



Gut microbiome and microbial metabolites: a new system affecting metabolic disorders

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Abstract

Introduction The gut microbiome is emerging as an important player in the field of metabolic disorders.

Materials and methods Currently, several studies are ongoing to determine whether the effect of gut microbiome on obesity, type 2 diabetes, non-alcoholic fatty liver disease, and other metabolic diseases is determined by singular species or rather by a functional role of bacterial metabolism at higher taxonomical level. Deciphering if a single or more species are responsible for metabolic traits or rather microbial metabolic pathways are responsible for effects on host metabolism may help to identify appropriate dietary interventions to support microbial functions according to the prevalent host disease. Furthermore, the combination of metagenomics and metabolomics-based signature might be applied in the future to improve the risk prediction in healthy subjects.

Conclusion In this review, I will summarize the current findings regarding the role of gut microbiome and metabolites in metabolic disorders to argue whether the current achievements may be translated into clinical practice.

Keywords Gut microbiome · Diabetes · Obesity · Metagenomics · Metabolomics

Introduction

Disorders of the gut microbiome have been connected to a multitude of adverse conditions, including obesity, type 2 diabetes, cardiovascular diseases, inflammatory bowel diseases, anxiety, autism, allergies, and autoimmune diseases [1]. This review will first summarize the basis of metabolic dysbiosis emerged from the analysis of the gut microbiome in the last years, and second, it will discuss some important signals used by the gut microbiome to influence host metabolism especially in metabolic disorders.

The human body and vast number of microbial species including bacteria, archaea, viruses, and unicellular eukaryotes co-evolved in a mutualistic fashion. Over the past decade, growing evidence has shown that the composition of the gut microbiota and its activity might be relevant to maintain metabolic homeostasis [1, 2].

Most of the microorganisms live in the gut, where they benefit from receiving constant supplies of nutrients.

Endowed with an immense gene catalog, the gut microbiome profoundly affect human metabolism. First, gut microbiota cooperate to human metabolic pathways, producing essential vitamins (especially the B group); second, gut microorganisms, through fermentation of indigestible carbohydrates, provide the human body with compounds that either are source of energy for the host or activate receptors to coordinate metabolic functions (i.e., short-chain fatty acids and bile acids) [3]. Third, gut microbiota takes part in other relevant physiological processes including regulation of the intestinal mucosal barrier and maturation of the immune system responses to antigens [1].

The gut microbiota in adults is constituted by two major bacterial phyla, *Bacteroidetes* or *Firmicutes*, altogether > 90% of the taxa present in the human gut, with a lower abundance of *Actinobacteria*, *Cyanobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* [2].

Therefore, it is not unexpected that the gut microbiome has been proposed to coordinate individual responses to environmental factors and might play a part in the complex penetrance of certain disorders not completely explained by genetics [4]. In fact, It has been recently hypothesized that loss of the microbiota-host equilibrium may explain the onset of “pre-disease” states [pre-diabetes, pre-hypertension,

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etc.] and thus explain the explosive development of non-communicable chronic diseases (NCDs) such as inflammatory bowel disease, obesity, diabetes, atherosclerosis, and other metabolic/inflammatory disorders [5].

Recent experimental studies suggested that alterations in gut microbial and metabolic composition may be responsible, in part, for induction of systemic chronic inflammation, thus promoting glucose intolerance and cardiovascular disease [6, 7]. For example, both the deregulation of the microbiota-host co-metabolism of bile acids and metabolic endotoxemia may alter glucose tolerance and promote metabolic dysfunction in liver and adipose tissue in experimental models [8–10]. Western style diets, that are typically enriched in saturated fats and deprived of fibers, have been shown to affect the gut microbiota structure with downstream detrimental effects on intestinal permeability, lipid accumulation, and inflammatory state [11, 12].

Conversely, triggering the adaptive immune system with commensal gut bacteria protects against insulin resistance and hyperglycemia, suggesting a possible therapeutic role for probiotics that favor regulation of intestinal immunity to protect against dysbiosis [13].

Gut microbiome and NCDs

Analysis of microbiota communities in human oral, gut, and atherosclerotic plaques from individuals with established atherosclerosis showed a reproducible correlation between cardiovascular disease (CVD) and bacterial pathogens, including *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Helicobacter pylori* and *Aggregatibacter actinomycetemcomitans* [14]. Another study found that *Collinsella* spp. is enriched in subjects with atherosclerosis, while *Eubacterium* spp. and *Roseburia* spp. are more abundant among healthy controls [15]. Finally, research over the past decade has uncovered several key microbial metabolites, such as trimethylamine-*N*-oxide (TMAO), short-chain fatty acids (SCFAs) and secondary bile acids that uniquely affect the progression of CVD [7].

A general consensus exists that also inflammatory bowel disease is associated with compositional and metabolic changes in the intestinal microbiota (dysbiosis) [16]. Increased *Enterobacteriaceae*, particularly some strains of *E. coli* and *Fusobacterium* species as well as reduction in a number of bacterial species, most notably the *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium* genera, may protect the host from mucosal inflammation via release of microbial metabolites such as short-chain fatty acids [17]. Analysis of gut microbiome in patients affected with multiple sclerosis suggested that proinflammatory *Acinetobacter (A.) calcoaceticus* increased, while anti-inflammatory

Parabacteroides (P.) distasonis and *Butyricimonas* decreased [18].

Gut microbiome in metabolic disorders

Morbid obesity, diabetes, and non-alcoholic fatty liver disease are very inter-connected disorders due to the effect of insulin resistance [19] and the gut microbiota [20]. Obesity was the first metabolic disorder, where altered ecology and structure of the gut microbiome were involved [21–24].

Studies in which germ-free mice were transplanted with feces from monozygotic twins discordant for body mass index demonstrate that the implanted gut microbiome transfers most of the metabolic features from the donor. A general scenario in obesity consider an increase in *Firmicutes* as well as loss of *Bacteroidetes*, particularly species such as *Bacteroides* spp. which are able to transfer the lean phenotype in functional experiments. Transplantation of gut microbiome from monozygotic twins discordant for BMI resulted in a transmission of the original phenotype in germ-free mice. Cohousing mice transplanted with either the lean microbiome or the obese microbiome resulted in a prevention of obesity due to the invasion of specific *Bacteroidetes* from the lean microbiome to the obese microbiome. This elegant experiment provided evidence that some species belonging to *Bacteroides* have a significant impact on metabolism. Intriguingly, metagenomics revealed that the acquisition of the lean phenotype was associated with increased expression of genes regulating bacterial metabolism belonging to BCAA degradation pathway, consistently with the reduced cecal levels of BCAA and reduction of BCAA in the host [25].

In type 2 diabetes mellitus a similar adjustment in *Firmicutes/Bacteroidetes* ratio has been proposed [26–28], although it is unclear what is the effect of the interplay among diet, obesity and insulin resistance on these changes [3, 29]. Intestinal bacterial species such as *Roseburia*, *Eubacterium halii* and *Faecalibacterium prausnitzii* are generally decreased, while *Lactobacilli gasseri*, *Streptococcus mutans* and *E. coli* are increased in subjects with type 2 diabetes. Data from metagenome-wide association studies (MGWAS) revealed that the degree of dysbiosis in patients with Type 2 diabetes is moderate when compared with Inflammatory Bowel Disease (IBD). Nevertheless MGWAS confirmed that butyrate-producing bacteria including *Roseburia intestinalis* and *Roseburia inulinivorans* as well as *Clostridiales* are decreased in type 2 diabetes, while opportunistic pathogens such as *Bacteroides caccae*, *Clostridium hathewayi*, *Clostridium ramosum*, and *Clostridium symbiosum* are increased [30]. Interestingly, the application of MGWAS markers

as T2DM classifier reached an AUROC of 0.81, suggesting that gut-microbiota-based T2D index could be used to identify subsets of the population that are at high risk for progressing to clinically defined T2D [30]. A similar approach was tested in Swedish people, where increases in *Lactobacillus* species were correlated with metabolic control markers such as fasting glucose and HbA1c, while decreases in *Clostridium* species were negatively correlated with fasting glucose, HbA1c, insulin, c-peptide and triglycerides and positively with HDL [31]. Intriguingly, a recent metagenomics study suggested that HDL is the most influenced, among several CVD biomarkers, by the gut microbiome [32]. The correlation of *Clostridiales* species with HDL and triglycerides is also suggestive for a role of the gut microbiome in shaping the so-called atherogenic or diabetic dyslipidemia [31].

Other metagenomics studies revealed a major effect of metformin on the gut microbiome. First, a comparison of T2DM patients treated or untreated with metformin with controls and T1DM patients allowed to identify unique characteristics of T2D microbiome independent from metformin or hyperglycemia phenotype. In fact, this study provided evidence that gene richness is decreased in type 2 diabetes, but increased in type 1 diabetes. Interestingly, decrease in *Roseburia* and some *Clostridiales* butyrate producers were reduced in T2D microbiome independently from metformin [33]. A randomized placebo-controlled study revealed that metformin but not calorie restriction had rapid effects on the composition and function of gut microbiota in parallel with improved metabolic control (HbA1c and fasting glucose) [34]. Both studies converge on *Escherichia* and *Intestini bacter* as substrate of metformin although it is unclear whether they are result of modified bacteria–bacteria interactions or of other physiological and/or environmental changes within the gut upon metformin treatment [33, 34].

A general emerging picture is that metabolic alterations are associated with low richness of microbial gene which is paralleled by reduced metabolic functions in the bacteria [35, 36].

Non-alcoholic fatty liver disease is another metabolic disorder interplaying with obesity and type 2 diabetes [19, 20, 37]. Metagenomics studies revealed a striking association between low microbial gene richness and hepatic steatosis as well as other metabolic variables such as HDL, LDL and insulin resistance [37]. Data from the FLORINASH Consortium provided evidence of a slight shift of the fecal microbiome in patients with steatosis to one that is more similar to that found in the human small intestine and oral cavity. For example, patients with steatosis had fewer *Lachnospiraceae* and *Ruminococcaceae*, which are responsible for butyrate production, and were enriched in *Acidaminococcus*, *Escherichia* spp.

and *Bacteroides* spp. which were associated with insulin resistance [38].

How the gut microbiome signals to affect host metabolism

The gut microbiome is the pivotal regulator of nutrients processing in mammals. Its actions also generate essential metabolites not generated by the host such as vitamins and other absorbable compounds. Recent meta-analysis showed no major differences between lean and obese people at phylum level suggesting that metabolic dysbiosis might not derive from changes in microbiome taxonomic but rather depend on loss of metagenomics genomic heterogeneity on genes transcripts codifying for enzymes regulating metabolic functions [39]. In the second part of this review we will focus on changes in gut microbiota organization that lead to generation of bacterial metabolite end-products especially that may act via an interaction with membrane or nuclear receptors.

Amino acid acid-related signals

Branched-chain amino acids

BCAA are well-known biomarkers for insulin resistance and predictors of incident diabetes and cardiovascular diseases [40, 41]. The effect of BCAA to induce IR is not completely defined although it might involve incomplete BCAA catabolism in adipose and hepatic tissues with consequent plasma BCAA elevations. BCAA catabolism may be shunted to skeletal muscle, where it indirectly leads to FA accumulation and insulin resistance via generation of 3-HIB [42, 43]. In insulin resistant individuals *P. copri* and *B. vulgatus* were found significantly associated with increased BCAA biosynthesis and decreased transport genes at fecal metagenomics level [6]. The variation in BCAA microbial genes directly associated with circulating BCAA in the host. These results may explain how and why BCAA increase in insulin resistance and type 2 diabetes [6]. Furthermore, BCAA were found the most associated metabolites to both microbial gene richness, steatosis and insulin resistance in obese women. Among the overlapping genes co-associated with hepatic steatosis and low microbial gene richness, *ACADSB* (which encodes short/branched-chain acyl-CoA dehydrogenase) and *INSR* (which encodes the insulin receptor) were the most anti-correlated, suggesting a molecular connection from low MGR to a reduced capacity to respond to insulin and increased circulating BCAA. These observational data

were corroborated by functional experiments based on fecal transplantation in which donor microbiota influenced the mouse phenotype, showing that the steatosis-associated microbiota influences multiple patterns of association with hepatic triglycerides and circulating BCAAs [38].

Aromatic amino acids and indoles

AAA are a source of microbial metabolites affecting metabolic functions in the host [44].

Recently, we observed phenylacetic acid (PAA) which is a by-product of bacterial AAA metabolism which significantly increases hepatic BCAA utilization and hepatic lipid accumulation in obese women [37]. Therefore, in the context of obesity and insulin resistance the gut microbiota regulates a feedback mechanism to increase host BCAA utilization concurrently to increased BCAA absorption, which, however, prompts liver steatosis [38]. Indolelactate was found associated with insulin resistance and steatosis in experimental models of metabolic syndrome [45], one of the several analyses reporting an association of microbial indoles with metabolic variables [44].

Serum indolepropionate, a metabolite resulting from microbial Trp metabolism in *Clostridium Sporogenes*, was associated with reduced risk of developing Type 2 diabetes and negatively correlated with low-grade inflammation [46, 47]. It has been suggested the indolepropionate in the host activates Pregnane X Receptor to exert anti-inflammatory effects and may also exert anti-oxidant properties [48].

A reduction in fecal indole-3-acetic (IAA) concentration was found in subjects with obesity and diabetes, showing also increased LPS confirming the concomitance of dysfunctional gut barrier in the same subjects as a marker of gut dysbiosis. The reduction in IAA was also correlated with increased Kynurenine metabolism via increased activity indoleamine 2,3-dioxygenase in the host. Therefore, increased Trp absorption from host may deprive gut microbiome with the source to generate indole and its derivatives [49].

Nevertheless, we should consider that not all the indole derivatives have beneficial effects on metabolism. In fact, indole compound itself, generated through tryptophanase-expressing bacteria, is first modified via hydroxylation and next by *O*-sulfation in the liver to generate indoxylsulfate, one of the uremic toxins which is known also to induce insulin resistance in the context of chronic kidney diseases [50].

Fermentation products (short short-chain fatty acids)

The fermentation of dietary fibers in the caecum and in the proximal colon by anaerobic bacteria leads to the generation

of short-chain fatty acids [51]. Butyrate, acetate and propionate are the most abundant SCFAs produced by this process. Their conversion into energy for the mucosal cells and after transfer into circulation for the body is well known and the role of SCFAs in metabolic disorders had been resumed recently [44]. There is now consistent agreement that SCFAs play a positive role to improve metabolic homeostasis acting on lipid oxidation [44]. An intervention with propionate at colon levels in overweight adults resulted in weight and liver steatosis reduction coupled with increased GLP-1 secretion [52].

The effects of SCFAs are in part mediated by G-protein-coupled receptors GPR41, GPR43 and GPR109A. GPR43 (also named FFAR2) is involved in GLP1 secretion, therefore, linking SCFAs to regulation of insulin sensitivity via incretin action [53].

Studies elucidating the bacteria involved in SCFAs generation are still lacking, although *Roseburia* species are often involved as well as *Faecalibacterium praeuniteszii* [6].

A recent contribution found that *Firmicutes* phylum, specifically those bacteria belonging to the *Ruminococcaceae* family, positively associated with plasma acetate levels and insulin sensitivity in subjects with obesity [54].

Gut microbiome microbiome-based therapeutics in metabolic disorders

Several clinical studies compared bariatric surgery techniques such as laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) surgery in obese patients with T2D [55, 56]. Meta-analysis of clinical studies suggested that post-operative gut microbiota improved to resemble that of lean subjects although most of these studies had very low numbers of recruited patients and results were often controversial [57]. Metagenomics studies on a Chinese cohort of young obese subjects observed decreased abundance of *Bacteroides thetaiotaomicron* in obese subjects. *B. thetaiotaomicron* is a glutamatefermenting commensal and was inversely correlated with serum glutamate concentration. Bariatric surgery intervention partially reversed the decreased gene richness observed in obesity and also reduced the abundance of *B. thetaiotaomicron* as well as the elevated serum glutamate concentration after 3 months from the intervention [58]. Interestingly, in a proof of concept experiment in mice gavage with *B. thetaiotaomicron* reduced plasma glutamate concentration and alleviated diet-induced body-weight gain [58]. However, another recent study combining metagenomics to bariatric surgery, in subjects of European ancestry with 12 months observation after the intervention, confirmed improved microbial gene richness but not a full rescue in most of the patients, despite all

subjects showed metabolic improvement [59]. Overall, it is still unclear whether the low microbial gene richness characterizing obesity and its metabolic sequels are a consequence or a cause of morbid obesity [60]. The 5 year follow-up of the Florinash study which has been recently completed will be able to answer some of these questions. In type 2 diabetes dietary fibers were shown to selectively modulate a group of SCFA-producing strains and positively affect level of glycosylated hemoglobin in part via increased secretion of glucagon-like-peptide-1 (GLP-1) [61].

Conclusions

Several efforts and contributions from many laboratories allowed to start a map of gut dysbiosis in metabolic disorders. Metabolic dysbiosis is the product of subtle changes in gut microbiota and Table 1 contains a summary of the most significant results recently reported.

There are still several questions before we may translate research on the gut microbiome to clinical practice in metabolic disorders.

Table 1 Examples of gut bacterial strains associated with metabolic disorders in human subjects

	↑ in T2DM	↑ in T2DM
Intestinal bacterial (phylum level)		
<i>Firmicutes</i>	x	
<i>Bacteroidetes</i>		x
Intestinal bacterial strains (genus or species level)		
<i>Roseburia</i> (genus)		x
<i>Eubacterium halii</i>		x
<i>Faecalibacterium prausnitzii</i>		x
<i>Lactobacillus gasseri</i>	x	
<i>Streptococcus mutans</i>	x	
<i>E. coli</i>	x	
<i>Prevotella copri</i>	x	
<i>Bacteroidetes vulgatus</i>	x	
<i>Akkermansia muciniphila</i>	X	
	↑ in NAFLD	↓ in NAFLD
<i>Actinobacteria</i> (phylum)		
<i>Proteobacteria</i> (phylum)		
<i>Verrucomicrobia</i> (phylum)		
<i>Eubacterium</i> (genus)		
<i>Escherichia</i> (genus)		
<i>Akkermansia</i> (genus)		
	Increased by metformin	Decreased by metformin
<i>Akkermansia muciniphila</i> (species)	x	
<i>Bifidobacterium Adolescentis</i> (species)	x	

Table 2 Examples of microbial metabolites associated with metabolic disorders in human studies

Metabolite	Microbial agent	Effect
Propionate	Unknown	Insulin sensitivity
Butyrate	<i>Anaerostipes hadrus</i>	Insulin sensitivity
Isoleucine, leucine, valine (BCAA)	<i>Prevotella copri</i> , <i>Bacteroidetes vulgatus</i>	Insulin resistance
Indole	<i>B. fragilis</i>	Incretin secretion
Coniugated linolenic acid (CLA)	<i>F. Prausnitzii</i>	Insulin sensitivity
Phenylacetate	Unknown	Liver steatosis

First, it is conceivable that effect of the gut microbiome is profoundly intertwined with the diet and the genetic background. We need more studies with a country focus and an in-depth analysis of the nutritional patterns of recruited subjects. Second, the impact of therapeutics remains to be determined. A recent study found associations among several therapeutic agents used in chronic disorders and gut microbiome, confirming that metformin/T2DM interaction is the most significantly associated with gut microbiome but revealing associations with other endocrine disorders such as hypothyroidism (an interplay between an anti-diabetic drug such as Metformin and the gut microbiome to explain part of the drug effect to improve metabolic control [18, 62–64]. Third, most of the gut microbiome species influence host metabolism and immunity via specific molecules and small metabolites (Table 2). Therefore, once a microbial metabolite is involved in a disease either as biomarker or as pathogenic agent we should make more efforts to explore the gut microbiome genetic potential to make specific metabolites.

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Compliance with ethical standards

Conflict of interest The author is co-inventor on pending patents held by INSERM Transfert, INSERM, University of Rome Tor Vergata, University of Girona and Imperial College on NAFLD diagnostics and has the right to receive royalty payments for inventions or discoveries related to NAFLD diagnostics.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

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