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# The Influences of Symbiotic Host Gut Microbiota During Obesity and Diabetes

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## Abstract

The resident gut microbiota is a complex and dynamic entity and at times their imbalance (dysbiosis) can trigger the onset of diseases. Dysbiosis are known to be correlated to host metabolic disease, liver disease, immune complications amongst few others. Dysbiosis can deregulate the biosynthesis and secretion of metabolites by the microbiota which is normally considered beneficial to the host. Altered metabolites availability can modulate host organs/tissues functions which may influence certain disease onset and progression. Obesity and diabetes are diseases that exhibits a correlation with significant change in gut microbiota composition and diversity. Modulation in the secretion of gut microbiota-derived metabolites during dysbiosis appears to influence the onset and progression of obesity and diabetes. However, direct physiological link between the gut microbiota and obesity and diabetes is not confirmed yet and remains a challenge for further investigations. In this article, findings where by perturbation of the gut microbiota may contribute towards obesity and diabetes in the host are reviewed.

**Keywords**: Dysbiosis, Gut, Metabolites, Metabolic disorders

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## Introduction

The large intestine (colon/gut) is a prominent segment of the gastrointestinal tract (GIT) that harbors a complex and dynamic microbial symbiont comprising of bacteria, fungi, archae, parasites and viruses whose total counts range in trillions (1,2). This microbial community is referred as the gut microbiota and performs various vital biological functions, including restraining pathogen colonization and propagation which is beneficial to the host. Impairment in microbiota diversity and composition leads to dysbiosis that has been attributed to influence the onset and progression of neurodegenerative disorders, inflammatory bowel disease (IBD), diabetes, liver disorders, colorectal cancer and others (3-6). Such pathogenesis might arise due to deregulation or alterations in the normal molecular communications between select gut microbes and the host. Metabolites such as *L*-tryptophan-derived indole and its derivatives released by select gut bacteria can act locally in the host GIT and also can exert their effect distally on other tissues/organs thereby maintaining mutualism and tolerance between them (1,7-9). Some of the gut microbial metabolites are known and characterized, however, majority of them are still unidentified (1).

Many bacterial populations dominate in the gut, with the phyla Firmicutes, Proteobacteria, Actinobacteria and Bacteroidetes comprising the most (10,11). Compositional perturbation in these gut bacteria phyla probably has health consequences that might be triggered at any given age. On the other hand, overpopulated symbiont bacterial species in the gut may turn into a pathogenic form (pathobiont) contributing to dysbiosis (12). However, it appears that dysbiosis largely require multi-factorial inputs in the form of dietary intake, host mucosa and immunity, deregulated symbiont-secreted metabolites, including overall microbiota composition and dynamics (13).

Dietary intake probably has the most significant influence on the composition and diversity of the gut microbiota. The gut microbiota has direct consequences on host nutrient digestion, absorption and metabolism. Moreover, the gut microbiota exerts effects both on the GIT and peripheral tissues modulating metabolism, including the host hormonal and immune systems (14). Short- or long-term alterations in dietary intake affect the nutritional state of the host which has a significant impact on microbiota richness (14). The bacterial phylum Firmicutes in the gut is sensitive to the abundance of excessive nutrients and becomes overpopulated that contributes to dysbiosis and obesity in humans, including OB/OB mice (15,16). Moreover, increased population of Firmicutes elevates inflammatory lipopolysachharide (LPS) level in the host circulation that contributes to immune-mediated chronic inflammation as observed during obesity. Consumption of high-protein diet has a positive influence on the Bacteroidetes population, whereas other bacteria numbers show only a moderate increase accompanied with elevated fermentation products. Protein-rich diet causes elevated production of N-nitroso compounds, including nitric oxide (NO), sulfide and ammonia which have anti-microbial activities in the gut (17,18). High circulating level of NO was detected in obese people and is likely associated with altered gut-microbial growth thereby favoring obesity (19). Thus, it appears that mechanisms exist whereby the gut microbiota directly and/or indirectly impinges upon the host functions that initiate pathogenesis. In this article, the current state of knowledge where reshaping of the microbiota causes homeostatic breakdown in the host, triggering metabolic complications like diabetes and obesity will be reviewed.



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## Resident Gut Microbiota and Metabolic Complications

Given the huge diversity of the resident GIT microbiota, pinpointing the pathogenic culprit(s) is a complicated task. Onset of diseases as a result of gut dysbiosis is a widely accepted theory now, though the mechanistic details are scanty and largely speculative. Also, it has not been possible to directly attribute low microbial diversity and composition to disease causation. Optimal microbial activities in the gut likely contributes towards host metabolic health, whereas a dysbiotic state may result in diabetes, malnutrition, non-alcoholic fatty liver disease, obesity and few others (20-22). Significant alterations in gut microbiota composition have been observed during such diseases and it is hypothesized that the gut microbes can be seen as an environmental input factor which can modulate host function and elicit metabolic changes contributing towards certain diseases.

## Obesity and the Gut Microbiota

When energy intake exceeds energy expenditure, it leads to fat deposit leading to overweight and obesity. Of late, obesity has assumed a pandemic status compromising the well-being of individuals and predisposing them to other complications involving cardiovascular, hypertension, diabetes and cancer. Obesity also has negative effects on nation's economic and social health. Altered gut microbiota seems to be one of the contributory factors in the onset and progression of being overweight and obese and has led to investigations of the resident gut microbial communities in such individuals (23). DNA sequencing data along with 16S rRNA gene sequencing studies on gut bacteria isolated from obese mice have revealed a relatively higher proportion of Firmicutes as against Bacteriodetes compared to lean animals with similar findings in other mammals, including humans (23-25).

However, few findings show that this ratio in humans is just the opposite and that the ratio of Firmicutes to Bacteriodetes is not the basis for obesity in humans (26). Moreover, there is no general agreement on the Firmicutes to Bacteroidetes ratio and obesity onset as recent data do not indicate direct involvement of any particular bacterial phyla. Furthermore, gut microbial composition imbalance is a cause or an effect of obesity in individuals is not confirmed yet. But it seems dysbiosis might be an influencing factor in diabetes and obesity onset as observed in germ-free mice studies. When high-fat diet was fed to wild-type and germ-free mice, obesity was triggered only in the wild-type animals indicating the requirement of functional microbiota in the onset of obesity (27). Interestingly, fecal transfer from the obese to the germ-free mice led to obesity onset (27,28). Also, fecal transfer from non-obese mice to obese led to dramatic improvement and shift towards a lean status (29). Dybiosis has been attributed to decrease in overall microbiota diversity, loss of beneficial microbes and high prevalence of harmful bacteria, all of which can occur together (30,31). Dietary intake has a major influence on gut microbiota diversity and composition and that changes in the type of diet consumption may favor dysbiosis and obesity onset.

Lifestyle factors seem to be not only the key inputs that modulate gut microbiota. Host genetics on the other hand has been attributed to influence the gut microbiome (32). However, data in this area of research is scanty but initial findings in rodents show a correlation between genetically-different inbred mice and obesity phenotypes and microbiota composition upon dietary input (33,34). In humans, few of the findings indicate specific genotype variability associated with metabolic functions with select microbiota abundance linked to body mass index and weight gain (32,35).

The triangular axis of host genetics, microbiota and obesity is complex and requires serious attempts to unravel the links in the future. Epigenetic changes in the host genome can cause gene expression modulation



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that might influence individual's health and elicit disease onset (36). Surprisingly, gut microbiome-secreted metabolites can communicate with the host epigenetic process. Dietary intake and various metabolite generation by the resident gut microbiota is innately linked and some of the metabolites can impinge upon the host epigenetic signatures to alter cell's metabolic functions. In fact, short-chain fatty acids (SCFAs) such as butyrate, propionate and acetate fermented obtained from dietary fiber intake can directly interact with host nuclear histone deacetylase causing gene expression reprogramming associated with lipid metabolism and food satiety (37-39).

Initial findings on the interplay between gut microbiota, epigenetic changes and obesity in humans are encouraging. In a comparison between lean and obese subjects, lower microbiota diversity and presence of *Faecalibacterium prausnitzii* were detected in obese individuals with concomitant reduction in methylation magnitude of the free fatty acid receptor 3 (*FFAR3*) gene was reported (40). The *FFAR3* under-methylation in obese individuals exhibited a positive correlation with higher BMI. Similarly, reduced microbiome diversity was observed in obese subjects as against the lean controls and was associated with under-methylation of the TLR2 and TLR4 genes which strongly-correlated with higher BMI (40).

Gut microbiota composition and diversity in healthy lean and obese individuals are distinctly altered as observed by epidemiological findings, which was supported by the previous important finding of Turnbaugh et al (41). In an important finding, human twins discordant for obesity, their transfer of fecal microbiota sample to germ-free mice led to the onset of obesity in animals in a diet-dependent manner (42). Initial findings have provided the evidence that dietary intervention in obese people might modulate their metabolic status in tandem with gut microbial diversity and composition in a positive manner (43). Species-relevant presence of bacteria in the gut might be important as studies have observed that SCFAs generating bacteria such as *Eubacterium ventriosum* and *Roseburia intestinalis* are plentiful in the gut and linked to obesity, whereas leanness may be associated with the butyrate producers *Oscillospira spp.* and *Methanobrevibacter smithii* (44-46). Important findings reported from Thingholm et al using resident microbial pathways and gene family analyses have shown significantly compromised bacterial one-way conjugation process along with reduced superoxide reductase expression in obesity compared to leanness (47). The initial observations by Ridaura et al (42) have stimulated the hunt for gut microbial-derived molecules that modulate the host metabolic functions which might have implications in obesity and other metabolic disorders. The metabolic activities undergoing within these microbes are challenging as they have to balance themselves so as to survive and propagate within the host boundary and limitations. Metabolism in the gut microbial population churns out metabolites few of which has been identified and characterized (such as L-trp-derived indole and its derivatives, SCFAs, succinate, secondary bile acids and others) that affect both the microbe as well as the host and help maintain a conjoint relationship (Table 1) (21,36,38).

Metabolomic studies in human saliva, urine and plasma samples have identified various metabolites whose levels may undergo modulation during dysbiosis associated with metabolic disorders. However, majority of the bacterial-secreted metabolites have not been identified and characterized which might harbour vital functional properties that may interact with the host cells and tissues and help maintain optimal health.

Few of the gut microbiota-secreted metabolites influence the host energy metabolism and adiposity. Metabolism of complex carbohydrates by the resident gut bacteria generates by-products including the SCFAs such as butyrate, propionate and acetate that provide energy for their own utilization and the host as well (48).



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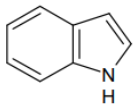
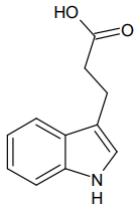
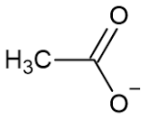
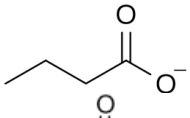
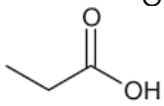
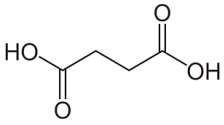
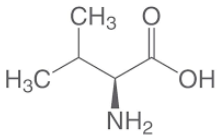
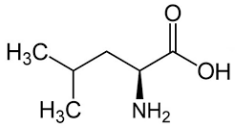
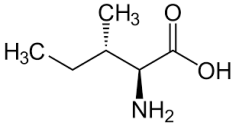
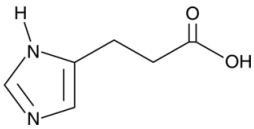
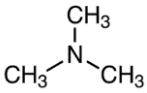
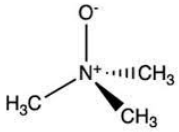
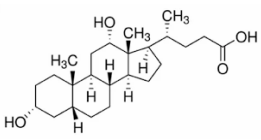
**Table 1. Gut microbiota-derived various metabolites which can influence obesity and/or diabetes.**

| Metabolites | Chemical structure | Remarks | References |
|---|---|---|---|
| **Indole** |  | Weak aryl hydrocarbon receptor (AhR) agonist with anti-inflammatory and insulin sensitivity actions. Stimulate GLP-1 secretion | (93-95) |
| **Indole 3-propionic acid (IPA)** |  | Pregnane X receptor (PXR) agonist with anti-inflammatory effects and insulin sensitivity actions. | (93-95) |
| **Acetate** |  | Directly interact with host nuclear histone deacetylase causing gene expression reprogramming (epigenetic modification). Has obesogenic effect by stimulating ghrelin secretion. | (37-39), (83-85) |
| **Butyrate** |  | Participates in epigenetic modification. Stimulates leptin secretion | (37-39), (83-85) |
| **Propionate** |  | Participates in epigenetic modification Stimulates leptin secretion | (37-39), (83-85) |
| **Succinate** |  | Enhances insulin sensitivity and glucose tolerance | (53-55) |
| **L-Valine** |  | Roles in regulating protein, lipid and glucose metabolism, BAT thermogenesis & insulin resistance. Systemic increase in L-valine observed during obesity and diabetes. | (86-88) |
| **L-Leucine** |  | Roles in regulating protein, lipid and glucose metabolism, BAT thermogenesis, insulin resistance. Systemic increase in L-leucine observed during obesity and diabetes. | (86-88) |
| **L-Isoleucine** |  | Roles in regulating protein, lipid and glucose metabolism, BAT thermogenesis, insulin resistance. Systemic increase in L-isoleucine observed during obesity and diabetes. | (86-88) |
| **Imidazole propionate** |  | Its level is significantly increased during T2D and is associated with insulin resistance. | (96,97) |
| **Trimethylamine (TMA)** |  | In hepatocytes it is metabolised by flavin monooxygenases 3 to yield TMA-N-oxide (TMAO) | (89) |
| **TMA-N-oxide (TMAO)** |  | Increased systemic TMAO level observed during diabetes and obesity | (89,90) |
| **Deoxycholic acid** |  | Agonist for farnesoid X receptor (FXR) and Takeda G-protein coupled receptor (TGR5). Increases hepatic insulin sensitivity, insulin secretion from the pancreas. | (51,52,82) |

Continued







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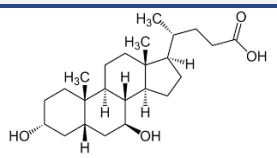
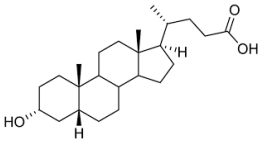
| Metabolites | Chemical structure | Remarks | References |
|---|---|---|---|
| **Ursodeoxycholic acid** |  | Agonist of FXR and TGR5.<br>Increases hepatic insulin sensitivity, insulin secretion from the pancreas. | (51,52,82) |
| **Lithocholic acid** |  | Agonist of FXR and TGR5.<br>Increases hepatic insulin sensitivity, insulin secretion from the pancreas. | (51,52,82) |

The levels of SCFAs as well as the related gut bacterial counts are diminished in fecal samples from mice with dysmetabolic condition as well as in humans afflicted with obesity and diabetes (48,49). The SCFAs can act as signalling messengers in the host with regard to adiposity and energy metabolism. Butyrate and propionate are considered as obesity antagonists through stimulation of the release of appetite suppressant hormones such as leptin. However, a number of conflicting reports by various investigations on the effect of SCFAs on adiposity has led to a no clear-cut link between them. Moreover, microbial acetate on the other hand seems to have an obesogenic effect as it is utilized by the adipose tissue and the liver as a precursor for lipogenesis (49). Dysbiotic state in mice led to an enhanced microbial-derived acetate level in the gut which stimulated ghrelin secretion leading to increased appetite and high adiposity through glucose-stimulated insulin release (50). In the liver, bile acids are synthesized from cholesterol and are vital in the digestion and absorption of lipids and vitamins in the intestine. Host-synthesized primary bile acids can be transformed by the gut microbiota to secondary bile acids that has been suggested to have play a role in obesity and energy metabolism. The secondary bile acids, such as deoxycholic acid, ursodeoxycholic acid and lithocholic acid can interact with host cell receptors such as the farnesoid X receptor (FXR) and Takeda G-protein coupled receptor (TGR5), both of which have opposing effects on carbohydrate metabolism in the host (table 1) (51). A new finding suggested C-6-hydroxylated secondary bile acids as an important regulator of leanness in rodents (52). Alteration in gut microbiota during metabolic disorders such as in obesity negatively influences primary bile acid metabolism causing its accumulation and compromising lipid metabolism in the host (52). Change in lipid metabolism due to alteration in bile acid metabolism as a result of dysbiosis modulates the bile acid pool which can drive pathogenesis associated with obesity. Succinate on the other hand is a metabolic intermediate that is made by the host as well as the gut microbiota. Succinate might play a role in obesity prevention and has been shown to elevate insulin sensitivity and glucose tolerance during preliminary studies in mice (53,54). Moreover, exogenous succinate administration to mice has been shown to promote UCP1-mediated thermogenesis in brown adipocytes and defended against diet-induced obesity (54). A similar effect of microbiota-secreted succinate on the human host in protecting against obesity however can only be speculated at present. White adipose tissue (WAT) is the primary site of lipid and energy storage with vital consequences on overall metabolism in mammals (55). Obesity is characterized by unregulated WAT expansion and inflammation onset that has serious consequences on the development of other metabolic disorders (56). Any role of the gut microbial population on WAT metabolism was unthinkable a couple of decade ago, however, preliminary data from recent findings indicate regulation of WAT functions by the gut microbial SCFAs such as butyrate. Dietary intake alteration leading to dysbiosis has been linked to obesity onset, but the



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underlying molecular mechanisms are largely unidentified (55-57) (Figure 1).

As discussed earlier, a limited number of the gut microbiota-derived small diffusible metabolites in the GIT have been linked to obesity and related metabolic disorders (55,58)

MicroRNAs (miRNAs) are small cellular RNAs that regulate gene expression and can play a vital role in maintaining metabolic homeostasis. On the other hand, regulatory breakdown in miRNAs might support obesity and insulin-resistance (IR) onset (59,60). A recent observation by Virtue et al has demonstrated an interesting outcome of gut microbiota presence and influence on WAT miRNA, *miR-181* expression in normal, germ-free and specific-pathogen free (SPF) mice (61). Presence of microbiota up-regulated the expression of *miR*-181 in WAT of normal mice compared to germ free (GF) and SPF animals. Moreover, gut microbial colonization in germ free and SPF mice significantly stimulated the expression of WAT *miR*-181. Furthermore, feeding high-fat diet (HFD) to normal mice led to increased *miR*-181 expression in the WAT, whereas *miR*-181 expression in HFD GF mice was abolished. The expression of *miR*-181 in WAT was associated with the presence of gut microbiota. Hence, through regulation of *miR*-181 expression in the WAT, the gut microbiota can promote obesity involving a discrete mechanism. Research reports from mice and human subjects have shown that the tryptophan-derived indole metabolites including indole-3-carboxylic acid and indoxyl sulphate generated by the gut microbiome negatively regulate *miR*-181 expression in the WAT and might help in reducing the progression of obesity (61).

Other hand, *in vitro* and mice investigations have shown that the indole metabolites might have a negative impact on *miR*-181 expression in adipocytes which compromised the progression of obesity. Knock out of the tryptophanase gene *tna A* responsible for metabolizing *L*-tryptophan to indole by the gut *E. coli* and inoculation of the bacterium into the mice gut caused fast gain of weight and obese state compared to mice colonized with wild type *E. coli* (61). Together, these findings provide a link between the presence and

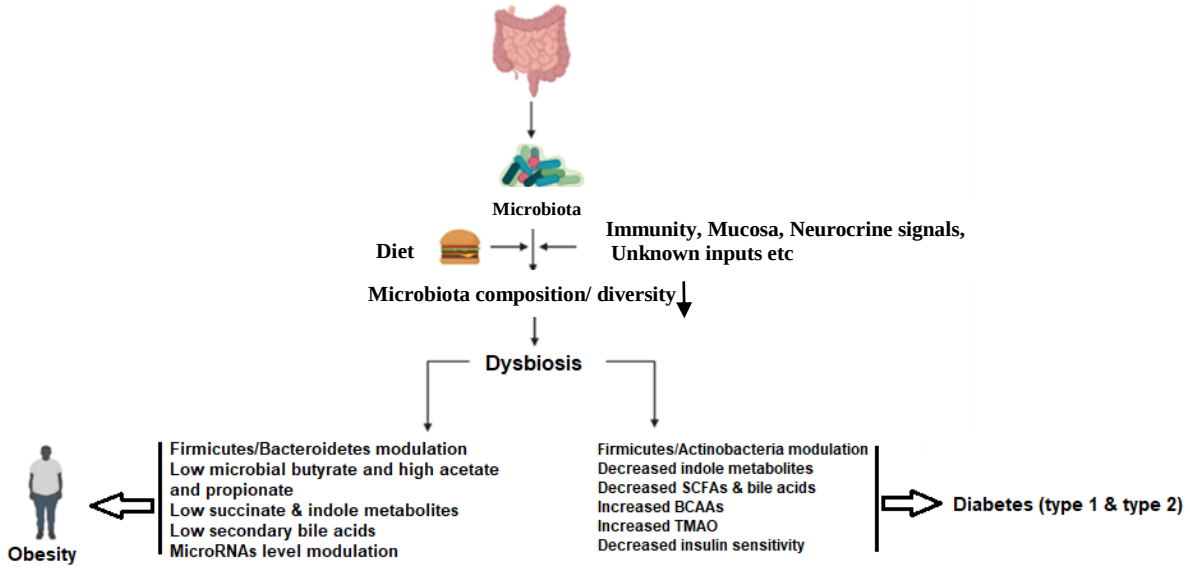


**Figure 1. Human gut microbiota dysbiosis and its link to obesity and diabetes. A schematic chart depicting alteration in dietary intake and/or other endogenous factors that can cause change in the gut microbiota composition and diversity leading to dysbiosis. Dysbiosis has multiple consequences such as the development of metabolic disorders like obesity and diabetes as a result of various molecular functional modulations in the host.**





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abundance of microbial indole derivates that regulate *miR*-181 expression in the adipose tissue of animals that govern weight gain and obesity.

Hence, a dysbiotic state due to excessive nutritional/caloric input provides strong environmental cue which attenuates gut bacteria generating indole derivates, whose scarcity might evoke high adiposity and obesity mediated via the up-regulated *miR*-181 family. Assmann et al (62) have demonstrated in human subjects that twenty-six miRNAs are differentially detected in the blood circulation of obese individuals compared to the non-obese. Moreover, 14 of the miRNAs detected in the plasma of obese persons were correlated to the relative richness of four gut-bacterial species (*D. longicatena, B. intestinihominis, B. eggerthii* and *H. parainfluenzae*) exhibited statistically significant differences between the obese and control subjects. These miRNAs in the gut lumen interacted with the bacterial species by regulating a number of genes that are involved in the metabolism of carbohydrate, lipid and energy sensing pathways (62,63).

In a meta-analysis, few of the circulating miRNAs detected in obese subjects were shown to be down-regulated. These findings support the involvement of miRNAs as novel communication agents between the gut microbiome and the host in regulating metabolic processes

## Diabetes Mellitus and The Gut Microbiota

Diabetes mellitus is a rapidly growing clinical complication worldwide whose pathogenesis is largely unclear as yet. In type 1 diabetes mellitus (T1D), impairment of insulin secretion from the pancreatic B cells is as a result of autoantibody/auto-reactive T cell generation that target and destroys the B cells. As a result, compromised insulin secretion leads to reduced plasma glucose uptake by tissues and organs causing hyperglycemia and ultimately T1D. Various findings have demonstrated a link between gut microbial composition and diversity in healthy host and those afflicted with T1D (64-66) (figure 1). In animal models, such as in Bio-Breeding diabetes-prone (BB-DP) rats there is a marked alteration in select gut bacterial species composition compared to the Bio-Breeding animals that are diabetes resistant (64,67). In humans, similar findings have been reported where significant changes in the gut bacterial species are observed between T1D and normal subjects. Murri et al have reported a distinct reduction in the level of Actinobacteria and Firmicutes with simultaneous lower ratio of Firmicutes to Bacteroidetes in T1D children as against the healthy ones (68). Also, the gut microbial diversity and balance was compromised in T1D children compared to the non-T1D children (69).

Moreover, in pre-clinical T1D subjects, appearance of auto-antibodies along with lower gut bacterial diversity and imbalance were observed with concomitant reduction in butyrate-generating bacteria was detected compared to the healthy ones (70). Thus, the relative abundance, balance and integration of the gut microbiome might be the critical factors responsible for the onset of T1D. Any perturbation of such factors, for example due to quality of diet intake might compromise the microbial richness and the relative availability of microbial-derived metabolites which might trigger T1D.

It is visualized that the gut microbiota-mediated modulation of the host immune response might be a strong factor in the onset of T1D. Gut Gram-negative bacteria release lipopolysaccharide (LPS/endotoxin) that has consequences on the host as a result of its ability to induce pro-inflammatory mediators and ultimately damage to pancreatic B cells which can trigger diabetes (71,72). Increased level of circulating LPS was detected in T1D compared to the non-diabetics in a case-control set up study, suggesting that LPS might serve as an important link between the gut microbiome, host inflammation and diabetes onset. Dysbiosis in the gut favors intestinal mucosal barrier disruption which





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may facilitate LPS entry into the tissue and activate host toll-like receptors (TLRs) such as TLR4 that can facilitate metabolic inflammation (73). In fact, non-obese diabetic (NOD) mice lacking TLR4 expedited the onset of diabetes and destruction of the pancreatic islet B cells (74).

The myeloid differentiation factor (MyD88) is a component of the TLR pathway and an activator of NF-$\kappa$B signalling. NOD mice with MyD88 knock-out when raised in SPF condition did not develop T1D whereas, when raised in GF condition spontaneously became diabetic and the absence of MyD88 changed the gut microbiota composition (65). The gut microbiota seems to be involved in influencing the level of interleukins that has a contributory role in T1D onset. Diet supplementation of *L. johnsonii* to BB-DP rats exhibited low level of pro-inflammatory interferon γ compared to diabetic rats (66). Whereas. NOD mice orally when supplemented with probiotics caused increased level of the anti-inflammatory interleukin-10 that reduced pancreatic inflammation and lowered T1D occurrence (75). These findings to some extent reveal a potential link between the gut microbiota, innate immunity and T1D.

Molecular mimicry might be a key mechanism by which the gut microbial-derived proteins/peptides share amino acid sequence similarity with pancreatic self-antigens may induce generation of auto-antibodies that target the pancreas islets leading to T1D. For example, release of certain peptides by the resident bacteria imitates auto-antigens associated with the pancreas and cause activation of the cytotoxic T ($CD8^+$) cells which promote pancreatic inflammation and T1D (76). The pancreatic islet-specific glucose-6-phosphatase-related protein (IGRP) and the Mgt protein released by the gut *Leptotrichia goodfellowii* might have a role in T1D onset. The $IGRP_{206-214}$ peptide (VYLKTNVFL) and $Mgt_{267-275}$ (TYLKTNVFT) peptide sequence show some amino acid sequence homology and the $Mgt_{267-275}$ (TYLKTNVFT) domain activated the diabetogenic NY8.3 T cells targeting the pancreatic islets and experimentally induced T1D in NOD mice (76). Similarly, some other gut bacteria (such as *Flavobacteriia bacterium*, *Bacillus cereus*, and *Enterobacter mori LMG 25706*) proteins also shares the $IGRP_{206-214}$ peptide (VYLKTNVFL) sequence homolog and their relative gut composition and stability might have a diabetogenic influence on the host.

Over the years, there has been increased speculation on the role played by the gut microbiome in the onset and maintenance of type 2 diabetes (T2D) (fig. 1). Recent findings from Yu *et al* have shown that the gut microflora in db/db mice (a murine model of T2D) have undergone marked change with abundance in the population of Verrucomicrobia along with decreased Bacteroidetes and Prevotellaceae counts as determined by 16S rRNA sequencing (77). Transplantation of fecal samples from the db/db and m/m (control) mice to germ-free (GF) mice caused significant alteration in gut microbiota composition and metabolic parameters, such as increase in fasting blood glucose, fluid and food intake, body weight etc. This probably indicates a role for the gut microbiota composition in the onset and the associated complications of T2D. In a recent clinical finding, the gut microbiota-related metabolites seem to be associated with T2D. Vangipurapu et al have shown in a large cohort study of 4851 Finnish males who made follow-up visit to the clinic for almost seven and a half years, a total of 522 developed T2D (78). Those with T2D exhibited significant rise in range of metabolites such as 1-palmitoleoylglycerol (16:1), 2-hydroxybutyrate/ 2-hydroxyisobutyrate, xanthine, xanthurenate, kynurenate, 1-oleoylglycerol (18:1), 1-myristoylglycerol (14:0), dimethylglycine, creatine, uric acid and 2-hydroxyhippurate (78).

Increase in the level of these metabolites in subjects heightened the risk of onset of T2D by reducing the secretion of insulin or insulin sensitivity or both. However, 1-



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linoleoylglycerophosphocholine (18:2) lowered the risk of T2D onset in the subjects. Humans and rodents with diabetes exhibit high level of circulating LPS, which impairs glucose metabolism in mice (79,80). In fact, a metagenome-wide association study in people with T2D show elevated population of *E. coli* in the gut which is speculated to contribute to the bulk of LPS in the gut that activate the release of pro-inflammatory cytokines which might induce insulin insensitivity (81).

As mentioned earlier, secondary bile acids generated by the gut microbiota have profound effect on host lipid metabolism acting via the FXR and TGR5 signalling pathways. However, microbial bile acids (such as deoxycholic acid, ursodeoxycholic acid and lithocholic acid) acting via the above pathways also stimulate hepatic insulin sensitivity, insulin secretion from the pancreas, liver glycogen synthesis, thermogenesis, hepatic and muscle energy expenditure ultimately supporting glucose homeostasis in the body (82). Shift in the gut microbiota-dependent bile acid metabolism can influence the onset and progression of T2D. Gut microbial-secreted acetate, butyrate and propionate have profound effect on glucose metabolism and homeostasis (83).

Humans and mice with diabetes exhibit reduced SCFAs as well as SCFA-generating gut bacterial species in their fecal samples (84). Diabetic mice when supplemented with SCFAs shows augmented glucose tolerance and homeostasis along with improved energy expenditure (85). Branched-chain amino acids (BCAAs) such as valine, leucine and isoleucine are essential to humans and are synthesized and secreted by the gut bacteria members (Table 1). *Prevotella copri* and *B. vulgatus* are the primary producers of BCAAs and their population in the gut positively correlates with the amount of BCAAs and insulin resistance. BCAAs have paramount roles in regulating protein, lipid and glucose metabolism, BAT thermogenesis, insulin resistance, immunity and maintenance of homeostasis (86). It has been observed that obesity and diabetes is associated with systemic increase in BCAAs levels and that in ob/ob mice (mice which are genetically obese as a result of homozygous leptin gene mutation) they promote insulin resistance (87,88).

Diet-derived choline and *L*-carnitine can be transformed by the gut bacteria to trimethylamine (TMA), which then in the liver hepatocytes is metabolised by flavin monooxygenases 3 to yield TMA-N-oxide (TMAO) (89). In humans, diabetes as well as obesity has been associated with increased systemic TMAO concentration. Mice when fed with diet-supplemented with TMAO, carnitine or choline changes the caecal microbiota composition with enhanced TMA/TMAO generation (90). In antibiotic treated mice, however, this effect is not observed thereby pointing to the requirement of thriving gut microbiota. Preliminary findings suggest that altered gut microbiota during metabolic disorders such as diabetes and obesity preferably supports the enhanced uptake of choline and carnitine from the diet thereby raising plasma TMAO level which can further accelerate the pathogenesis associated with metabolic disorders, including cardiovascular disease. *L*-tryptophan (*L*-trp), an essential amino acid to humans. *L*-trp which is released from ingested proteins in the host is metabolized by dual pathways, namely the kynurenine and the serotonin routes (91,92). Additionally, *L*-trp metabolism by select gut bacteria produces different metabolites, including indole and its derivatives many of which act via the aryl hydrocarbon receptor (AhR) pathway with vital implications for the host (93). In T2D, perturbation of the gut microbiota is associated with decreased ability to metabolize *L*-trp to indole and its derivatives as observed from clinical findings (94). Reduced production of AhR agonists such as indole and some of its derivatives led to defective AhR activation leading to altered intestinal permeability and increased LPS translocation stimulating insulin resistance, inflammation and liver



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steatosis (95). However, administration of AhR agonists or supplementation of *Lactobacillus reuteri* (which produces endogenous AhR agonists) can override metabolic aberration (94). On the other hand, histidine metabolism by the gut microbiota generates imidazole propionate (IMP), whose level is significantly increased during T2D and is associated with insulin resistance. In fact, IMP in hepatocytes alters the insulin signalling pathway and impairs glucose metabolism and its level was raised in individuals with prediabetes and diabetes and associated with altered gut microbiota diversity (96). Such individuals were characterized with low bacterial gene richness and Bacteroides 2 enterotype, a feature also encountered in obesity. In a MetaCardis cohort study belonging to three European countries it was confirmed that during T2D the gut microbiota alteration favors higher IMP production thereby negatively influencing the host metabolic and inflammatory responses (97). Gut microbiota composition differences observed in subjects with T2D or without diabetes seems not to however provide a direct causal explanation. Identifying the mechanistic linkages between metabolic disorders and dysbiosis using metabolomic approach and microbial profiling shall be the key which can strengthen our understanding of the functional control of resident microbiome during metabolic dysfunction.

## Conclusion

Alteration in gut microbiota composition and diversity leading to dysbiosis has consequences for the host in the form of onset of metabolic complications. Data obtained from obese and germ-free mice are encouraging regarding the contribution of gut microbiota in the progression of obesity and diabetes. During dysbiosis, alteration in the amount of gut microbiota-derived metabolites triggers metabolic dysfunction in the host which can favor obesity and diabetes. Few of the metabolites can act as epigenetic modifiers in the host thereby reprogramming the gene expression pattern associated with lipid metabolism and weight gain. Also, certain gut bacteria-derived metabolites can modify satiety signals and insulin sensitivity in the host that can rewire energy metabolism and induce obesity and diabetes development. Such microbial metabolites can be prospective biomarkers in the early diagnosis and prognosis of metabolic disorders. Direct relationship between obesity and diabetes vis a vis gut microbiota, however needs further exploration. Identification of resident gut bacterial strains and its linkage with diabetes and obesity will be paramount. Moreover, microbial metabolomic investigation will be the corner stone that can unravel the axis between the gut microbiota and metabolic disorders and together with microbial metabolite mimicry might aid in the development of therapeutic strategies for their control in the future.

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## Authors' contributions

Sole responsibility for the conception of the study, presented results and manuscript preparation.



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