



REVIEW ARTICLE

Personalized microbiome-based approaches to metabolic syndrome management and prevention

Highlights

- The microbiome plays pivotal roles in the pathogenesis of multiple manifestations of metabolic syndrome (MetS). Understanding the molecular mechanisms driving these effects will constitute an exciting challenge of microbiome research in the coming decade.
- As such, decoding how altered host–microbiome interactions effect MetS will enable the development of microbiome-targeting approaches as means of personalized treatment of MetS.

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Abstract

Personalized or precision medicine is a novel clinical approach targeted to the individual patient and based on integration of clinical, genetic, and environmental factors that define a patient uniquely from other individuals featuring similar clinical symptoms. Such a personalized medicine approach is increasingly applied for diagnosis, clinical stratification, and treatment of metabolic syndrome (MetS)-associated risks and diseases, including obesity, type 2 diabetes, non-alcoholic fatty liver disease, and their complications. One emerging factor that governs MetS manifestations is the microbiome, the composition, function, growth dynamics, associated metabolite profile and diverse effects of which on host immune and metabolic systems can all significantly affect metabolic homeostasis. Interindividual differences in microbiome composition and function, as well as personal variations in microbial-derived products, pave the way towards microbiome-based personalized medicine in treating MetS-related diseases.

Keywords: metabolic syndrome, microbiome, personalized medicine.

Introduction**Metabolic syndrome and personalized medicine**

In recent years modern medicine has shifted rapidly from classical approaches focusing on disease-centered diagnosis and treatment paradigms to a more individually tailored approach termed “personalized medicine.” Personalized or precision medicine is defined as treatment targeted to the individual patient on the basis of genetic, phenotypic, biomarker-based, and possibly environmental and psychological factors that distinguish one patient from others with similar clinical characteristics.¹ One example for conditions in which precision medicine has been proposed as a therapeutic approach is the metabolic syndrome (MetS), a group of co-associated diseases including obesity, insulin resistance, type 2 diabetes (T2D), cardiovascular disease and non-alcoholic fatty

liver disease (NAFLD).² Common risk factors predispose to these diseases and, in fact, each of these MetS diseases is considered a risk factor for the others. Common risk factors for features of MetS include abdominal obesity, hyperglycemia, hypertension, elevated triglyceride levels, and low high-density lipoprotein cholesterol levels.² The prevalence of MetS is increasing globally and estimated to encompass around 25%–35% of the adult population worldwide,² highlighting the need for controlling the risk factors, development, and progression of MetS-linked diseases.

Limited efficacy of global dietary recommendations in MetS

In obese individuals, weight loss can improve glycemic control, lower blood pressure, and normalize cholesterol levels.³ Consequently, a change of dietary habits

(mostly a reduction in caloric intake) is probably the most commonly prescribed strategy for the prevention and treatment of MetS. Nevertheless, obese individuals who successfully complete weight-loss diets often regain weight,^{4–6} rendering the long-term efficacy of current recommended diet regimens questionable and disappointing.

In addition to facilitating weight loss, diet plays an important role in maintaining healthy glucose homeostasis.^{7,8} Diets aimed at preventing and treating hyperglycemia often take into account the meal carbohydrate content⁹ and the glycemic index (GI),¹⁰ which estimates the postprandial glycemic response (PPGR) to specific food items. Nevertheless, the ability of such diets to aid in controlling glucose levels showed mixed results in several randomized trials.¹¹ Several caveats of the GI may contribute to this inconsistency, including the difficulty in determining the GI of real-life meals containing multiple food items with different GIs, and poor predictive accuracy of GI in diabetic individuals.

An important limitation of global dietary recommendations is the sole consideration of food intrinsic properties, such as the GI. For example, Vega-López et al.¹² reported significant interindividual variation in the PPGR to white bread. Such person-to-person variation in the PPGR to an identical food, as well as to several other test foods, was also reported by Vrolix and Mensink.¹³ In a recent study on 800 participants, marked differences were found in PPGRs to standardized and real-life meals, with many participants exhibiting different responses to the same food, in contrast with the previously expected and reported GI values.¹⁴ These findings question the applicability of global dietary recommendations based solely on the properties of food as dietary guidelines for individuals and may explain the limited efficacy of such approaches in reducing or maintaining weight across human populations. Thus, understanding the factors that drive interindividual differences in responses to food is crucial for improving personalized dietary management and prevention of MetS. As is highlighted in the following sections, some of the interindividual variability in human MetS manifestations and response to treatment may be associated with interindividual differences in the gut microbiome. Understanding these microbial variations and how they contribute to disease manifestations may help in the development of potential personalized treatment for MetS.¹⁴

The microbiome in MetS

Interindividual differences in the risk of developing MetS, disease manifestations, and responses to diet and medical treatment are often ascribed to human genetics

and lifestyle. In addition to these factors, the composition of the microbiome also exhibits considerable variability in human population,¹⁵ stemming from several determinants, including diet,^{16–18} age,¹⁹ and host genetics.²⁰ The composition of the microbiome and its association with the host can affect various physiological functions and play a pivotal role in numerous diseases, including metabolic diseases^{21,22} (Fig. 1). Seminal studies by Jeffrey Gordon's group showed that the gut microbiome is different in obese compared with lean people and rodents^{23,24} and that its interaction with the host can significantly affect the development of obesity.^{24,25} Follow-up studies have since shown an association and contribution of microbial dysbiosis to other MetS-related diseases, such as T2D,²⁶ NAFLD,^{27,28} and atherosclerosis.^{29,30} Beyond a description of bacterial community composition and disease association, microbiome research is moving towards mechanistic elucidation of the molecular pathways and metabolites activated and produced by the microbial community, as well as characterization of their effects on host MetS-related manifestations. These studies are performed via a combination of multi-omics next-generation sequencing, metabolomics techniques,¹⁴ and experimentation in gnotobiotic mouse models. Together, these studies are aimed at identifying bacterial communities and host changes at the level of microbial species, gene, transcript, and metabolite abundances. These analyses may help develop, in coming years, a new precision medicine approach for diagnosing and treating MetS-related pathologies.³¹

Metabolic consequences of interindividual variations in the microbiome

The gut microbiome features a high interindividual variability in community composition, function, and interaction with the host, all potentially bearing an influence on variable MetS features in different individuals. As such, the microbiome may be considered as a personal trait contributing to individual susceptibility to develop discrete MetS complications, yet this notion has only been addressed by a limited number of studies. As noted above, one recent study aimed at personally tailoring diets that may maintain a normal-range PPGR found considerable variation in interindividual PPGR to identical real-life and standardized meals.¹⁴ When dissecting the factors that contributed to this variation, microbiome composition and function emerged as important drivers, with positive associations noted between levels of multiple commensal members and pathways and inadequate glycemic responses.¹⁴ Considering these findings, it seems unlikely that global dietary

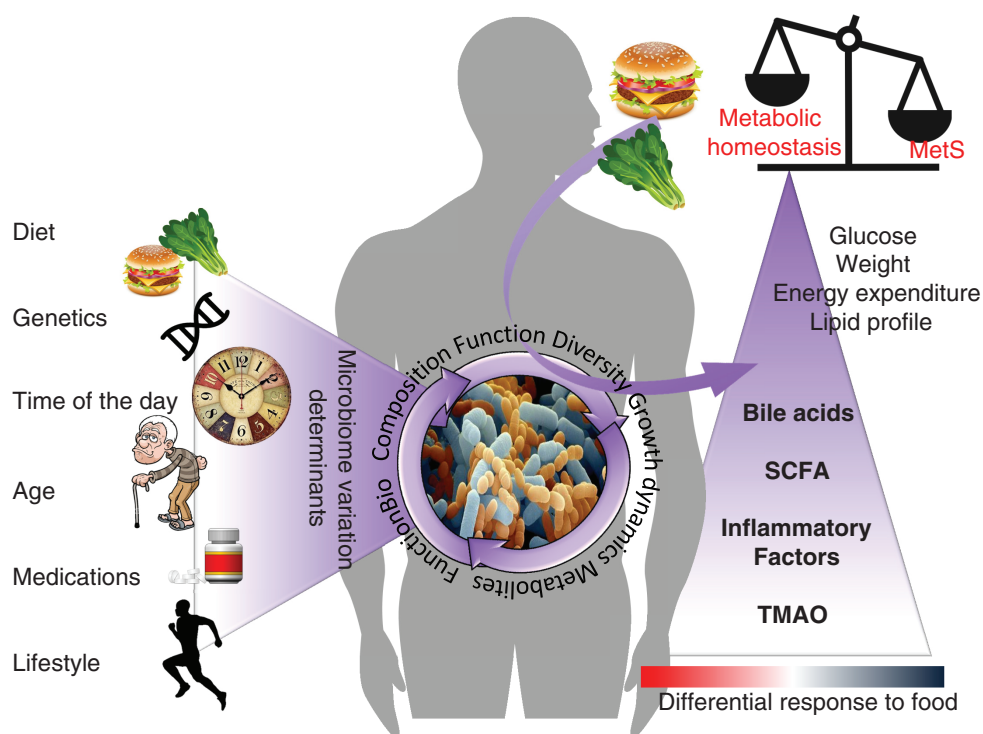


Figure 1 Variations in the microbiome mediate differential effects of the environment on metabolic homeostasis. Multiple host and environmental factors contribute to interindividual variations in the microbiome. This, in turn, leads to a person-specific microbiome regulation of metabolic homeostasis. SCFA, short-chain fatty acids; TMAO, trimethylamine-*N*-oxide; MetS, metabolic syndrome.

recommendations aimed at preventing and treating MetS complications would be useful to the entire population; rather, they may be beneficial to defined human subgroups, ineffective in others, and may even be harmful to some. In one of our group's studies,¹⁴ a computational algorithm based on clinical metadata, PPGR of reported meals, and microbiome composition and function produced a suggested personalized diet individually tailored to the study participants. The diets designed by the algorithm were successfully validated in a cohort of 26 participants, mostly prediabetic individuals. Importantly, the "good" diets of some participants were "bad" for others.¹⁴

Additional support for the importance of the microbiome when considering diets beneficial for glucose homeostasis can be found in the study of Kovatcheva-Datchary et al.³² who found improvement in glycemic response following consumption of barley kernel bread (BKB) in a subset of individuals whose microbiomes were characterized by high levels of the genus *Prevotella*. The importance of the microbiome in mediating the beneficial effects of BKB was demonstrated by assessing glucose tolerance in germ-free (GF) mice transplanted with microbiome from human responders

to BKB or with *Prevotella copri*. Functional analysis of the microbiome suggested that *Prevotella* may exert its beneficial effects by contributing enzymes facilitating metabolism of the dietary fiber in BKB, and increasing glycogen storage.³²

In addition to mediating the beneficial effects of food choices on human health, certain microbial compositions may exert individualized negative effects on their host in response to dietary stimuli. One such example is consumption of non-caloric artificial sweeteners (NAS), leading to perturbed microbiome composition, thereby promoting MetS in several studies in rodents.^{33–35} Some of these perturbations in microbiome composition and function had a causative role in promoting metabolic derangements³⁴ and, in humans, the ability of NAS to promote glucose intolerance was affected by the host microbiome. Validation of these findings in larger human cohorts may enable determination of which individuals may benefit from NAS, in contrast with those who should avoid them.

Personalized aspects of the microbiome in MetS expand beyond the scope of glucose homeostasis. In obese and overweight subjects, dietary intervention in obesity was reported to be more beneficial in subjects

who had high microbial gene richness.³⁶ Adding to the complexity is the finding that not only does the composition, function, and richness of the microbiome play a role in disease, but that the growth dynamics of the bacteria in the gut are also associated with MetS, and dietary changes may exert differential effects on these human dynamics.³⁷

Atherosclerosis, another diet-mediated condition, is closely associated with multiple risk factors and conditions comprising MetS and may lead to devastating complications, including ischemic heart disease, heart failure, and cerebrovascular disease. Like other manifestations of MetS, atherosclerosis was suggested to be affected by interindividual microbiome differences. Microbial metabolism of L-carnitine^{29,38} and phosphatidylcholine,³⁹ nutrients abundant in animal products and specifically red meat, produces trimethylamine-*N*-oxide (TMAO), a proatherogenic species. The production of TMAO by the microbiome was dependent on the diet (omnivorous vs vegan or vegetarian) and its associated microbiome configuration. This suggests that recommendations for dietary modification in individuals suffering atherosclerosis would potentially modulate the microbiome composition, thereby affecting disease pathogenesis.

Effects of mechanisms implicated in gut microbiome on MetS

Despite many associations implicating gut microbes in whole-body metabolic responses and MetS-related morbidities, the underlying mechanisms are exceptionally complex and currently elusive. Emerging data suggest that inflammation and microbial-derived metabolites, such as short-chain fatty acids (SCFAs) and bile acids, may significantly affect MetS-related disorders and disease progression.

Microbial-derived metabolites

Metabolites produced, degraded, or modulated by the microbiota serve as “communication channels” by which the host and its microbiome signal to each other.^{40,41} Changes in bacterial metabolites contribute to several MetS-related risks and pathologies.^{30,42} Although the best-studied metabolites include SCFAs, bile acids, and trimethylamines (TMAs), many other metabolites may come into play and significantly affect host metabolism. Although the existence of interindividual differences in microbiome composition is well established, much less is known about person-to-person metabolomics variability, stemming from individual differences in diet, host genetics, and the microbiome.⁴³

Short-chain fatty acids

Short-chain fatty acids, including acetate, propionate, and butyrate, are produced by bacterial fermentation of polysaccharides in the gastrointestinal tract.⁴⁴ Short-chain fatty acids may play a role in the maintenance of body weight, intestinal homeostasis, and improved lipid and glucose metabolism.^{42,45–47} Most studies in obese humans and rodents suggest that elevated SCFA levels combined with enriched pathways for generating SCFAs are correlated with an increased capacity to harvest energy.^{25,48,49} In most animal studies, SCFA dietary supplementation improved MetS manifestations by reducing weight gain, improving insulin sensitivity, and lowering triglycerides.^{45,50–52}

Colonic epithelial cells use SCFAs produced by the bacteria as an energy source.^{53,54} The beneficial effects of propionate and butyrate on energy expenditure and glucose homeostasis may possibly derive from increased secretion of intestinal incretins such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1).^{55,56} Chambers et al.⁵⁵ tested the effects of inulin-propionate ester in overweight people and found that acute administration of propionate decreased weight gain, abdominal adiposity, fatty liver, and insulin resistance and significantly increased postprandial PYY and GLP-1.

Short-chain fatty acids are ligands for the G-protein-coupled receptors GPR41, GPR43, and GPR109a expressed in colonic epithelium, pancreatic β -cells, adipose tissues, and other tissues.⁵⁷ Mice lacking GPR41 were leaner with reduced expression of the gastric incretin PYY.⁵⁸ Acetate and propionate are potent ligands for GPR43, and GPR43-deficient mice fed a high-fat diet (HFD) gained more weight with increased MetS-related complications.⁵⁹ Antibiotics or germ-free (GF) conditions abrogated the metabolic phenotypes of GPR41- and GPR43-null mice, suggesting that bacterial SCFAs induce GPR43 and GPR41 activation, controlling whole-body energy and glucose homeostasis.⁵⁸

The response of the host to SCFAs can also be mediated via glucose sensing by the gut–brain axis. De Vadder et al.⁴⁵ showed that propionate sensing in the colon induced intestinal gluconeogenesis, which was sensed by the gut–brain neural circuit and led to improved glucose and weight control. Perry et al.⁵¹ recently found that HFD-fed rats exhibited increased incorporation of acetate in the colon, and that chronic administration of acetate caused obesity-associated MetS complications. In that study, acetate infusion led to parasympathetic excitation stimulating β -cell insulin secretion.⁵¹ Although most of the above studies indicate a beneficial role for SCFAs in energy and glucose homeostasis, larger human studies are needed to elucidate possible personalization in the SCFA response.

Understanding personalized responses to SCFAs may enable the development of SCFA supplementation as a novel individualized or generalized treatment modality for MetS manifestations.

Bile acids

Bile acids are produced primarily by hepatic cholesterol catabolism and are transported into the gallbladder and the intestinal lumen by postprandial peristalsis.^{60–62} The microbiome at the distal small intestine and colon can transform primary bile acids into secondary bile acids.^{60–62} Mice treated with antibiotics or GF mice feature low concentrations of secondary bile acids, with an altered expression profile of genes involved in bile acid conjugation and reabsorption indicating that the gut microbiota is responsible for bile acid synthesis, diversity, and possibly host epithelial uptake.^{63–65} In addition to the role of bile acids in facilitating dietary fat digestion, they are now recognized as participating in the regulation of metabolic homeostasis.^{66,67} As such, some bile acids have shown promising initial results in the treatment of MetS disorders such as insulin resistance, hypercholesterolemia, and NAFLD.^{67,68}

Most of the physiological effects of bile acids are mediated by the G-protein-coupled receptor TGR5 and the nuclear receptor farnesoid X receptor (FXR), which is a transcription factor that controls the endogenous synthesis and release of bile acids, with FXR activation resulting in inhibition of hepatic bile acids biosynthesis.^{63,69} Obese and insulin-resistant mice exhibited decreased gut microbiota diversity, accompanied by a reduction in secondary bile acids and hepatic enzymes involved in bile acid biosynthesis, with increased FXR and decreased TGR5 expression.⁷⁰ Activation of TGR5 by bile acids led to improved insulin sensitivity, whereas binding of bile acids to FXR resulted in lowered cholesterol and reduced liver and serum triglycerides.⁶⁷

Experiments in GF and antibiotic-treated mice suggest that the microbiome may modulate FXR and FXR-related genes that control bile acid synthesis.^{63,64,71} Intestinal FXR-deficient mice fed an HFD exhibited decreased weight gain, glucose intolerance, and insulin resistance and were protected against the development of fatty liver.^{72,73} Blocking intestinal FXR by administration of an FXR antagonist modified bile acid composition and promoted differentiation of white adipose to thermogenic brown tissue (also termed “adipose tissue browning”), and decreased obesity and insulin resistance.⁷⁴ Ryan et al.⁷⁵ found that the beneficial effects of bariatric surgery on metabolism, including improvement in glucose tolerance, were associated with changes in gut microbiota and were diminished in

FXR-null mice. Together, all these animal studies pointed towards a dominant role for the gut microbiota in regulating bile acid diversity and FXR signaling, which, in turn, regulates MetS complications.

Obese humans followed after bariatric surgery featured long-term changes in their gut microbiome independent of body mass index. Yet, the causal connection between gut microbiota, bile acid production and signaling, the pathogenesis of MetS-related disorders, and potential perturbation of these pathways as modes of MetS treatment merit further investigation in prospective human trials.

Trimethylamines

Trimethylamine is a metabolite generated by microbial metabolism of L-carnitine derived from red meat and by conversion of phosphatidylcholine derived from cheese and eggs. Trimethylamine is carried to the liver by portal circulation where it is converted into TMAO by flavin mono-oxygenases (FMOs). It has been found that TMAO is proatherogenic and associated with the development of coronary heart disease³⁸ and thrombosis³⁰ in mice and humans. Mice treated with antibiotics or GF mice had undetectable or levels of TMA and TMAO,²⁹ GF mice placed in conventional cages under specific pathogen-free (SPF) conditions (termed conventionalized mice) featured increased levels of TMAO, indicating an obligatory role of the microbiota in TMAO production.²⁹ Correspondingly, mice treated with antibiotics or GF mice fed with L-carnitine or phosphatidylcholine diets had a lower number of atherosclerotic lesions, reduced accumulation of foam cells, and a lower number of hyperactive platelets.^{29,30} An essential role for the gut microbiota in generating TMAO was further confirmed in human subjects treated with L-carnitine or phosphatidylcholine and antibiotics, driving a near complete suppression of TMAO.^{29,39} These interesting, and potentially clinically important, direct roles of TMAO in the development and progression of cardiovascular diseases merit further prospective studies.

Microbiota modulation of inflammation

Obesity, insulin resistance, atherosclerosis, and steatohepatitis are all MetS disorders associated with inflammation. Adipose tissue inflammation is mostly studied in the context of obesity and T2D, where it contributes to disease pathogenesis and involves both innate and adaptive immune responses.⁷⁶ Although microbial-derived endotoxins (e.g. lipopolysaccharide [LPS]) were detected in T2D patients and in obese and insulin-resistant mice, leading to augmented adipose and systemic inflammation,^{77,78} the role of microbiota-driven

adipose tissue inflammation in MetS complications remains unclear.^{79,80} Diet may play a major role in determination of the effects of the microbiome on MetS-associated inflammation. Mice fed a lard diet exhibited induction of adipose Toll-like receptor (TLR) immune signaling and inflammation, with increased serum LPS and adiposity.⁸¹ The metabolic effect was transferrable to GF mice, whereas gut microbiota from fish-oil diet-fed mice given to lard-fed mice counteracted the metabolic phenotype, suggesting that diet has a major effect on microbial composition, which, in turn, modulates adipose tissue inflammation and adiposity.⁸¹

Similarly, a key link was suggested between intestinal inflammation, gut microbial alterations, and NAFLD.⁸² In one study, mice deficient in inflammasome signaling exhibited changes in gut microbiota composition that aggravated hepatic steatosis, driven by massive influx into the portal circulation of TLR4 and TLR9 agonists, ultimately leading to increased hepatic tumor necrosis factor (TNF)- α secretion and resulting in hepatic damage and inflammation.⁸² The metabolic effects were transferable by cohousing, suggesting an important cross-talk between gut microbes and host in NAFLD progression. Another study⁸³ showed that the bile acid taurine controls microbiome composition, leading to activation of Nod-like receptor 6 (NLRP6) inflammasome. Mice treated with taurine exhibited amelioration of colitis and the effect depended on the microbiome and inflammasome activation.⁸³ The effects of taurine on metabolic complications remain to be determined.

Together, these observations may point towards the microbiota as a potential new therapeutic target, with microbiome changes, or supplementation or inhibition of microbiome-associated metabolite signaling, used as part of a personalized MetS treatment approach. Such treatment may potentially enable modification of host adipose and mucosal inflammation, thereby affecting metabolic homeostasis and the risk of MetS diseases.

Summary and future perspectives: from personal microbiome to personalized treatments

The potential contribution of the microbiome to MetS pathogenesis and clinical manifestations, coupled with its plasticity, make the microbiome an appealing therapeutic target for the diagnosis and treatment of features of MetS. However, key limitations currently preclude the widespread incorporation of microbiome characterization and modification into the diagnosis and treatment schemes for MetS. First, the microbiome is highly variable between individuals. As such, accurate

characterization of the microbiome in an individual is often confounded by compositional changes induced by medications,⁸⁴ age,⁸⁵ and even the time of the day at which a sample is collected.⁸⁶ Specifically, the importance of considering medication use as a potential confounder in microbiome analysis of MetS patients was recently demonstrated by Forslund et al.,⁸⁷ who reported a confounding effect of metformin (an antidiabetic drug) in two reports characterizing the “diabetic microbiome” in human patients.^{26,88} In addition, diet itself is a potent driver of changes to the microbiome,^{89,90} a feature that is also observed in personalized nutritional interventions.^{14,32} This may compromise long-term microbiome-based nutritional recommendations and necessitate repeated periodic sampling and adjustment of dietary recommendations based on a patient’s updated dietary routine and associated microbiome configuration. Finally, the microbiome is only one factor affecting personalized response to diet, thus requiring its integration into multivariable prediction algorithms that include multiple host and environmental variables; only a combination of these person-specific measurements may enable adequate personalized dietary recommendations to be devised.

In addition, when developing means of microbiome modulation as modifying treatment for features of MetS, unrelated microbiome-mediated effects on host health should be taken into consideration. As one example, several studies have demonstrated a beneficial role for a higher microbial biodiversity (alpha diversity) in maintaining healthy body weight and glucose homeostasis,^{91,92} whereas reduced diversity is associated with a variety of disease states, such as inflammatory bowel disease. Distinct dietary habits, associated with specific microbial configurations,¹⁷ may reduce biodiversity in some individuals. As such, certain dietary recommendations may potentially contribute to reduced microbial diversity, putatively associated with some disease risks. Thus, microbiome-based tailoring of individualized diets should not only consider how the microbiome mediates the effect of food on host metabolism, but also how the diet may affect microbial biodiversity and consequently other features of host health.

Nutritional interventions

Dietary modifications are considered key to the prevention and treatment of features of MetS. Recent studies^{14,32} indicate that this approach may yield superior long-lasting results if individually tailored. Integration of personalized microbiome parameters in the diagnosis of and dietary planning for individuals predisposed to or suffering from MetS is considered an appealing new

avenue of clinical research, yet it is still in its infancy.⁹³ Questions remain as to the long-term efficacy of this approach, which merits prospective human-based studies.

Fecal microbiome transplantation

Fecal microbiome transplantation (FMT) is based on transferring a microbiome purified from the feces of a healthy donor to an individual with a microbiome-associated condition (e.g. obesity or diabetes), in which the “transplanted” microbiome may correct or replace the pathological one. One promising proof-of-concept study using FMT in MetS demonstrated that microbiome transplanted from lean donors to obese individuals improved the recipients’ insulin sensitivity, accompanied by changes in their microbiome, including expansion of butyrate producers.⁹⁴ The efficiency of this approach in treating the multiple conditions that underlie MetS remains to be validated in additional long-term clinical studies. One potential caveat to this approach is the unclear ability of the transplanted microbiome to alter the composition of the existing, pathological microbiome. It is possible that factors driving microbial dysbiosis in a given individual, such as host genetics and lifestyle, will persist even after FMT and resist or revert the microbial changes induced by FMT back towards the diseased configuration.

Probiotics and prebiotics

Rather than transplanting an entire microbial community, a more specific microbial-based approach involves supplementation of the diet with a limited number of viable bacterial strains (probiotics) or using nutrients such as non-digestible carbohydrates that promote the growth of so-called “beneficial” endogenous bacteria (prebiotics). Despite great public interest and extensive research, the efficacy of pre- and probiotics in promoting health benefits remains questionable, and there is currently no clinical indication for their consumption. In mice, supplementation with probiotic strains of *Lactobacillus* and/or *Bifidobacteria* was suggested to have beneficial effects on the onset and progression of both type 1 diabetes and T2D.^{95,96} In humans, some studies demonstrated beneficial effects of probiotics on MetS, but this effect was not uniformly reproducible,⁹⁷ and in some studies a controversial link was even suggested to exist between the consumption of probiotics and weight gain.⁹⁸ Considering this significant variability in clinical results, it is possible that, like with the response to diets, humans exhibit interindividual variability in their responses to probiotics. In turn, this individualized response may be dependent on variations in the

microbiome, and the ability of the supplemented bacterial strains or nutrients to positively alter the resident microbial community. Thus, additional studies in healthy individuals, as well as in those with MetS, are required to determine the efficacy, if any, of the use of probiotics and the role of their potential “personalization.”

Microbiome-associated metabolites

Analysis of microbial metabolites in combination with metagenomic analysis of the pathways and genes involved in the metabolism of these metabolites will possibly enable designing personal approaches to treat patients with MetS complications through targeting of metabolites and signaling pathways. We have recently demonstrated that certain pathological microbial communities in mice produce metabolites that modify the host immune system to resist colonization by an exogenous microbiome.⁸³ Given the potential adverse effects of FMT and the substantial interindividual variability in microbiome composition precluding probiotic and prebiotic approaches, an approach based on administration of a microbial metabolite cocktail may circumvent the interindividual microbial differences and thus constitute a safer and more efficient approach for treating MetS. One such example is supplementation of the diet with SCFAs that protected mice from HFD-induced insulin resistance.^{45,50,52} It remains to be determined whether SCFA supplementation has therapeutic potential in humans. Other microbial-derived metabolites currently being tested in humans are bile acids. In preliminary studies, the microbial-derived bile acid obeticholic acid, which is a potent FXR activator that decreases liver fat and fibrosis in mice, improved the histological features of the liver in non-alcoholic steatohepatitis patients.⁶⁸

Similarly, microbiome-modulated metabolites may affect plasma lipid levels and atherosclerosis. As described above, microbial production of TMAs, such as TMAO, derived from red meat is directly linked to the development of atherosclerosis.²⁹ The generation by gut microbiota of secondary bile acids facilitates dietary fat digestion and improves the plasma and liver lipid profile and, indeed, bile acids have been used for the treatment of hypercholesterolemia.⁶⁷ Furthermore, and as described above, microbiota may modulate the immune system, thereby inducing low-grade inflammation, contributing to the development of many MetS-related diseases, including atherosclerosis. Identifying small molecules whose access or deficiency drives these immune-mediated downstream effects may enable the

development of new “post-biotic” metabolite interventions³¹ as treatments for MetS comorbidities.

In summary, the potential modulatory effects of the microbiome on the development and progression of MetS-related diseases make its manipulation a promising therapeutic approach in preventing, ameliorating, or treating the MetS. Analyzing the microbial configuration at the individual level may provide new insights into the specific contributions of the microbiome to person-specific MetS clinical manifestations, enable boosting or predicting individualized responses to medical intervention, and may lead to the development of precision medicine approaches for patients suffering of MetS and its complications.

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Disclosure

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