Chapter 6
Gut Microbiota and Chronic Kidney Disease

Antonio Augusto Ferreira Carioca, Suiani da Silva Sales, and Bárbara Rebeca Cordeiro de Melo

6.1 Epidemiological Scenario

Chronic kidney disease (CKD) is a syndrome characterized by the progressive decrease in the function or structure of the kidneys, which lose their functional capacity to filter blood and maintain the body's homeostasis. It is associated with high morbidity and mortality rates, posing a major challenge to public health as it has a major socioeconomic impact [1]. Adult patients are identified with CKD when they present, for a period equal to or longer than 3 months, a glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m^2, or GFR higher than 60 mL/min/1.73 m^2, but with evidence of kidney structure damage. Some indicators of kidney damage are albuminuria, renal imaging changes, hematuria, leukocyturia, persistent hydroelectrolyte disturbances, histological changes on renal biopsy, and previous kidney transplantation. Albuminuria is defined by the presence of more than 30 mg of albumin in the 24-h urine or more than 30 mg/g of albumin in an isolated urine sample adjusted by urinary creatinine. Major causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatory drugs, autoimmune diseases, polycystic kidney disease, Alport syndrome, congenital malformations, and long-term acute kidney disease [2]. The prevalence and incidence of CKD in many countries are unknown, but they stand out as being highly prevalent and are associated with an increased risk of cardiovascular disease, severity, and death. The United States estimates 14.8% prevalence of CKD in the adult population from 2011 to 2014 and 703,243 cases, with 124,114

A. A. F. Carioca (✉)
Department of Nutrition, School of Nutrition, University of Fortaleza, Fortaleza, CE, Brazil
e-mail: carioca@unifor.br

S. da Silva Sales · B. R. C. de Melo
Postgraduate Program in Nutrition and Health, Ceara State University, Fortaleza, CE, Brazil

G. Bezerra da Silva Junior, M. Nangaku (eds.), *Innovations in Nephrology*,
https://doi.org/10.1007/978-3-031-11570-7_6

new cases in 2015, showing an incidence rate of 378 patients per 1,000,000 people (pmp), with 87.3% of these on renal replacement therapy. In Latin America, the incidence was 167.8 pmp in 2005 and, in Brazil, 431 pmp in 2004 [3]. Global data from 2013 showed that reduced GFR was associated with 4% of deaths worldwide, i.e., 2.2 million deaths. More than half of these deaths were caused by cardiovascular disease, while 0.96 million were related to end-stage renal disease [2].

Epidemiological surveys addressing the disease are still scarce in regard to CKD risk factors before renal replacement therapies. Among these, the CKD Study, the National Health and Nutrition Examination Survey (NHANES), and the United States Renal Data System (USRDS) Report pointed out the increased prevalence of CKD at ages over 70 years and the association of the disease with hypertension in the United States and with diabetes in Mexico [3].

Chronic kidney disease is estimated to have affected about seven million individuals in 2017. As CKD is related to a large socioeconomic burden and a high mortality risk, identifying causal factors for CKD is important to elucidate biological pathways that are potential therapeutic targets [2].

6.2 Gut Microbiota and Chronic Kidney Disease

The human microbiome, a term derived from the Greek *mikros* (small) and Latin, *bio* (life) and *oma* (group or mass), is characterized by a set of microorganisms, their genomes, and the environmental conditions present in tissues and different parts of the human body [4]. There is extensive search to understand the human microbiome, its metabolites, its action on the host, and the importance of the complexity of these relationships in health and disease. Thus, advances in high-throughput sequencing methods have paved the way for decoding bacterial genomes from different parts of the human body, a fundamental basis for microbiome analysis. Besides, the use of new technologies, especially those related to "omics" technologies—genomics, proteomics, metabolomics, and others [5].

There is evidence of the likelihood that the development of the human microbiome begins formation in the womb, continues at birth, and beyond [6, 7]. However, the origin and means of transmission of early childhood microorganisms are poorly understood. Ferreti et al. (2018) obtained interesting findings: it was possible to identify a very high microbial diversity and strain heterogeneity in the pioneer infant intestinal microbiome; another important factor is that microbial strains present in infants, for which there is strong evidence of transmission from their mothers, are more likely to adapt and persist in the infant intestines; however, they gradually decline over time shifting to acquire strains from the environment and different places [8].

The set of these microorganisms that make up the microbiome is called microbiota, which is composed mainly of bacteria, viruses, fungi, protozoa, and archaea; they colonize the human body in the cutaneous, oral, respiratory, gastrointestinal, and genitourinary tracts [9]. The largest amount is present in the gastrointestinal

tract, which hosts more than 100 trillion microorganisms, including at least 1000 different species of bacteria [10]. It is also in the gastrointestinal tract (GI tract) that we find most of the immune system, thus associating it as an indicator of health [11]. The microbiota has an influence on the modulation of the immune system in both health and disease, for this and other factors are associated in the development or cause of chronic noncommunicable diseases (NCDs) [12]. This perspective of the microbiome universe is relevant in the current panorama of global public health, since NCDs have been the leading cause of death in the world population [13].

There is a connection between intestines and kidneys that can be classified into metabolic and immunological pathways. In the metabolic pathway, mediated by metabolites produced by the gut microbiota, an inadequate diet is the possible inducer, resulting in a high production and accumulation of toxic substances, called uremic toxins (UTs) in the intestinal environment, such as indoxyl sulfate (IS) and para-cresyl sulfate (PCS) (Fig. 6.1). They are excreted by the kidneys, and the accumulation of these elements in the intestines causes damage to the mucosal barrier leading to increased intestinal permeability (leaky gut). This leads to the influx of endotoxins and UTs into the kidneys via the circulation, which contributes to renal inflammation. In the immune pathway, the gut microbiota activates intestinal immune cells as well as modulates the profile of immunoprogenitor cells in the bone marrow. In this scenario, activated immune cells and pro-inflammatory cytokines

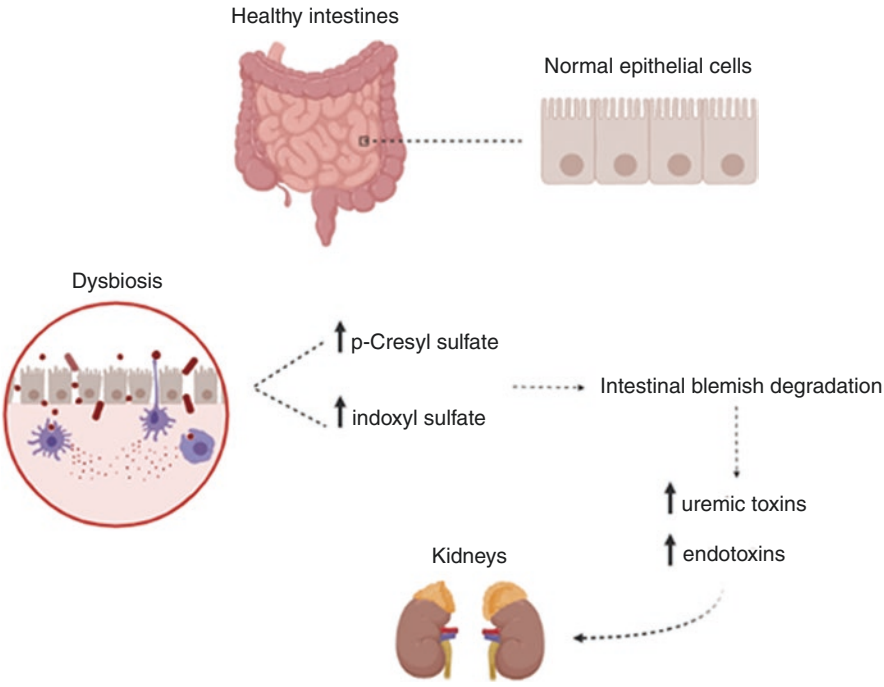

Fig. 6.1 Connection between gut microbiota and chronic kidney disease

contribute to renal inflammation via the circulation. In addition, there is an increase in plasma levels of the soluble plasminogen activator urokinase receptor (suPAR), caused in the early phase and progression of CKD. The concentration of bacteria and their products in the circulation considerably contributes to chronic low-grade inflammation, which plays a critical role in the maintenance of many chronic non-communicable diseases (NCDs), being hypertension and CKD among them [14]. The results of IS and IPS accumulation include reactive oxygen species production, cardiac fibrosis, inflammation, inflammatory gene expression, activation of the renin-angiotensin-aldosterone system, renal tubular damage, and others [15].

UTs from IS, PCS, and TMAO (trimethylamine *N*-oxide) induce in CKD risk factors such as inflammation, oxidative stress, and fibrosis. Cardiovascular injury is the leading cause of morbidity and mortality in CKD patients, and studies point to dysbiosis as a factor that plays a significant role in this context [1].

6.2.1 Microbiome: An Evolutionary Perspective

In the course of evolution, humans have adapted not only to climatic and environmental conditions but to the food and resources available. Humans have undergone anatomical, physiological, and metabolic changes, mainly due to the availability of food from different regions and climate. Some anthropologists claim that the eating patterns of Paleolithic human ancestors significantly influenced neural expansion, increasing the size of the brain and decreasing the size of the gastrointestinal tract [16–18]. These dietary patterns of pre-agricultural hominin diets are useful for understanding how the current Western diet may predispose modern populations to chronic diseases.

The Paleolithic diet was based on plants, vegetables, animals and fish they hunted, and insects with their by-products, such as honey, quite different from today's diet, based on processed and ultra-processed foods, high in salt and sugars [19]. This Paleolithic nutritional transition to the Western diet, associated with the lack of corresponding genetic adaptations, causes significant deleterious changes in metabolism [20]. With this new Western lifestyle and diet almost everywhere in the world, overweight and chronic diseases are also increasing rapidly in developing countries. Some observed features of this dietary adaptation process include: an increased production of reactive oxygen species and oxidative stress, development of hyperinsulinemia and insulin resistance, low-grade inflammation, and an abnormal activation of the sympathetic nervous system and renin-angiotensin, which play key roles in the development of chronic diseases. This explains the close relationship between obesity and a wide range of comorbidities, such as type 2 diabetes mellitus, cardiovascular disease, and others. Lifestyle changes according to genetic makeup, including diet and physical activity, can help prevent or limit the development of these diseases [21].

Diet as a major modulator of the microbiome has also shaped microbiota profiles throughout human evolution [22]. The microbiota has evolved to achieve homeostasis in the host in response to profound changes in lifestyle, especially in the last

10,000 years [23]. Studies and knowledge of how the microbiome changed during evolution are rare. In an attempt to understand some aspects, Schnorr et al. (2014) explored the Hadza gut microbiota from Tanzania, a modern hunter-gatherer population that lived as Paleolithic humans. This study showed the first map of the composition of the Hadza microbiota that reflects functional adaptation to a foraging lifestyle, with high bacterial diversity and enrichment in fibrolytic microorganisms (such as xylan degrading Prevotella and Treponema), representing adaptations to provide SCFA from their plant-rich diet. However, despite the absence of Bifidobacterium and an enrichment of potential opportunists such as Proteobacteria and Spirochaetes in this population, they have relatively low rates of infectious diseases, metabolic diseases, and nutritional deficiencies compared to other groups established in northern Tanzania [24, 25].

Based on these aspects, the modern paleolithic diet was developed, characterized by the consumption of vegetables, fruits, roots, nuts, seeds, eggs, fish and lean meat, excluding grains, dairy products, oils, cereals, legumes, salt, and refined sugar, and has gained attention for its multiple health benefits [26]. Based on these characteristics, Barone et al. (2019) sought to identify in a small group the effects of the modern paleolithic diet (MPD) on microbiota structure and diversity in Western urban populations. Despite limitations, the findings suggest that MPD may be a means of counteracting the risk of losing the bacterial memory that accompanied our ancestors throughout human evolutionary history. Another important finding was that Paleolithic dietary traits may indeed act synergistically in maintaining the homeostasis of microbial diversity.

Furthermore, the high intake of monounsaturated fatty acids found in MPD suggests that these may play a role in supporting high microbiota diversity, which can be explored in further studies. However, some factors still need to be elucidated, such as how long these benefits will remain, genetic and/or lifestyle factors [27].

Although some studies suggest potential benefits of the modern paleolithic diet in obese patients and those with type 2 diabetes in the medium and long term, by improving insulin sensitivity, glycemic control, and leptin levels and reducing total fat mass and triglyceride levels [28–30], special attention is needed when following a paleolithic diet for a long time because the percentages of macronutrients are far from the nutritional recommendations, until some factors are elucidated in further longitudinal studies and randomized clinical trials, fully evaluating the impact on host health over time. In addition, the presence of some warning signs, such as overrepresentation of bile- and fat-loving microorganisms, requires attention to potential long-term health effects [27].

6.3 Microbiota and Its Implications for Pathologies

The composition of the gut microbiota is influenced by several factors, such as diet, medication use, the intestinal mucosa, psychological and physiological stress, age, the immune system, and the microbiota itself [31]. This change in the quantitative

and qualitative composition of the microbiota resulting in microbial imbalance is called dysbiosis, and this process explains the microbiota–illness relationship [32].

As a consequence, it is possible to observe an increase in intestinal permeability, with the breakdown of the intestinal barrier and the epithelial occlusion zone, causing an increase in the translocation of microorganisms, their metabolites, endotoxins, lipopolysaccharides (LPS) that cause the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), and translocation of other substances into the circulation, providing a low-grade inflammation and deregulation of the immune system [33]. This chronic low-grade inflammation leads to increased systemic levels of bacterial products, insulin resistance, and a concomitant effect on plasma lipids [34].

The increased intestinal permeability and penetration of antigens alter the physiological functions, leading to activation of innate immunity generating inflammation at chronic levels and may be related to the clinical progression of neuropsychiatric diseases, through the gut–brain axis [35]. The gut–brain axis is the ensemble of the enteric nervous system (ENS) and the central nervous system (CNS). This bidirectional connection is maintained by several modulators and can be influenced by external and internal factors that affect the gastrointestinal tract (GI tract) [36]. The gut microbiome has a strong influence on the motor function of the GI tract, as well as on the modulation of the immune system and neuroendocrine intercellular signaling [37].

Other ways that the microbiome interacts with the host is through various metabolites, including short-chain fatty acids, the bile acid pathway, and via the trimethylamine (TMA)/trimethylamine-N-oxide (TMAO) [32]. The microbiome is in intense metabolic activity producing numerous biologically active compounds, which can be transported in the circulation, distributed to various sites and influencing essential biological processes. Furthermore, some endogenous gut endotoxins, such as lipopolysaccharides (LPS), indoxyl sulfate, and p-cresyl sulfate, which are related to important metabolic functions related to atherosclerosis and potentially contribute to the pathogenesis of cardiovascular disease (CVD) as well as chronic kidney disease [38–40].

In the early stages of CKD, the microbiome is dysbiotic. Due to reduced renal function, the high concentration of urea generates a high influx of urea into the gastrointestinal tract, where microbial ureases catalyze the hydrolysis of urea and generate large amounts of ammonia. A byproduct of ammonia, ammonium hydroxide, increases the intestinal pH, causing mucosal irritation and interference with the growth of commensal bacteria, favoring the establishment of intestinal dysbiosis [41]. Dysbiosis favors the growth of microorganisms that possess enzymes capable of generating uremic toxins, such as indoxyl sulfate (IS), *p*-cresyl sulfate (*p*-CS), indole-3-acetic acid (IAA), and trimethylamine *N*-oxide (TMAO), stimulating inflammation and oxidative stress contributing to the progression of kidney damage, as well as increased intestinal permeability and consequent dysregulation of the immune system [42, 43].

GCFAs play an important role in regulating metabolism and inflammation and are involved in health and disease through signaling molecules, including

modulation of autonomic systems and systemic blood pressure, as well as inflammatory responses and other cellular functions. Some of physiological functions include inhibition of histone deacetylases (HDACs), activation of G-protein-coupled receptors (GPCRs), chemotaxis and phagocytosis modulation, induction of reactive oxygen species (ROS), altering cell proliferation and function, altering intestinal barrier integrity, having anti-inflammatory, antitumorigenic, and antimicrobial effects, and altering intestinal integrity. Some GPCRs, particularly GPR43, GPR41, and GPR109A, have been identified as receptors for GCFA [32, 38].

In addition to these mechanisms, there is a relationship between microbiota and TMAO and SCFA, in which some of these metabolites interact with other endocrine hormones, such as ghrelin, leptin, glucagon-like peptide-1 (GLP-1), and YY-PYY peptide4 [44, 45]. SCFAs provide necessary energy for the intestinal epithelium, regulating lipid metabolism and stimulating incretin production. The microbiota transforms choline, L-carnitine, and phosphatidylcholine from the diet into trimethylamine (TMA). In this way, hepatic flavin monooxygenase (mainly FMO3 and FMO1) converts TMA to TMAO [45].

6.4 Microbiota and Its Influence on Therapy

Exploring the diversity of the microbiome requires an evolutionary perspective to fully understand it [46]. Some recent bioinformatic methods for functional metagenomics are used to understand microbial composition and next-generation sequencing that focuses on taxonomic assignments through DNA sequences, allowing previously uncultured bacteria to be identified in order to gain understanding of the "new." Metagenomics refers to a collective genome of microorganisms from an environmental sample that informs the microbial ecosystem. Direct metagenomic sequencing uses a "shotgun" approach to directly compare with reference genomes or gene catalogs, improving taxonomic resolution and allowing the observation of single-nucleotide polymorphisms and other variant sequences with functional capabilities determined by comparing the sequences with functional databases. These microbial nucleic sequences are then used as a proxy to estimate organism identity and the relative abundance of complex microbial communities [32].

With the knowledge of the result of these new technologies undertaken, new therapeutic tools have been developed, such as probiotics, prebiotics, and synbiotics, with important applicability in clinical practice [47]. The World Gastroenterology Organization (WGO) defines probiotics as live microorganisms that, when administered in adequate amounts, have a beneficial effect on the health of the host. Prebiotics are ingredients that are selectively fermented by the gastrointestinal microbiota, causing specific changes in the composition and/or activity of the gastrointestinal microbiota, their growth, activity, or both, providing health benefits to the host. A combination of products containing prebiotics and probiotics is called synbiotics [48].

There is a relationship between the supplementation of probiotics, mainly *Lactobacillus* and *Bifidobacteria*, and significant improvements in mood, anxiety, and state of depression and reductions in cortisol and pro-inflammatory cytokines [49]. Some other beneficial functions have been attributed to *Lactobacillus plantarum* supplementation in intestinal disorders, such as inflammatory bowel diseases, metabolic syndromes, dyslipidemia, hypercholesteremia, obesity and diabetes, and aspects of brain health involving psychological disorders [40].

Next-generation sequencing (NGS) technology is part of a future prospect of integrated sequencing systems for genome and transcriptome exploration that aims to overcome unmet research and clinical challenges, such as in oncology. NGS has enabled the development of new molecular subclassifications of putative clinically meaningful tumor, particularly through gene expression analysis with RNAseq [50]. This has the ability to delineate the phase of variants in the HLA antigen recognition site with non-coding regulatory polymorphisms. These relationships are critical for understanding the qualitative and quantitative implications of HLA gene diversity and provide a rich resource for linking HLA regulatory polymorphisms to their HLA antigen recognition site to understand the specific expression of allotypes and haplotypes and their consequences for disease susceptibility [51].

6.5 Conclusion

Science is breaking new ground with the exploration of the genome and transcriptome in time and space to develop new specific "drugs" and predictive biomarkers for individualized drug-sensitive therapy. This future perspective is essential not only in the production of drugs but also to understand the processes and mechanisms that are involved in the course of pathology.Conflicts of InterestNone.

References

1. Cosola C, Rocchetti M, Sabatino A, et al. Microbiota issue in CKD: how promising are gut-targeted approaches? J Nephrol. 2019;32(1):27–37.
2. Ammirati A. Chronic kidney disease. Rev Assoc Med Bras. 2020;66:s03–9. https://doi.org/10.1590/1806-9282.66.S1.3.
3. Aguiar L, Prado R, Gazzinelli A, Malta D. Fatores associados à doença renal crônica: inquérito epidemiológico da pesquisa nacional de saúde. Rev Bras Epidemiol. 2020;23. https://doi.org/10.1590/1980-549720200044.
4. Requena T, Velasco M. Microbioma humano en la salud y la enfermedad. Rev Clin Esp. 2021;221(4):233–40. https://doi.org/10.1016/j.rce.2019.07.004.
5. Di Renzo L, Gualtieri P, Romano L, et al. Role of personalized nutrition in chronic-degenerative diseases. Nutrients. 2019;11(8):1707. https://doi.org/10.3390/nu11081707.
6. Perez-Muñoz M, Arrieta M, Ramer-Tait A, Walter J. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. Microbiome. 2017;5(1):1–19. https://doi.org/10.1186/s40168-017-0268-4.

7. Schoenmakers S, Steegers-Theunissen R, Faas M. The matter of the reproductive microbiome. Obstet Med. 2019;12:107–15.
8. Ferretti P, Pasolli E, Tett A, et al. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. Cell Host Microbe. 2018;24(1):133–45. https://doi.org/10.1016/j.chom.2018.06.005.
9. Noce A, Marrone G, Di Daniele F, et al. Impact of gut microbiota composition on onset and progression of chronic non-communicable diseases. Nutrients. 2019;11(5):1073. https://doi.org/10.3390/nu11051073.
10. Luca M, Di Mauro M, Di Mauro M. Luca a gut microbiota in Alzheimer's disease, depression, and type 2 diabetes mellitus: the role of oxidative stress. Oxid Med Cell Longev. 2019;2019:4730539. https://doi.org/10.1155/2019/4730539.
11. Nagano T, Otoshi T, Hazama D, et al. Novel cancer therapy targeting microbiome. Onco Targets Ther. 2019;12:3619. https://doi.org/10.2147/OTT.S207546.
12. Knauf F, Brewer J, Flavell R. Immunity, microbiota and kidney disease. Nat Rev Nephrol. 2019;15(5):263–74. https://doi.org/10.1038/s41581-019-0118-7.
13. World Health Organization. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. World Health Organization; 2019.
14. Yang T, Richards E, Pepine C, Raizada M. The gut microbiota and the brain–gut–kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol. 2018;14(7):442–56. https://doi.org/10.1038/s41581-018-0018-2.
15. Pereira M, Gouveia F. Modulação intestinal:fundamentos e estratégias práticas. 1st ed. Brasília; 2019.
16. Otten J, Ryberg M, Mellberg C, et al. Postprandial levels of GLP-1, GIP and glucagon after 2 years of weight loss with a paleolithic diet: a randomised controlled trial in healthy obese women. Eur J Endocrinol. 2019;180(6):417–27. https://doi.org/10.1530/EJE-19-0082.
17. Ghaedi E, Mohammadi M, Mohammadi H, et al. Effects of a paleolithic diet on cardiovascular disease risk factors: a systematic review and meta-analysis of randomized controlled trials. Adv Nutr. 2019;10(4):634–46.
18. Churuangsuk C, Griffiths D, Lean M. Impacts of carbohydrate-restricted diets on micronutrient intakes and status: a systematic review. Obes Rev. 2019;20(8):1132–47. https://doi.org/10.1111/obr.12857.
19. Challa H, Bandlamudi M, Uppaluri K. Paleolithic diet. Treasure Island, FL: StatPearls; 2020. https://www.ncbi.nlm.nih.gov/books/NBK482457. Accessed 1 Dec 2021.
20. Dufour D, Piperata B. Reflections on nutrition in biological anthropology. Am J Phys Anthropol. 2018;165(4):855–64. https://doi.org/10.1002/ajpa.23370.
21. Kopp W. How western diet and lifestyle drive the pandemic of obesity and civilization diseases. Diabetes Metab Syndr Obes. 2019;12:2221. https://doi.org/10.2147/DMSO.S216791.
22. Requena T, Martínez-Cuesta M, Peláez C. Diet and microbiota linked in health and disease. Food Funct. 2018;9(2):688–704. https://doi.org/10.1039/C7FO01820G.
23. Rampelli S, Schnorr S, Consolandi C, et al. Metagenome sequencing of the Hadza hunter-gatherer gut microbiota. Curr Biol. 2015;25(13):1682–93. https://doi.org/10.1016/j.cub.2015.04.055.
24. Schnorr S, Candela M, Rampelli S, et al. Microbioma intestinal dos caçadores-coletores de hadza. Nat Commun. 2014;5:3654.
25. Quercia S, Candela M, Giuliani C, et al. From lifetime to evolution: timescales of human gut microbiota adaptation. Front Microbiol. 2014;5:587. https://doi.org/10.3389/fmicb.2014.00587.
26. Jamka M, Kulczyński B, Juruć A, et al. The effect of the paleolithic diet vs. healthy diets on glucose and insulin homeostasis: a systematic review and meta-analysis of randomized controlled trials. J Clin Med. 2020;9(2):296. https://doi.org/10.3390/jcm9020296.
27. Barone M, Turroni S, Rampelli S, et al. Gut microbiome response to a modern paleolithic diet in a western lifestyle context. PLoS One. 2019;14(8):e0220619. https://doi.org/10.1371/journal.pone.0220619.

28. Jonsson T, Granfeldt Y, Ahren B, et al. Beneficial effects of a paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. Cardiovasc Diabetol. 2009;8:35. https://doi.org/10.1186/1475-2840-8-35.
29. Mellberg C, Sandberg S, Ryberg M, et al. Long-term effects of a palaeolithic-type diet in obese postmenopausal women: a 2-year randomized trial. Eur J Clin Nutr. 2014;68(3):350–7.
30. Otten J, Stomby A, Waling M, et al. Benefits of a paleolithic diet with and without supervised exercise on fat mass, insulin sensitivity, and glycemic control: a randomized controlled trial in individuals with type 2 diabetes. Diabetes Metab Res Rev. 2017;33(1):e2828. https://doi.org/10.1002/dmrr.2828.
31. Weiss G, Hennet T. Mechanisms and consequences of intestinal dysbiosis. Cell Mol Life Sci. 2017;74(16):2959–77. https://doi.org/10.1007/s00018-017-2509-x.
32. Tang W, Bäckhed F, Landmesser U, Hazen S. Gut microbiota in cardiovascular health and disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(16):2089–105.
33. Tilg H, Zmora N, Adolph T, Elinav E. The gut microbiota fueling metabolic inflammation. Nat Rev Immunol. 2020;20(1):40–54. https://doi.org/10.1038/s41577-019-0198-4.
34. Pushpanathan P, Mathew G, Selvarajan S, et al. Gut microbiota and its mysteries. Indian J Med Microbiol. 2019;37(2):268–77. https://doi.org/10.4103/ijmm.IJMM_19_373.
35. Sochocka M, Donskow-Łysoniewska K, Diniz B, et al. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease—a critical review. Mol Neurobiol. 2019;56(3):1841–51. https://doi.org/10.1007/s12035-018-1188-4.
36. Ristov I, Vaz I, Guimarães V, et al. Relação do eixo intestino-cérebro e suas influências no corpo. Anais da Mostra de Saúde. 2017. http://anais.unievangelica.edu.br/index.php/medicina/article/view/154. Accessed 1 Dec 2021.
37. Zorzo R. Impacto do microbioma intestinal no eixo cérebro-intestino. Int J Nutrol. 2017;10:S298–305. https://doi.org/10.1055/s-0040-1705652.
38. Tang W, Hazen S. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest. 2014;124(10):4204–11. https://doi.org/10.1172/JCI72331.
39. Tang W, Kitai T, Hazen S. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183–96. https://doi.org/10.1161/CIRCRESAHA.117.309715.
40. Liu W, Tomino Y, Lu K. Impacts of indoxyl sulfate and p-cresol sulfate on chronic kidney disease and mitigating effects of AST-120. Toxins. 2018;10(9):367. https://doi.org/10.3390/toxins10090367.
41. Andrade L, Ramos C, Cuppari L. The cross-talk between the kidney and the gut: implications for chronic kidney disease. Forum Nutr. 2017;42(1):1–14. https://doi.org/10.1186/s41110-017-0054-x.
42. Deltombe O, Van Biesen W, Glorieux G. Exploring protein binding of uremic toxins in patients with different stages of chronic kidney disease and during hemodialysis. Toxins. 2015;7(10):3933–46. https://doi.org/10.3390/toxins7103933.
43. Mikusic N, Kouyoumdzian N, Choi M. Gut microbiota and chronic kidney disease: evidences and mechanisms that mediate a new communication in the gastrointestinal-renal axis. Pflügers Arch Eur J Physiol. 2020;472(3):303–20. https://doi.org/10.1007/s00424-020-02352-x.
44. Ryan K, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014;509(7499):183–8. https://doi.org/10.1038/nature13135.
45. Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab. 2015;22(2):228–38. https://doi.org/10.1016/j.cmet.2015.07.009.
46. Davenport ER, Sanders JG, Song SJ, Amato KR, Clark AG, Knight R. The human microbiome in evolution. BMC Biol. 2017;15(1):1–12. https://doi.org/10.1186/s12915-017-0454-7.
47. Gómez-López A. Microbiome, health and illnesses: probiotics, prebiotics and synbiotics. Biomedica. 2019;39(4):617–21.
48. Guarner F, Sanders M, Eliakim R, et al. Diretrizes Mundiais da Organização Mundial de Gastroenterologia. Milwaukee, WI: World Gastroenterology Organisation; 2017.

49. Long-Smith C, O'Riordan K, Clarke G, et al. Microbiota-gut-brain axis: new therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2020;60:477–502. https://doi.org/10.1146/annurev-pharmtox-010919-023628.
50. Kyrochristos I, Ziogas D, Goussia A. Bulk and single-cell next-generation sequencing: individualizing treatment for colorectal cancer. Cancer. 2019;11(11):1809. https://doi.org/10.3390/cancers11111809.
51. Petersdorf E, O'hUigin C. The MHC in the era of next-generation sequencing: implications for bridging structure with function. Hum Immunol. 2019;80(1):67–78. https://doi.org/10.1016/j.humimm.2018.10.002.