ROLE OF DIET IN DEVELOPMENT OF NON-COMMUNICABLE DISEASES: FOCUS ON GUT MICROBIOME

Andrea Fričová[1], Anna Zavaďáková[1], Monika Bludovská[1, 2]
[1]Department of Public Health and Preventive Medicine, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic
[2]Department of Pharmacology and Toxicology, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

SUMMARY

Objectives: The dietary composition is able to rapidly and significantly influence the diversity of the gut microbiome. This article focuses on how various types of diet affect the composition of the gut microbiome and how dietary changes are able to prevent or slow down the development of non-communicable diseases including obesity, type 2 diabetes mellitus, cardiovascular diseases, and low-grade inflammation.

Methods: A review in PubMed and a hand search using references in identified articles were performed. Studies published in English from 2000 to 2024 were included.

Results: The studies showed the significant effect of diet on the development of non-communicable diseases dependent on the state of the gut microbiota and molecules it produces. The Western diet that continues to gain in popularity for Czech people, leads to dysbiosis and production of bacterial lipopolysaccharide or trimethylamine N-oxide causing systemic chronic inflammation in the body and thus promoting the development of non-communicable diseases.

Conclusions: Findings from this review emphasize the importance of healthy eating habits in the prevention of intestinal dysbiosis and still increasing prevalence and incidence of obesity and other non-communicable diseases.

Key words: gut microbiome, diet, obesity, non-communicable diseases, dysbiosis

Address for correspondence: A. Zavaďáková, Department of Public Health and Preventive Medicine, Faculty of Medicine in Pilsen, Charles University, Alej Svobody 76, Pilsen, Czech Republic. E-mail: anna.zavadakova@lfp.cuni.cz

https://doi.org/10.21101/cejph.a8138

INTRODUCTION

The gut microbiome, i.e., the organized community of microorganisms that inhabit the digestive tract, is gaining increasing attention in the field of medical research. It is now known that the gut microbiome exerts a major impact on digestion and a wide range of physiological functions in the body and in the development of a number of chronic non-communicable diseases.

Previous studies have suggested a link between the composition of the gut microbiome and the incidence of chronic diseases such as idiopathic bowel disease (IBD), type 2 diabetes mellitus (DM2), obesity, atherosclerosis, inflammatory skin diseases (atopic eczema, psoriasis), etc. For example, IBD patients typically evince lower microbial diversity along with lower levels of bacteria in the phyla Bacillota and Bacteroidota (formerly the Firmicutes and Bacteroidetes), which may result in reduced butyrate concentrations. Butyrate and other short-chain fatty acids (SCFAs) are considered an energy source for intestinal epithelial cells which strengthens gut barrier function and exerts an anti-inflammatory impact in the gut (1). Dysbiosis, a disturbance in the balance of the gut microbiome in terms of both its composition and function, has been demonstrated in patients with DM2. Moreover, the functional analysis of such patients suggests a decrease in butyrate-producing bacteria and an increase in opportunistic pathogens (2).

The afore-mentioned data demonstrates the importance of the gut microbiome in terms of the prevention and treatment of chronic non-communicable diseases (NCD). Finally, it is important to mention that although the gut microbiome is influenced, *inter alia*, by genetics, dietary history, stress factors, environment, and other variables, diet exerts the most significant impact and is the easiest factor to influence. In addition, intestinal integrity plays an important role. Factors such as stress, an unbalanced diet and the excessive intake of alcohol, antibiotics and other medications, all have the potential to disrupt the balance of the gut microbiome and the functioning of the gut barrier, which lead to increased intestinal permeability (so-called "leaky gut") and the subsequent onset of leaky gut syndrome (3).

MATERIALS AND METHODS

A review of the topic was conducted in October 2023 employing the MEDLINE database accessed via the free-to-use PubMed interface. Related studies were searched for applying the keywords "gut microbiome", "vegetarian", "plant-based", "vegan", "Mediterranean diet", "Western diet", "gluten-free", "diabetes mellitus", "idiopathic bowel diseases", "cardiovascular diseases", "microbiota", "obesity", "protein", "carbohydrates" and "fat". Only publications written in English and

published between the year 2000 and the present were considered in the review.

RESULTS

Macronutrients and Micronutrients

Changing the amounts of the dietary intake of macronutrients, i.e., carbohydrates, proteins and fats, significantly affects the composition of the gut microbiome. A diet high in fermentable carbohydrates acts to quantitatively support the occurrence of the beneficial *Bifidobacterium*, *Prevotella*, *Ruminococcus*, *Dorea* and *Roseburia* bacterial genera (4).

Prebiotics, i.e., indigestible and non-absorbable food components, play an important role in the gut microbiome. They enter the large intestine unchanged and are utilized by the intestinal bacteria (mainly *Bifidobacterium* spp. and *Lactobacillus* spp.) to promote their growth, colonization and longevity. The most important sources of prebiotics comprise oligosaccharides and galactooligosaccharides. Several important substances are formed during the fermentation of prebiotics, including SCFAs, e.g., butyric, propionic and acetic acids, and vitamins K and B12. The microorganisms that produce SCFAs, the afore-mentioned *Bifidobacterium* spp. and *Lactobacillus* spp., help to prevent the development of the pathogenic genera of bacteria (5).

Artificial sweeteners such as sucralose and acesulfame K are often advertised as a healthy substitute for sugar. However, in recent years, a number of potential negative effects of the use of such sweeteners have come to light. Artificial sweeteners have been shown to adversely affect the diversity and functioning of the gut microbiome (6). One of the studies has suggested that the consumption of aspartame and acesulfame K is more likely to cause impaired glucose tolerance (prediabetes) than the consumption of sugar (7). Neotame has been shown to reduce gut microbiota diversity, decrease in Bacillota and increase in Bacterioidota. Moreover, the metabolic profile was altered – the concentrations of multiple fatty acids, lipids as well as cholesterol in the faeces were consistently higher (8). In addition, aspartame, sucralose and saccharin have been shown to have significant inhibitory actions on the Gram-negative bacteria quorum sensing, the cell-cell communication system, which affect the balance of the gut microbial community (9). On the other hand, polyols (e.g. isomalt), a specific group of compounds used as food additives, increases bifidobacteria numbers in healthy subjects and may have prebiotic actions (10).

It has been suggested that diets that are high in saturated fatty acids and trans-fatty acids lead to the overgrowth of pathogenic bacteria (e.g. *Bilophila*) (4). Moreover, a range of studies have suggested that diets high in saturated fats lead to a reduction in the diversity of the gut microbiota compared to low-fat diets. On the other hand, diets that contain monoenoic and polyenoic fatty acids exert an anti-inflammatory effect and promote the growth of beneficial bacteria (11).

The excessive intake of animal protein is associated with intestinal dysbiosis and a significantly higher risk of IBD. Animal foods associated with the risk of IBD include the high consumption of meat and fish in contrast to milk and eggs, which do not act to increase this risk (12).

Micronutrients, especially vitamin D, are also essential for the gut microbiome. This vitamin and its receptors play a key role in the regulation of the functions of the gut microbiota and the immune response. Vitamin D acts to suppress inflammatory reactions and autoimmune diseases (13) and is considered one of the protective factors against the development of IBD (14, 15). Low levels of vitamin D binding protein (VDBP) and total 25-OH vitamin D (vitamin D2 + vitamin D3) correlate with the incidence of cancers, including breast, prostate and colon cancer, and the development of DM2 (16). Studies in mice have shown that vitamin D deficiency leads to reduced microbial diversity, an altered gut microbiota composition and a higher risk of ulcerative colitis (17). Humans are unable to extract more than 20% of the recommended daily dose of vitamin D from dietary sources. Around 80% is synthesized in the skin via UV radiation from the sun. People with dark skin pigmentation, infants, the elderly, obese patients – due to volumetric dilution (18), and those with low UVB exposure (the use of sunscreen, covering up with clothing, non-exposure to sunlight during the day) may suffer from the insufficient synthesis of vitamin D through the skin. The geographical location is also a very important factor. Populations that live at higher and lower altitudes are predisposed to vitamin D deficiency, especially during the winter months (19). An increase in the solar zenith angle causes UVB photons to travel a longer path, which explains why there is minimal to no production of vitamin D3 in the skin at higher latitudes (above ~35° latitude) from November to March (20).

Vegetarian Diets

It is well known that the gut microbiome profile of vegetarians differs from that of omnivores, the gut microbiomes of whom contain bile-tolerant, potentially pathogenic microorganisms. A strictly vegan diet is usually low in fats, consisting primarily of monoenoic and polyenoic fatty acids, which leads to an increase in the ratio of the Bacillota and Bacterioidota bacterial phyla. Compared to a standard diet with its predominance of animal fats, the vegan diet microbiota is characterized by the increase of *Proteobacteria* genera, the increase of bacteria that ferment dietary fibre such as *Clostridium*, *Lactobacillus*, *Ruminococcus*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii* and a concomitant decrease in the beneficial *Bifidobacterium* spp. strain (21).

As mentioned previously, the excessive intake of animal protein may be associated with the development of intestinal dysbiosis. The inclusion of plant protein sources in the diet allows for the development of intestinal diversity. For example, the consumption of pea protein increases the production of the *Bifidobacterium* and *Lactobacillus* protective strains and reduces the levels of *Clostridium perfringens* and *Bacteroides fragilis*, which, although not pathogenic, may be threatening if overgrown. A beneficial effect was also observed following the consumption of walnut protein, which led to an increase in the production of *Ruminococcus* spp. and *Bifidobacterium* spp. strains and a concomitant decrease in *Clostridium perfringens*. Vegetarian diets also contain higher amounts of fermentable fibre, which acts as a substrate for the metabolism of gut bacteria (22).

Mediterranean Diet and Western Diet

The Mediterranean diet, characterized by the high consumption of local vegetables and fruits, the considerable representation of fish in the diet and the moderate consumption of red wine, is considered to be one of the world's healthiest diets. It is rich in complex carbohydrates, antioxidants and polyene fatty acids, which act to prevent atherogenesis. Following the Mediterranean diet correlates with the restoration of dysbiosis, i.e., eubiosis, increases in the *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, *Eubacterium*, and *Prevotella species* and certain beneficial *Clostridium* genus groups and decreases in the levels of potentially pathogenic *Proteobacteria* and *Bacillaceae* (23).

In contrast, the Western diet leads to very serious problems with concern to the incidence of obesity, cardiovascular diseases, DM2, osteoporosis, and other chronic NCD. This diet is rich in animal protein and fat, highly processed foods, salt, simple sugars, and trans-fatty acids, while critically poor in fibre and both mono and polyunsaturated fats. It is considered as a predominant trigger implicated in development of IBD (24).

Meal, particularly a fatty meal, increases levels of lipopolysaccharide (LPS), which is able to cross the gut mucosa and to enter into the systemic circulation via chylomicrons and promote development of inflammation (25, 26). The long-term consumption of the Western diet leads to significant changes in the gut microbiome, which exerts a substantial impact on the entire immune system, e.g., it promotes the development of systemic chronic inflammation in the body (23). In addition, this diet results in decreases in intestinal diversity and the representation of *Bifidobacterium*, *Lactobacillu*s, *Eubacterium* and an increase in the representation of *Blautia*, *Ruminococcus*, *Bacteroides*, *E. coli*, and total *Enterobacteriaceae*, which may include further opportunistic pathogens (21, 27).

Moreover, diets rich in animal products like Western diet contain large amounts of trimethylamine (TMA) precursors derived by gut microbiota, which increase trimethylamine N-oxide (TMAO) levels in the blood. In contrast, vegetarian diet is associated with a lesser microbiota-derived TMA and TMAO (25). Increased levels of TMAO are associated with various NCD including DM2, heart failure, atherosclerosis, hypertension, and cancer (28, 29).

Gluten-free Diet

A gluten-free diet is prescribed for those with celiac disease or non-celiac gluten/wheat sensitivity, since strict adherence to a gluten-free diet is currently the only effective treatment.

One of the most relevant studies in this area indicated a reduction in the *Bifidobacteria* and *Lactobacilli* genera and a relative increase in opportunistic human pathogens, e.g., *Bacteroides fragilis*, *E. coli*, *Proteobacteria*, *Hemophilus*, *Serratia*, and *Klebsiella* in patients with celiac disease. These findings suggest that intestinal dysbiosis in patients with celiac disease may be one of the factors that triggers the disease (30). Other researchers detected decreases in *Lactobacilli*, *Eubacteria* and *Prevotella* and increases in *Enterobacteria* and *Roseburia* in patients diagnosed with celiac disease (21). The analysis of patients with celiac disease who had followed a gluten-free diet for at least two years revealed that they had a gut microbiota composition comparable to that of the healthy controls. This suggests that the gut microbiota of patients with celiac disease may become normalized when following a gluten-free diet (31). In contrast, other researchers observed only restoration of the alpha diversity (microbial diversity within a sample) but not the gut microbiome composition (32). This diet is generally poorer in terms of fibre consumption due to the necessity to restrict the intake of whole grains. Thus, patients with celiac disease should ensure that their diet contains sufficient fibre, which, as mentioned previously, acts as a prebiotic. It is advised that those with celiac disease replace cereals with pseudocereals (buckwheat, quinoa, amaranth), which are naturally gluten-free and rich in fibre. It is particularly important to consume fruit, vegetables and legumes in sufficient quantities so as to meet the recommended daily fibre intake requirement which is consistent with proposals from other studies (33–35).

A certain percentage of the population has adopted a gluten-free diet without the need to do so aimed at following a healthier lifestyle. However, it is important to note that following a gluten-free diet by healthy individuals even for four weeks changes the gut microbiome composition and alters the activity of microbial pathways (36).

Obesity

Obesity is a chronic disease and a global health problem that has reached pandemic dimensions, and its incidence continues to increase. Research on the gut microbiome has opened up new perspectives in terms of understanding obesity and the introduction of new treatment approaches. The gut microbiota has been linked to the regulation of the energy metabolism, immune responses and inflammatory processes in the body (37). Both animal and observational studies in humans suggest that excessive weight gain and inflammation in the body correlate with the occurrence of dysbiosis (38). A recent systematic review of the analysis of 60 studies on this topic reported the increased prevalence of the *Proteobacteria* genus, i.e., gram-negative bacteria that may contain endotoxins and exert a pro-inflammatory effect, as the most common association in obese patients. The composition of the gut microbiome, including *Proteobacteria*, is strongly influenced by dietary habits (39).

Forming an understanding of the relationship between the gut microbiota and adipose tissue has the potential to allow for the determination of new intervention strategies for the treatment of obesity. A range of studies have demonstrated the interaction of the gut microbiota in relation to the function of adipose tissue (40). The gut microbiome is able to influence adipose tissue through secreted metabolites and microbial components that subsequently enter the blood circulation system, via which these molecules are able to reach the adipocytes themselves. The chemical nature of these molecules is diverse and includes SCFAs, pattern recognition receptors (PRR), ligands, flavonoids, indoles, and others (41).

Intestinal microorganisms play an important role in the inflammatory response. The communication of gut microbes with the immune system is able to induce or suppress inflammation. A varied, wholesome diet contributes to the production of SCFAs, which are associated with a reduction in inflammation and an increase in satiety (42). LPS, also play an important role in terms of initiating the inflammatory responses associated with obesity and insulin resistance. LPS infiltrate adipose tissue and the liver after entering the bloodstream and trigger an innate immune

response (43). Intestinal dysbiosis may thus be a source of LPS, which penetrate the bloodstream and continuously activate the human immune system especially in cases of enhanced intestinal permeability. Consequently, the human body experiences chronic low-grade inflammation, which contributes to the development of autoimmune diseases such as celiac disease, IBD, irritable bowel syndrome (IBS), obesity, etc. (3).

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a NCD characterized by insulin resistance with absolute or relative insulin deficiency. Global data from the International Diabetes Federation (IDF) states that in 2021, approximately 537 million adults suffered from DM2. This is expected to rise to nearly 642 million adults by 2030. This situation may put significant economic pressure on the global health system (44).

The gut microbiota of DM2 patients is characterized by an increased presence of pathogenic and opportunistic Gram-negative bacteria at the expense of commensal microorganisms. In particular, there is an increase in Clostridiales, *E. Coli*, *Bacteroides caccae*, *Lactobacilli*, *Prevotella copri*, *Bacteroides vulgates* and *Eggerthella* sp. (45–47). A study analysing the gut microbiome of individuals with insulin resistance showed that the serum metabolome of individuals with insulin resistance is characterized by elevated levels of branched-chain amino acids (BCAAs), which correlates with a gut microbiome. The bacterial species *Prevotella copri* and *Bacteroides vulgatus* have been identified as the main species underlying the association between BCAA biosynthesis and insulin resistance. In an animal model, *P. copri* has been shown to induce insulin resistance, exacerbate glucose intolerance and increase circulating BCAA levels (45).

Cardiovascular Diseases

According to the World Health Organization (WHO), globally, cardiovascular diseases (CVD) are the leading causes of death. Nearly 18 million people die each year from CVD causes. One recent study investigating the relationships between the gut microbiome, blood lipids and heart failure identified six gut microbial taxa with a potentially causal effect on heart failure, with *Bacteroides dorei* being the most significant (48).

Since LPS is able to enter the systemic circulation, it may lead to atherosclerosis, possibly via chronic inflammation, and thrombosis. From a clinical viewpoint, increasing *Bacteroides* abundance in the gut could potentially be a new therapeutic approach to prevent CVD because of its ability to reduce faecal LPS levels (49). Gut microbiota produces molecules such as TMAO, which may be implicated in atherosclerosis and thrombosis. Clinical study demonstrates that plasma levels of TMAO predicted CVD such as myocardial infarction, stroke and cardiovascular death (50, 51).

CONCLUSION

Studies conducted to date have indicated that diet significantly influences the composition of the gut microbiome and contributes to the functioning of the immune system and the pathogenesis of chronic NCD. The most frequently cited nutritional approaches positively influencing the gut microbiome include the sufficient consumption of fibre, i.e., whole grain cereals, pseudocereals, vegetables, fruit, legumes, and nuts. The latest guidelines issued by health organizations recommend the consumption of 30 grams of fibre per day. In addition, fermented foods (e.g., kimchi, kombucha, tempeh, sauerkraut) and fermented milk products containing probiotic bacteria should be incorporated into the diet. In general, fresh, unprocessed foods should be preferred to highly processed foods that contain artificial sweeteners and other additives, accompanied by the moderate consumption of animal proteins, saturated fats, simple sugars, and food additives.

Although the gut microbiome has been studied in the context of nutrition for many years, many questions remain unanswered including, for example, how the various microorganisms of the gut microbiota mutually interact and how to positively influence the environment in the gastrointestinal tract. Moreover, we still do not fully understand the long-term effects of dietary changes on the microbiome and overall health. Thus, further research is necessary so as to better understand the origin of NCD. The latest available technologies that allow for the study of the microbiome at the metabolite level (metabolome) have significant potential in terms of the shift toward personalized medicine approaches.

Acknowledgement

The study was supported by Cooperatio No. 207032 – Immunity and Infection; project No. CZ.02.1.01/0.0/0.0/17_048/0007267.

Conflicts of Interest

None declared

REFERENCES

1. Lucas López R, Grande Burgos MJ, Gálvez A, Pérez Pulido R. The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: a state of the science review. APMIS. 2017 Jan;125(1):3-10.
2. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006 Dec 21;444(7122):1027-31.
3. Aleman RS, Moncada M, Aryana KJ. Leaky gut and the ingredients that help treat it: a review. Molecules. 2023 Jan 7;28(2):619. doi: 10.3390/molecules28020619.
4. Dahl WJ, Rivero Mendoza D, Lambert JM. Chapter Eight - Diet, nutrients and the microbiome. Prog Mol Biol Transl Sci. 2020;171:237-63.
5. Hijova E, Chmelarova A. Short chain fatty acids and colonic health. Bratisl Lek Listy. 2007;108(8):354-8.
6. Conz A, Salmona M, Diomede L. Effect of non-nutritive sweeteners on the gut microbiota. Nutrients. 2023 Apr 13;15(8):1869. doi: 10.3390/nu15081869.
7. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014 Oct 9;514(7521):181-6.
8. Chi L, Bian X, Gao B, Tu P, Lai Y, Ru H, et al. Effects of the artificial sweetener neotame on the gut microbiome and fecal metabolites in mice. Molecules. 2018 Feb 9;23(2):367. doi: 10.3390/molecules23020367.
9. Markus V, Share O, Shagan M, Halpern B, Bar T, Kramarsky-Winter E, et al. Inhibitory effects of artificial sweeteners on bacterial quorum sensing. Int J Mol Sci. 2021 Sep 13;22(18):9863. doi: 10.3390/ijms22189863.
10. Gostner A, Blaut M, Schäffer V, Kozianowski G, Theis S, Klingeberg M, et al. Effect of isomalt consumption on faecal microflora and colonic metabolism in healthy volunteers. Br J Nutr. 2006 Jan;95(1):40-50.
11. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009 Nov;137(5):1716-24.e1-2.

12. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. Am J Gastroenterol. 2010 Oct;105(10):2195-201.
13. Jeffery LE, Qureshi OS, Gardner D, Hou TZ, Briggs Z, Soskic B, et al. Vitamin D antagonises the suppressive effect of inflammatory cytokines on CTLA-4 expression and regulatory function. PLoS One. 2015;10(7). doi: 10.1371/journal.pone.0131539.
14. Scolaro BL, Barretta C, Matos CH, Malluta EF, Almeida IBT de, Braggio LD, et al. Deficiency of vitamin D and its relation with clinical and laboratory activity of inflammatory bowel diseases. J Coloproctol. 2018 Jun 8;38(2):99-104.
15. Mechie NC, Mavropoulou E, Ellenrieder V, Kunsch S, Cameron S, Amanzada A. Distinct association of serum vitamin D concentration with disease activity and trough levels of infliximab and adalimumab during inflammatory bowel disease treatment. Digestion. 2020;101(6):761-70.
16. Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, et al. Vitamin D and chronic diseases. Aging Dis. 2017;8(3):346-53.
17. Lagishetty V, Misharin AV, Liu NQ, Lisse TS, Chun RF, Ouyang Y, et al. Vitamin D deficiency in mice impairs colonic antibacterial activity and predisposes to colitis. Endocrinology. 2010 Jun;151(6):2423-32.
18. Vranić L, Mikolašević I, Milić S. Vitamin D deficiency: consequence or cause of obesity? Medicina (Kaunas). 2019 Aug 28;55(9):541. doi: 10.3390/medicina55090541.
19. Chang SW, Lee HC. Vitamin D and health - the missing vitamin in humans. Pediatr Neonatol. 2019 Jun;60(3):237-44.
20. Bouillon R. Vitamin D: photosynthesis, metabolism, and action to clinical applications. In: Degroot L, Jameson JL, Burger HG, editors. Endocrinology. 3rd ed. Philadelphia: WB Saunders; 2001. p. 1009-28.
21. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017 Apr 8;15(1):73. doi: 10.1186/s12967-017-1175-y.
22. Sakkas H, Bozidis P, Touzios C, Kolios D, Athanasiou G, Athanasopoulou E, et al. Nutritional status and the influence of the vegan diet on the gut microbiota and human health. Medicina (Kaunas). 2020 Feb 22;56(2):88. doi: 10.3390/medicina56020088.
23. García-Montero C, Fraile-Martínez O, Gómez-Lahoz AM, Pekarek L, Castellanos AJ, Noguerales-Fraguas F, et al. Nutritional components in western diet versus Mediterranean diet at the gut microbiota-immune system interplay. Implications for health and disease. Nutrients. 2021 Feb 22;13(2):699. doi: 10.3390/nu13020699.
24. Chapman-Kiddell AC, Davies SWP, Gillen L, Radford-Smith LG. Role of diet in the development of inflammatory bowel disease. Inflamm Bowel Dis. 2010 May 21;16(1):137-51.
25. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, et al. Lack of toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. Proc Natl Acad Sci U S A. 2004 Jul 20;101(29):10679-84.
26. Vors C, Pineau G, Drai J, Meugnier E, Pesenti S, Laville M, et al. Postprandial endotoxemia linked with chylomicrons and lipopolysaccharides handling in obese versus lean men: a lipid dose-effect trial. J Clin Endocrinol Metab. 2015 Sep;100(9):3427-35.
27. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8.
28. Tang WHW, Hazen SL. Microbiome, trimethylamine N-Oxide, and cardiometabolic disease. Transl Res. 2017 Jan;179:108-15.
29. Krueger ES, Lloyd TS, Tessem JS. The accumulation and molecular effects of trimethylamine N-Oxide on metabolic tissues: it's not all bad. Nutrients. 2021 Aug 21;13(8):2873. doi: 10.3390/nu13082873.
30. Caio G, Lungaro L, Segata N, Guarino M, Zoli G, Volta U, et al. Effect of gluten-free diet on gut microbiota composition in patients with celiac disease and non-celiac gluten/wheat sensitivity. Nutrients. 2020 Jun 19;12(6):1832. doi: 10.3390/nu12061832.
31. Nistal E, Caminero A, Herrán AR, Arias L, Vivas S, Ruiz De Morales JM, et al. Differences of small intestinal bacteria populations in adults and children with/without celiac disease: effect of age, gluten diet, and disease. Inflamm Bowel Dis. 2012;18(4):649-56.
32. Palmieri O, Castellana S, Bevilacqua A, Latiano A, Latiano T, Panza A, et al. Adherence to gluten-free diet restores alpha diversity in celiac people but the microbiome composition is different to healthy people. Nutrients. 2022 Jun 14;14(12):2452. doi: 10.3390/nu14122452.
33. Polo A, Arora K, Ameur H, Di Cagno R, De Angelis M, Gobbetti M. Gluten-free diet and gut microbiome. J Cereal Sci. 2020 Sep;95:103058. doi: 10.1016/j.jcs.2020.103058
34. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? J Hum Nutr Diet. 2005 Jun;18(3):163-9.
35. Sue A, Dehlsen K, Ooi CY. Paediatric patients with coeliac disease on a gluten-free diet: nutritional adequacy and macro- and micronutrient imbalances. Curr Gastroenterol Rep. 2018 Jan 22;20(1):2. doi: 10.1007/s11894-018-0606-0.
36. Bonder MJ, Tigchelaar EF, Cai X, Trynka G, Cenit MC, Hrdlickova B, et al. The influence of a short-term gluten-free diet on the human gut microbiome. Genome Med. 2016 Dec 21;8(1):45. doi: 10.1186/s13073-016-0295-y.
37. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016 Apr 20;8(1):42. doi: 10.1186/s13073-016-0303-2.
38. Maya-Lucas O, Murugesan S, Nirmalkar K, Alcaraz LD, Hoyo-Vadillo C, Pizano-Zárate ML, et al. The gut microbiome of Mexican children affected by obesity. Anaerobe. 2019;55:11-23.
39. Xu Z, Jiang W, Huang W, Lin Y, Chan FKL, Ng SC. Gut microbiota in patients with obesity and metabolic disorders - a systematic review. Genes Nutr. 2022 Jan 29;17(1):2. doi: 10.1186/s12263-021-00703-6.
40. Xiao H, Kang S. The role of the gut microbiome in energy balance with a focus on the gut-adipose tissue axis. Front Genet. 2020 Apr 7;11:297. doi: 10.3389/fgene.2020.00297.
41. Lundgren P, Thaiss CA. The microbiome-adipose tissue axis in systemic metabolism. Am J Physiol Gastrointest Liver Physiol. 2020;318(4):G717-24.
42. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014 Jan 16;156(1-2):84-96.
43. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761-72.
44. Boyko EJ, Magliano DJ, Karuranga S, Piemonte L, Riley P, Saeedi P, et al., editors. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
45. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BAH, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016 Jul 13;535(7612):376-81.
46. Larsen N, Vogensen FK, van den Berg FWJ, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010 Feb 5;5(2):e9085. doi: 10.1371/journal.pone.0009085.
47. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013 Jun 29;498(7452):99-103.
48. Dai H, Hou T, Wang Q, Hou Y, Wang T, Zheng J, et al. Causal relationships between the gut microbiome, blood lipids, and heart failure: a Mendelian randomization analysis. Eur J Prev Cardiol. 2023 Sep 6;30(12):1274-82.
49. Yoshida N, Yamashita T, Kishino S, Watanabe H, Sasaki K, Sasaki D, et al. A possible beneficial effect of Bacteroides on faecal lipopolysaccharide activity and cardiovascular diseases. Sci Rep. 2020 Aug 3;10(1):13009. doi: 10.1038/s41598-020-69983-z.
50. Randrianarisoa E, Lehn-Stefan A, Wang X, Hoene M, Peter A, Heinzmann SS, et al. Relationship of serum trimethylamine N-Oxide (TMAO) levels with early atherosclerosis in humans. Sci Rep. 2016 May 27;6:26745. doi: 10.1038/srep26745.
51. Li XS, Obeid S, Klingenberg R, Gencer B, Mach F, Räber L, et al. Gut microbiota-dependent trimethylamine N-Oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. Eur Heart J. 2017 Mar 14;38(11):814-24.

Received December 27, 2023
Accepted in revised form August 21, 2024