Review Article

THE INTESTINAL MICROBIOME AS A NOVEL THERAPEUTIC TARGET IN THE INTEGRATED MANAGEMENT OF CARDIO-RENAL-METABOLIC SYNDROME

Irida Kecaj[1], Ergita Nelaj[1], Ilir Gjermeni[1], Kei Xhixhabesi[2], Ina Refatllari[3], Sonila Gozhita[4], Margarita Gjata[1]

[1]Department of Internal Medicine, University Hospital Center ”Mother Teresa”, Tirana, Albania.
[2] Mediterranean University of Albania, Tirana, Albania.
[3]Department of Cardiology, University Hospital Center ”Mother Teresa”, Tirana, Albania.
[4]Department of Internal Medicine, Hygeia Hospital, Tirana, Albania

Correspondent E-mail: irida.kecaj@yahoo.com.

ABSTRACT

The group of cardio-renal-metabolic diseases, encompassing chronic kidney disease, obesity, type 2 diabetes mellitus, atherosclerotic cardiovascular diseases, and heart failure, represents a significant global health challenge, contributing substantially to the increasing burden of morbidity and cardiovascular mortality.

In recent years, considerable attention has been directed toward the relationship between the intestinal microbiota and the host organism, as studies have revealed the essential metabolic role of the intestinal microbiome and its impact on immune dysregulation within the gastrointestinal tract. The intestinal microbiome functions as an endocrine organ, producing bioactive metabolites such as short chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and bile acids, which directly and indirectly influence inflammation, metabolic function, and intestinal barrier integrity. Furthermore, the microbiome modulates immunological and hormonal mechanisms of the host, mediating bidirectional communication between the gut and key organs, including the heart, kidneys, and metabolic systems.

This review examines the intricate relationships between the intestinal microbiome, the cardiovascular system, renal function, and metabolism. It highlights the critical roles of the gut cardiovascular, gut renal, and gut metabolic axes in the pathogenesis and progression of multisystem diseases encompassed within the cardio-reno-metabolic syndrome, while also discussing innovative therapeutic strategies. Modulation of the intestinal microbiome represents a promising opportunity for the prevention and personalized management of metabolic diseases and their cardiovascular and renal complications, thereby addressing a critical global public health concern.

Keywords: Intestinal microbiome, microbial metabolites, dysbiosis, cardio-renal-metabolic syndrome, therapeutic targets.

MIKROBIOMA E ZORRËS SI NJË OBJEKTIV I RI TERAPEUTIK NË MENAXHIMIN E INTEGRUAR TË SINDROMËS KARDIO-RENO-METABOLIKE

ABSTRAKT

Grupi i sëmundjeve kardio-reno-metabolike, që përfshin Sëmundjen Kronike të Veshkave, Obezitetin, Diabetin Mellitus tip 2, Sëmundjen Kardiovaskulare Aterosklerotike dhe Insuficiencën Kardiake, përbën një sfidë të rëndësishme globale shëndetësore, duke kontribuar në rritjen e barrës së sëmundshmërisë dhe vdekshmërisë kardiovaskulare.

Në vitet e fundit, lidhja ndërmjet mikrobiotës intestinale dhe organizmit pritës ka tërhequr vëmendje të konsiderueshme, pasi studimet kanë evidentuar rolin metabolik thelbësor të mikrobiomës intestinale si dhe efektet e saj në disbalancimin imun të traktit gastrointestinal. Mikrobioma intestinale vepron si një organ endokrin, duke prodhuar metabolitë bioaktivë si acide yndyrore me zinxhir të shkurtër (SCFA), trimetilaminë N-oksid (TMAO) dhe acide biliare, të cilët ndikojnë në mënyrë direkte dhe indirekte në inflamacion, funksionin metabolik dhe integritetin e barrierës intestinale. Gjithashtu, mikrobioma ndikon në mekanizmat imunologjikë dhe hormonalë të organizmit, duke ndërmjetësuar komunikimin bidireksional mes zorrëve dhe organeve kryesore si zemra, veshkat dhe sistemi metabolik.

Në këtë përmbledhje, analizohen ndërveprimet komplekse midis mikrobiomës intestinale, sistemit kardiovaskular, funksionit renal dhe metabolizmit. Artikulli thekson rëndësinë e boshtit zorrë - sistem kardiovaskular, boshtit zorrë - veshka dhe boshtit zorrë – metabolizëm, si rrugë kyçe në patogjenezën dhe progresionin e sëmundjeve multisistemike brenda sindromës kardio-reno-metabolike, si dhe eksploron qasjet terapeutike inovative. Modifikimi i mikrobiomës intestinale paraqet një mundësi premtuese për parandalimin dhe menaxhimin e personalizuar të sëmundjeve metabolike dhe ndërlikimeve të tyre kardiovaskulare dhe renale, duke adresuar kështu një problematikë kritike në shëndetin publik global.

Fjalë kyçe: Mikrobioma intestinale, metabolitë mikrobiomikë, disbioza, sindroma kardio-reno-metabolike, objektiva terapeutike.

INTRODUCTION

Cardiovascular Kidney Metabolic (CKM) syndrome affects multiple organ systems, contributing to complications such as kidney failure, cognitive decline, MASLD, sleep apnea, and increased cancer risk (1). However, its greatest impact is on cardiovascular disease (CVD), which drives most of the associated morbidity and premature mortality (1). CKM disrupts vascular integrity, promotes atherogenesis, and impairs myocardial function, leading to higher risks of coronary heart disease, stroke, heart failure, peripheral artery disease, atrial fibrillation, and sudden cardiac death (1, 2). Since 2008, the AHA and NHLBI have promoted the term “Cardio Reno Metabolic Syndrome” to highlight the need for integrated management of cardiovascular, renal, and metabolic diseases (3). In October 2023, the AHA officially recognized “Cardiovascular Kidney Metabolic Syndrome” as a unified clinical entity, emphasizing the shared pathophysiology of heart disease, kidney disease, type 2 diabetes, and obesity, and urging a reassessment of current strategies for cardiovascular risk prediction and prevention (1). CKM syndrome is stratified into five progressive stages: stage 0, absence of CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, presence of metabolic risk factors such as hypertriglyceridemia, hypertension, diabetes mellitus, and metabolic syndrome; stage 3, subclinical cardiovascular disease within the CKM context; and stage 4, manifest clinical cardiovascular disease in CKM syndrome (1). Importantly, the current classification excludes the liver, an organ central to metabolic dysfunction. MASLD, and its progressive form MASH, are strongly associated with insulin resistance and obesity, and directly affect cardiovascular and renal health. Thus, we propose expanding the framework to Cardiovascular Kidney Hepatic Metabolic (CRHM) syndrome to better capture these inter-organ interactions (4).

In Albania, as in many other countries, this syndrome is an increasing public health challenge due to the high rates of cardiovascular, renal, and metabolic diseases. Implementing an integrated, multidisciplinary approach to CKM/CRHM syndrome management offers hope for better treatment outcomes and preventive measures across these interconnected disease areas. Recent research highlights the crucial role of the intestinal microbiota in host metabolism and immune regulation. Beyond maintaining health, it contributes to the development of diseases such as hypertension, atherosclerosis, heart failure, chronic kidney disease, type 2 diabetes, and obesity (5, 6). The gut microbiota is a diverse and dynamic community of trillions of microbes, bacteria, viruses, fungi, and archaea that inhabit the gastrointestinal tract (7). It supports host health through digestion, vitamin synthesis, and immune modulation (8). Metabolically, it processes nutrients via two main pathways: saccharolytic fermentation of carbohydrates into SCFAs, and proteolytic fermentation of proteins into SCFAs and potentially harmful byproducts like ammonia and indoles, especially relevant in kidney dysfunction (9). Acting like an endocrine organ, the gut microbiome communicates with the host via immune pathways and both metabolite-dependent and independent mechanisms. Key microbial products, such as TMAO, SCFAs, and bile acids, regulate various physiological processes, underscoring the microbiome’s central role in systemic health and disease (5).

Pathophysiological Impact of the Microbiome and Its Metabolites in Cardio-reno-Metabolic Diseases

The gut microbiota varies significantly between individuals, influenced by environmental factors, genetics, and lifestyle. It includes archaea, bacteria, and eukarya, with bacteria mainly *Firmicutes* and *Bacteroidetes* making up over 90% of the population (10). Advances in sequencing and bioinformatics have enabled deeper insight into these microbes and their roles in cardiometabolic disease (11). The gut microbiota influences systemic health through complex signaling pathways. Microbial molecules like LPS and peptidoglycans cross the intestinal barrier and activate innate immunity via pattern recognition receptors (PRRs). When gut barrier integrity is impaired, these signals can also affect vascular endothelial cells directly (12). Beyond structural components, microbiota affects distant organs through bioactive metabolites like TMA/TMAO, SCFAs, and bile acids (13, 14). These metabolites interact with hormones such as ghrelin, leptin, GLP-1, and PYY, and influence the parasympathetic nervous system, thereby regulating glucose homeostasis and metabolic syndrome pathways (15). Cardio-renal-metabolic (CKM) syndrome involves intertwined metabolic, cardiovascular, and renal dysfunctions, manifesting as hypertension, heart failure, dyslipidemia, abdominal obesity, insulin resistance, hyperglycemia, hyperuricemia, and chronic kidney disease.

Gut Microbiota and Hypertension

Hypertension is the leading modifiable risk factor for cardiovascular disease and a key clinical target. Evidence shows that the gut microbiota significantly regulates blood pressure: germ-free animals exhibit higher blood pressure, highlighting the microbiota's role (16). In angiotensin II–induced hypertensive mice show gut dysbiosis characterized by reduced diversity and increased Firmicutes/Bacteroidetes ratio (17). Antibiotics have lowered blood pressure in resistant hypertension patients, indicating a microbial influence (18). Additionally, higher levels of butyrate-producing *Odoribacter* are linked to lower blood pressure in overweight pregnant women (19). Microbial metabolites like short-chain fatty acids (SCFAs) regulate blood pressure by interacting with host G protein-coupled receptors such as GPR41 and Olfr78. Olfr78 activation causes vasoconstriction and raises blood pressure, while GPR41 promotes vasodilation and lowers it (20). The gut microbiota also influences vascular regulation by modulating enteric and sympathetic nervous systems, affecting neuronal signaling and lymphocyte movement in the gut (21). Therapeutically, probiotics, particularly strains within the genus *Lactobacillus*, have demonstrated beneficial effects in blood pressure reduction, as evidenced by recent meta-analytical data (22).

Microbiota-Driven Mechanisms in Atherosclerosis and Ischemic Heart Disease

Both intestinal and oral microbiota contribute to atherosclerosis and cardiovascular disease (CVD). Bacterial DNA has been found in atherosclerotic plaques, supporting a microbial role in plaque formation and stability (11). Patients with unstable plaques show altered fecal microbiota, including reduced *Roseburia*, increased pro-inflammatory peptidoglycan production, and lower anti-inflammatory carotenoids (23). Animal studies reveal that gut microbiota affects infarct size and cardiac function, with probiotics like *Lactobacillus plantarum* and *L. rhamnosus* GR-1 providing cardioprotection by reducing hypertrophy and preventing heart failure (24). A key mechanism involves microbial metabolism of dietary choline and carnitine into trimethylamine (TMA), which the liver converts to trimethylamine N-oxide (TMAO). High plasma TMAO levels are linked to increased risks of myocardial infarction, stroke, and sudden cardiac death, with the highest quartile showing a 2.5-fold greater incidence of major cardiovascular events over three years, independent of other risk factors (14, 25). TMAO also promotes plaque instability, rupture, and thrombosis by affecting platelet calcium signaling (26). Targeting microbial enzymes to lower TMAO is a promising therapeutic approach in CVD (27).

Gut Microbiota and Heart Failure

The gut hypothesis of heart failure postulates that diminished cardiac output and systemic congestion lead to ischemia and edema of the intestinal mucosa. This compromised intestinal barrier function facilitates bacterial translocation and elevates circulating endotoxin levels, thereby perpetuating chronic systemic inflammation in heart failure patients. Clinical evidence indicates that individuals with heart failure accompanied by peripheral edema exhibit increased endotoxin concentrations and heightened inflammatory cytokine levels, both of which are significantly reduced following diuretic therapy. Additionally, these patients display alterations in intestinal microbiota composition alongside increased intestinal permeability (28). The microbial metabolite trimethylamine N-oxide (TMAO) is markedly elevated in patients with heart failure and serves as a prognostic biomarker independent of conventional risk factors, correlating with an increased risk of clinical deterioration and mortality (14, 28). Experimental studies utilizing animal models have demonstrated that a choline-enriched diet elevates TMAO levels and exacerbates ventricular remodeling, myocardial fibrosis, and progression of heart failure via activation of the TGF-β/Smad3 signaling pathway (27). Nonetheless, the therapeutic potential of targeting microbial TMA production to mitigate heart failure development or improve clinical outcomes in humans remains to be conclusively determined.

Gut Microbiota and Dyslipidemia

Emerging evidence demonstrates that the gut microbiota plays a mechanistic role in modulating host lipid profiles, showing associations with serum triglycerides and high-density lipoprotein (HDL) cholesterol levels, independently of body mass index and underlying metabolic conditions (28, 29). Microbial metabolites, notably secondary bile acids, regulate lipid and glucose metabolism via activation of nuclear and membrane receptors such as the farnesoid X receptor (FXR) and G protein-coupled receptor 131 (GPR131). Additionally, trimethylamine N-oxide (TMAO) exerts proatherogenic effects by impairing cholesterol transport and disrupting bile acid metabolism (29). Furthermore, hepatic genetic modulation of flavin-containing monooxygenase 3 (FMO3), the enzyme responsible for TMA oxidation, significantly influences plasma lipid metabolism and circulating lipid concentrations, underscoring its critical role in maintaining lipid homeostasis (30).

Gut Microbiota and Obesity and Type 2 Diabetes Mellitus (T2DM)

The gut microbiota plays a critical role in the pathophysiology of obesity, type 2 diabetes mellitus (T2DM), and metabolic regulation through the production of key metabolites, including short-chain fatty acids (SCFAs) and bile acids (BAs). Alterations in the microbial community, characterized by an increased Firmicutes-to-Bacteroidetes ratio and a reduction in butyrate-producing bacteria, have been consistently associated with obesity and T2DM (31). SCFAs mediate their effects via G protein-coupled receptors GPR41 and GPR43, modulating inflammatory responses, glucose homeostasis, and secretion of hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (31). Concurrently, microbiota-mediated metabolism of bile acids influences host energy balance by activating the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), with dysregulated bile acid profiles linked to insulin resistance and obesity (28, 32). Notably, bariatric surgery induces significant modifications in both the gut microbiota composition and bile acid pools, which contribute to improvements in glucose and lipid metabolism. Moreover, fecal microbiota transplantation from post-bariatric surgery patients to murine models has demonstrated protective effects against adiposity gain (28, 32).

Gut Microbiota and Hyperuricemia

The intestinal microbiota plays a pivotal role in purine metabolism and the regulation of serum uric acid levels. Gut microorganisms produce key enzymes such as uricase, allantoinase, and allantoicase, which facilitate the degradation of uric acid and reduce purine absorption within the intestinal tract, thereby mitigating the progression of hyperuricemia. Additionally, intestinal urate transporters, including ATP-binding cassette sub-family G member 2 (ABCG2) and glucose transporter 9 (GLUT9) are modulated by commensal gut bacteria and are crucial for uric acid secretion and homeostasis. This interplay underscores a significant mechanistic link between the gut microbiome and the pathogenesis of hyperuricemia (33).

Gut Microbiota and Chronic Kidney Disease

Chronic kidney disease (CKD) is frequently accompanied by dysbiosis of the intestinal microbiota, which contributes to increased production of ammonia via microbial urease activity. This ammonia production compromises the integrity of the intestinal epithelial barrier, facilitating translocation of uremic toxins and bacterial DNA into systemic circulation, thereby exacerbating systemic inflammation (28,34). Among the microbial-derived toxins, indoxyl sulfate and p-cresyl sulfate are particularly noteworthy due to their association with cardiovascular complications and insulin resistance; these toxins accumulate as a result of impaired renal clearance and are poorly removed by conventional dialysis modalities (34). A principal source of indoxyl sulfate is the enzymatic activity of tryptophanases expressed by intestinal Bacteroides species, with modulation of these bacteria significantly impacting systemic toxin levels. Additionally, trimethylamine N-oxide (TMAO), another gut microbiota-derived metabolite, accumulates in CKD patients and correlates with disease progression and elevated mortality risk (28, 35). Collectively, these findings highlight the intestinal microbiota and its metabolites as promising therapeutic targets in CKD management, complementing advancements in dialysis techniques (28).

Gut Microbiota and the Potential for Novel Therapeutic Interventions

Advances in understanding the role of the gut microbiota have stimulated considerable interest in harnessing its therapeutic potential for disease management. Given the microbiota's influence on multiple physiological systems, modulating its composition presents a promising strategy to prevent or ameliorate various disorders. Consequently, numerous clinical studies are investigating approaches aimed at microbiota manipulation to improve metabolic and cardiovascular health (Figure 1).

- **Gut Microbiota-Modifying Preparations: Evaluating the Effects of Probiotics, Prebiotics, and Symbiotics on Metabolic Health**

Prebiotics, probiotics, and symbiotics represent distinct but complementary strategies to modulate the intestinal microbiota. Prebiotics non-digestible fermentable fibers such as inulin and fructooligosaccharides promote the growth of beneficial microbial populations and have demonstrated positive effects on insulin resistance. Probiotics, primarily composed of bacterial genera *Lactobacillus* and *Bifidobacterium*, have shown efficacy in stabilizing glucose metabolism in patients with type 2 diabetes mellitus. However, challenges related to the viability of probiotics during gastrointestinal transit necessitate advanced delivery methods, such as microencapsulation, to enhance their therapeutic potential. Symbiotics, which combine probiotics with prebiotics, aim to facilitate the colonization and metabolic activity of beneficial microbes and are under investigation as promising agents for diabetes and metabolic disease management (36).

- **Fecal Microbiota Transplantation**

Fecal microbiota transplantation (FMT) involves the transfer of fecal material from healthy donors to recipients to restore a balanced microbial ecosystem. While FMT is established in treating recurrent *Clostridioides difficile* infections with cure rates exceeding 80%, emerging evidence suggests its potential utility in cardiometabolic diseases. Allogeneic FMT from metabolically healthy donors to obese patients with metabolic syndrome has been shown to enhance hepatic and peripheral insulin sensitivity independent of weight loss. This intervention also increases microbiota richness and diversity, notably boosting populations of butyrate-producing bacteria such as *Roseburia*, which are linked to improved glucose homeostasis. Despite these promising outcomes, concerns about safety persist, including the risk of transmitting endotoxins or pathogens, warranting caution and further research. An alternative under consideration involves transplantation of defined microbial consortia rather than whole fecal material to mitigate these risks (37).

- **Bacteriophages**

Bacteriophages, viruses that specifically infect bacteria, offer a targeted approach to modulate the microbiota and treat antibiotic-resistant infections by lysing pathogenic bacterial cells without disrupting the host's microbial environment. Nonetheless, bacterial resistance mechanisms including CRISPR-Cas systems and spontaneous mutations can limit phage efficacy. Furthermore, the acidic gastric environment may impair phage viability, necessitating precise identification of bacterial targets and optimized delivery systems for clinical effectiveness (38).

- **Genetic Modification of Intestinal Bacteria**

Recent advances in genetic engineering have enabled the development of modified probiotics capable of delivering therapeutic molecules. Engineered bacterial strains have been employed experimentally to treat conditions such as colitis, diabetes, obesity, and infectious diseases. For instance, *Lactobacillus jannaschii* has been genetically altered to express cyanovirin-N, a protein that reduced simian immunodeficiency virus infection by up to 63% in rhesus monkeys. Additional engineered therapies include bacterial expression of synthetic immunoregulatory proteins and targeted protein delivery systems, representing innovative avenues in microbiome-based treatment modalities (39).

- **Psychobiotics**

Psychobiotics, encompassing probiotics, prebiotics, postbiotics, and symbiotics, modulate the gut-brain axis and exert effects on mental health. These agents operate via immunoregulatory pathways, neuroendocrine signaling, and vagal nerve stimulation to influence emotional and cognitive processes, while also attenuating inflammation associated with depression. Psychobiotics show therapeutic promise for neurodegenerative and psychiatric disorders, although robust clinical trials are necessary to validate their efficacy and safety in human populations (40).

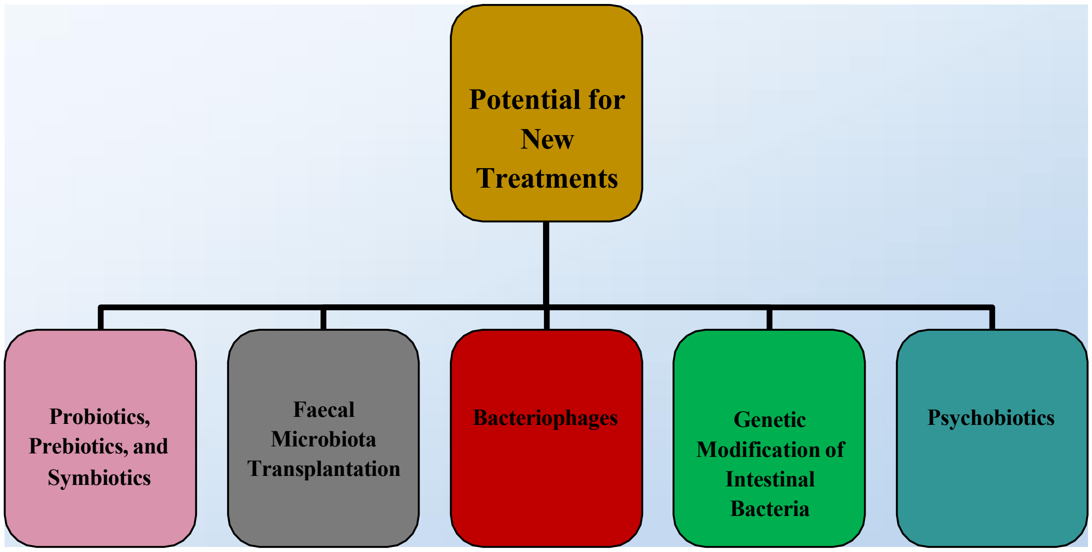

Figure 1. Gut microbiota and the potential for new treatments

Current Limitations in Understanding and Therapeutic Challenges

Although strong links exist between gut microbiota, microbial metabolites, and cardiovascular disease (CVD), definitive mechanistic proof of a causal role in atherosclerosis and its complications remains limited. Many studies, including antibiotic trials and fecal microbiota transplants, lack precise identification of the responsible microbes, metabolites, and molecular pathways. Bridging these gaps requires integrative mechanistic research alongside large prospective cohorts to clarify causality and inform targeted microbiota-based therapies.

Therapeutic modulation of microbiota shows promise but faces challenges such as identifying effective bacterial strains for complex diseases, accounting for disease phenotype and location, and addressing variable clinical responses. Most evidence stems from animal models, with human translational relevance still uncertain.

Advancing mechanistic understanding and therapeutic accuracy requires sophisticated in vitro models like chemostats that mimic native microbial ecosystems. However, microbiota-based therapies, especially those using genetically modified organisms (GMOs), raise safety and regulatory concerns—such as horizontal gene transfer and ecological risks from environmental release. Containment methods, including auxotrophic bacterial strains unable to survive outside the host, help mitigate these risks. Bacteriophage therapies also face challenges like functional loss and need careful adaptation to host environments. These complexities highlight the need for strong collaboration between researchers and regulators to develop frameworks ensuring safe, effective, and ethical use of microbiota-targeted treatments.

CONCLUSIONS AND RECOMMENDATIONS FOR THE FUTURE

Extensive research in animals and humans shows that intestinal microbiota profoundly impacts health and disease development. Culture-independent methods reveal the microbiome's complexity and diverse bacterial metabolites, which regulate key physiological processes. These metabolites and their host receptors offer promising targets for treating cardiometabolic diseases. Modulating microbiota through diet, probiotics, prebiotics, or enzyme inhibitors can beneficially influence host metabolism. Future personalized medicine may use microbial metabolite levels as biomarkers to tailor therapies, similar to glucose or cholesterol monitoring. These strategies offer promising advances in preventing, diagnosing, and treating cardiometabolic syndromes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

REFERENCES

1. Ndumele CE, Neeland IJ, Tuttle KR, et al.; American Heart Association. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023; 148(20):1636-1664. https://doi.org/10.1161/CIR.0000000000001186

2. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010. https://doi.org/10.1161/CIR.0000000000000973

3. Whaley-Connell A, Sowers JR. Basic science: Pathophysiology: cardiorenal metabolic syndrome. J Am Soc Hypertens. 2014 Aug;8(8):604-6. doi: 10.1016/j.jash.2014.07.003. Epub 2014 Jul 5. PMID: 25151323; PMCID: PMC4170524.
4. Theodorakis N, Nikolaou M. From Cardiovascular-Kidney-Metabolic Syndrome to Cardiovascular-Renal-Hepatic-Metabolic Syndrome: Proposing an Expanded Framework. Biomolecules. 2025 Feb 2;15(2):213. doi: 10.3390/biom15020213. PMID: 40001516; PMCID: PMC11853431.
5. Lai Y, Zhu Y, Zhang X, Ding S, Wang F, Hao J, Wang Z, Shi C, Xu Y, Zheng L, Huang W. Gut microbiota-derived metabolites: Potential targets for cardiorenal syndrome. Pharmacol Res. 2025 Apr;214:107672. doi: 10.1016/j.phrs.2025.107672. Epub 2025 Feb 24. PMID: 40010448.
6. Ezenabor EH, Adeyemi AA, Adeyemi OS. Gut Microbiota and Metabolic Syndrome: Relationships and Opportunities for New Therapeutic Strategies. Scientifica (Cairo). 2024 Jul 15;2024:4222083. doi: 10.1155/2024/4222083. PMID: 39041052; PMCID: PMC11262881.

7. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 2016 Aug 19;14(8):e1002533. doi: 10.1371/journal.pbio.1002533. PMID: 27541692; PMCID: PMC4991899.
8. Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. Curr Opin Gastroenterol. 2015 Jan;31(1):69-75. doi: 10.1097/MOG.0000000000000139. PMID: 25394236; PMCID: PMC4290017.
9. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D. Gut microbiome in chronic kidney disease: challenges and opportunities. Transl Res. 2017 Jan;179:24-37. doi: 10.1016/j.trsl.2016.04.007. Epub 2016 Apr 30. PMID: 27187743; PMCID: PMC5086447.
10. Turroni F, Ribbera A, Foroni E, van Sinderen D, Ventura M. Human gut microbiota and bifidobacteria: from composition to functionality. Antonie Van Leeuwenhoek. 2008 Jun;94(1):35-50. doi: 10.1007/s10482-008-9232-4. Epub 2008 Mar 13. PMID: 18338233
11. Ott SJ, El Mokhtari NE, Musfeldt M, Hellmig S, Freitag S, et.al.. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. Circulation. 2006 Feb 21;113(7):929-37. doi: 10.1161/CIRCULATIONAHA.105.579979. PMID: 16490835.
12. Larsson E, Tremaroli V, Lee YS, Koren O, Nookaew I, Fricker A, Nielsen J, Ley RE, Bäckhed F. Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88. Gut. 2012 Aug;61(8):1124-31. doi: 10.1136/gutjnl-2011-301104. Epub 2011 Nov 23. PMID: 22115825; PMCID: PMC3388726.
13. Pluznick JL, Protzko RJ, Gevorgyan H, Peterlin Z, Sipos A, Han J, Brunet I, Wan LX, Rey F, Wang T, Firestein SJ, Yanagisawa M, Gordon JI, Eichmann A, Peti-Peterdi J, Caplan MJ. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. Proc Natl Acad Sci U S A. 2013 Mar 12;110(11):4410-5. doi: 10.1073/pnas.1215927110. Epub 2013 Feb 11. PMID: 23401498; PMCID: PMC3600440.
14. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013 Apr 25;368(17):1575-84. doi: 10.1056/NEJMoa1109400. PMID: 23614584; PMCID: PMC3701945.
15. Tremaroli V, Karlsson F, Werling M, Ståhlman M, Kovatcheva-Datchary P, Olbers T, Fändriks L, le Roux CW, Nielsen J, Bäckhed F. 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 Aug 4;22(2):228-38. doi: 10.1016/j.cmet.2015.07.009. PMID: 26244932; PMCID: PMC4537510.
16. Honour J. The possible involvement of intestinal bacteria in steroidal hypertension. Endocrinology. 1982 Jan;110(1):285-7. doi: 10.1210/endo-110-1-285. PMID: 7053989.

17. Adnan S, Nelson JW, Ajami NJ, Venna VR, Petrosino JF, Bryan RM Jr, Durgan DJ. Alterations in the gut microbiota can elicit hypertension in rats. Physiol Genomics. 2017 Feb 1;49(2):96-104. doi: 10.1152/physiolgenomics.00081.2016. Epub 2016 Dec 23. PMID: 28011881; PMCID: PMC5336599.
18. Qi Y, Aranda JM, Rodriguez V, Raizada MK, Pepine CJ. Impact of antibiotics on arterial blood pressure in a patient with resistant hypertension - A case report. Int J Cardiol. 2015 Dec 15;201:157-8. doi: 10.1016/j.ijcard.2015.07.078. Epub 2015 Jul 30. PMID: 26301638; PMCID: PMC4711349.
19. Gomez-Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Dekker Nitert M; SPRING Trial Group. Increased Systolic and Diastolic Blood Pressure Is Associated With Altered Gut Microbiota Composition and Butyrate Production in Early Pregnancy. Hypertension. 2016 Oct;68(4):974-81. doi: 10.1161/HYPERTENSIONAHA.116.07910. Epub 2016 Aug 15. PMID: 27528065.
20. Evans JM, Morris LS, Marchesi JR. The gut microbiome: the role of a virtual organ in the endocrinology of the host. J Endocrinol. 2013 Aug 28;218(3):R37-47. doi: 10.1530/JOE-13-0131. PMID: 23833275.
21. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, Shenoy V, Cole-Jeffrey CT, Lobaton GO, Stewart DC, Rubiano A, Simmons CS, Garcia-Pereira F, Johnson RD, Pepine CJ, Raizada MK. Hypertension-Linked Pathophysiological Alterations in the Gut. Circ Res. 2017 Jan 20;120(2):312-323. doi: 10.1161/CIRCRESAHA.116.309006. Epub 2016 Oct 31. PMID: 27799253; PMCID: PMC5250568.
22. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension. 2014 Oct;64(4):897-903. doi: 10.1161/HYPERTENSIONAHA.114.03469. Epub 2014 Jul 21. PMID: 25047574.
23. Karlsson FH, Fåk F, Nookaew I, Tremaroli V, Fagerberg B, Petranovic D, Bäckhed F, Nielsen J. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat Commun. 2012;3:1245. doi: 10.1038/ncomms2266. PMID: 23212374; PMCID: PMC3538954.
24. Lam V, Su J, Hsu A, Gross GJ, Salzman NH, Baker JE. Intestinal Microbial Metabolites Are Linked to Severity of Myocardial Infarction in Rats. PLoS One. 2016 Aug 9;11(8):e0160840. doi: 10.1371/journal.pone.0160840. PMID: 27505423; PMCID: PMC4978455.
25. Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WH. Trimethylamine N-Oxide and Mortality Risk in Patients With Peripheral Artery Disease. J Am Heart Assoc. 2016 Oct 19;5(10):e004237. doi: 10.1161/JAHA.116.004237. PMID: 27792653; PMCID: PMC5121520.
26. Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, Li L, Fu X, Wu Y, Mehrabian M, Sartor RB, McIntyre TM, Silverstein RL, Tang WHW, DiDonato JA, Brown JM, Lusis AJ, Hazen SL. Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. Cell. 2016 Mar 24;165(1):111-124. doi: 10.1016/j.cell.2016.02.011. Epub 2016 Mar 10. PMID: 26972052; PMCID: PMC4862743.

27. Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, Gu X, Huang Y, Zamanian-Daryoush M, Culley MK, DiDonato AJ, Fu X, Hazen JE, Krajcik D, DiDonato JA, Lusis AJ, Hazen SL. Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis. Cell. 2015 Dec 17;163(7):1585-95. doi: 10.1016/j.cell.2015.11.055. PMID: 26687352; PMCID: PMC4871610.
28. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circ Res. 2017 Mar 31;120(7):1183-1196. doi: 10.1161/CIRCRESAHA.117.309715. PMID: 28360349; PMCID: PMC5390330.
29. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013 May;19(5):576-85. doi: 10.1038/nm.3145. Epub 2013 Apr 7. PMID: 23563705; PMCID: PMC3650111.
30. Shih DM, Wang Z, Lee R, Meng Y, Che N, Charugundla S, Qi H, Wu J, Pan C, Brown JM, Vallim T, Bennett BJ, Graham M, Hazen SL, Lusis AJ. Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis. J Lipid Res. 2015 Jan;56(1):22-37. doi: 10.1194/jlr.M051680. Epub 2014 Nov 6. PMID: 25378658; PMCID: PMC4274068.
31. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, et.al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012 Oct 4;490(7418):55-60. doi: 10.1038/nature11450. Epub 2012 Sep 26. PMID: 23023125.**32.** Fava S. Glucagon-like peptide 1 and the cardiovascular system. *Curr Diabetes Rev*. 2014;*10*:302–310.
32. Kohli R, Bradley D, Setchell KD, Eagon JC, Abumrad N, Klein S. Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. J Clin Endocrinol Metab. 2013 Apr;98(4):E708-12. doi: 10.1210/jc.2012-3736. Epub 2013 Mar 1. PMID: 23457410; PMCID: PMC3615197.
33. Yamada N, Iwamoto C, Kano H, Yamaoka N, Fukuuchi T, Kaneko K, Asami Y. Evaluation of purine utilization by Lactobacillus gasseri strains with potential to decrease the absorption of food-derived purines in the human intestine. Nucleosides Nucleotides Nucleic Acids. 2016 Dec;35(10-12):670-676. doi: 10.1080/15257770.2015.1125000. PMID: 27906630.
34. Shi K, Wang F, Jiang H, Liu H, Wei M, Wang Z, Xie L. Gut bacterial translocation may aggravate microinflammation in hemodialysis patients. Dig Dis Sci. 2014 Sep;59(9):2109-17. doi: 10.1007/s10620-014-3202-7. Epub 2014 May 15. PMID: 24828917.
35. Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, Li XS, Levison BS, Hazen SL. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res. 2015 Jan 30;116(3):448-55. doi: 10.1161/CIRCRESAHA.116.305360. Epub 2014 Nov 5. PMID: 25599331; PMCID: PMC4312512.

36. Perraudeau F, McMurdie P, Bullard J, Cheng A, Cutcliffe C, Deo A, Eid J, Gines J, Iyer M, Justice N, Loo WT, Nemchek M, Schicklberger M, Souza M, Stoneburner B, Tyagi S, Kolterman O. Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation. BMJ Open Diabetes Res Care. 2020 Jul;8(1):e001319. doi: 10.1136/bmjdrc-2020-001319. PMID: 32675291; PMCID: PMC7368581.
37. Ianiro G, Maida M, Burisch J, Simonelli C, Hold G, Ventimiglia M, Gasbarrini A, Cammarota G. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: A systematic review and meta-analysis. United European Gastroenterol J. 2018 Oct;6(8):1232-1244. doi: 10.1177/2050640618780762. Epub 2018 Jun 3. PMID: 30288286; PMCID: PMC6169051.
38. Weynberg KD, Jaschke PR. Building Better Bacteriophage with Biofoundries to Combat Antibiotic-Resistant Bacteria. Phage (New Rochelle). 2020 Mar 1;1(1):23-26. doi: 10.1089/phage.2019.0005. Epub 2020 Feb 25. PMID: 36147618; PMCID: PMC9041446.
39. Lagenaur LA, Sanders-Beer BE, Brichacek B, Pal R, Liu X, Liu Y, Yu R, Venzon D, Lee PP, Hamer DH. Prevention of vaginal SHIV transmission in macaques by a live recombinant Lactobacillus. Mucosal Immunol. 2011 Nov;4(6):648-57. doi: 10.1038/mi.2011.30. Epub 2011 Jul 6. PMID: 21734653; PMCID: PMC3433722.
40. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015 Apr 9;161(2):264-76. doi: 10.1016/j.cell.2015.02.047. Erratum in: Cell. 2015 Sep 24;163:258. PMID: 25860609; PMCID: PMC4393509.