have confirmed that the composition of the gut microbiota in patients with CKD is markedly altered, which leads to an increase in urea and other uremic toxins in the intestinal lumen (25–28). In the gastrointestinal tract, urease hydrolyzes urea to produce large amounts of ammonia, which is then converted to ammonium hydroxide. Ammonia and ammonium hydroxide damage the close contacts of the mucosa in patients with CKD and cause mucosal barrier dysfunction. This allows bacterial components and uremic toxins to pass from the gut into the systemic circulation and triggers systemic inflammation (8,29). Recently, intestinal DNA microbiota with 16S rRNA amplification and DNA sequencing were detected in the plasma of patients with CKD during chronic hemodialysis. Bacterial DNA levels matched elevated plasma levels of inflammatory markers (30). Uremic toxins associated with poorly dialyzable proteins (e.g., indoxyl sulfate and p-cresol sulfate) are associated with an adverse outcome in the patient. These two metabolites originate from the amino acid metabolism of the microbiota and are in renal dysfunction inefficiently cleared from the circulation (27). TMAO is known to accumulate in the plasma of patients with CKD. Higher TMAO levels, however, were associated with higher mortality and progressive renal impairment (28,31). Data from the Framingham Heart Study showed that TMAO was one of the rare metabolites in the plasma of healthy subjects, the level of which predicted the development of CKD (32).

3.7 Gut microbiota and metabolic diseases

In recent years, researchers have also studied the links between dysbiosis and obesity, type 2 diabetes, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD) (33,34). Initial animal and human studies supported associations between obesity and abundance of the *Firmicutes* phylum compared to the *Bacteroidetes* phylum; type 2 diabetes was associated with a reduced abundance of butyrate-forming bacteria and an increased abundance of *Lactobacillus spp* (1,3,8,9). In the development of dyslipidemias, the intestinal microbiota participates through secondary bile acids, which it produces and by modulating the metabolism of liver and/or systemic lipids, as well as glucose (35,36). In the field of NAFLD research, it was

found that some bacteria (*Clostridium coccoides, Lactobacillus reuteri, Parabacteroides*) affect fat metabolism, gut wall integrity and the process of fibrosis, and therefore affect the progression of this disease (35).

Although we have presented only some of the mechanisms linking the gut microbiota and some cardiovascular diseases, we need to be aware of the potential of this research area in the development of potential drugs in the future. We must not forget that we already are using part of the acquired knowledge in this field. This includes treatment with "fecal microbiota transplantation" and influencing the course of chronic inflammatory bowel disease and ulcerative colitis, as well as the treatment of recurrent infections with *Clostridium difficile* (37). The newly elucidated links between dysbiosis and the pathogenesis of cardiovascular disease offer new opportunities for early and targeted action. However, a number of research questions and therapeutic options also open up in other areas (38,39). The abundance of recent research contributions in this field confirms the importance of this field and the interest that has emerged in research environments.

4 Application in practice

Examples of clinical aplicability of microbiota changes that have been known for a long time are: fecal transplantation, dietary measures, pre- and probiotic therapy, antibiotic therapy, intake of TMA lyase inhibitors, etc. (40).

Research has shown that even a five-day change in diet leads to a short-term rearrangement of the number and types of gut microbiota (4). An example of this is the DASH diet (Dietary Approaches to Stop Hypertension), which consists of meals with fruits, vegetables, whole grains, etc. (41). Patients in the study had better results in the six-minute walk test, better quality of life and reduced arterial elasticity after three months of implementing the diet (42). In addition, the individuals who do not follow a prescribed diet are found to have elevated levels of TMAO in the urine compared to patients who followed the prescribed regimen (43,44). A high-fibre diet can also improve the growth of acetate-producing bacteria, lower high blood pressure, and prevent cardiac fibrosis and hypertrophy (45). The addition of probiotics (bifidobacteria, yeast, lactic acid bacteria, etc.) has, according to previously described studies on animals, contributed to better heart function and maintaining it (23,46).

The use of antibiotics affects the composition, diversity and function of the normal flora. Non-steroidal anti-inflammatory drugs also lead to changes in the flora in elderly patients, which can cause side effects (47). However, antibiotics can also be helpful. We have already explained that antibiotics have been successfully used in animal models to reduce translocation as well as to reduce the extent of cardiac cell damage after infarction (48,49). Polymyxin B and tobramycin have, for example, reduced levels of LPS in the gastrointestinal tract as well as the IL-1β, IL-6 and TNF-α levels in patients with heart failure (50).

Worthy of note are the results of a study in which mice were given choline analogues that inhibit the functioning of the enzyme CutC/D in the metabolism of TMA and thereby reduce the plasma concentration of TMAO, which is associated with increased thrombogenicity. The use of choline analogues could therefore allow for a possible new approach to reducing the chances of developing thrombosis (51). Another interesting active ingredient recently de-

scribed in the Nature journal that acts as a protective factor for the intestinal mucosa is Urolithin A (UroA) and its synthetic analogue UAS03. The active substance triggers the signaling pathways of aryl hydrocarbon receptor (AhR) and nuclear factor erythroid 2-related factor 2 (Nrf2), which enhances close contact and gastrointestinal barrier function (52).

5 Conclusion

New technologies are radically changing medicine and enabling a new, different view of the body, organs and health, as well as causal factors of disease. Recent research work and some surprising findings have confirmed that the gut microbiota can affect the health of the host and trigger disease by a variety of pathophysiological mechanisms. Intestinal microbiota and dysbiosis are areas of research that are likely to change some of today's established methods of disease prevention and treatment in the future. Although we can change the composition of the microbiota with prebiotics, probiotics, antibiotics, diet and "targeted enzyme inhibitors", we unfortunately cannot yet predict these effects and evaluate them in the prevention of various diseases. With all the data obtained in biomedicine in recent decades, it seems unusual that it took so long before researchers began to systematically deal with the impact of as much as 2 kg of microorganisms that colonize us and live with us "for better or for worse".

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