Chapter

An Insight into the Changing Scenario of Gut Microbiome during Type 2 Diabetes

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Abstract

The gut microbiome consists of bacteria, protozoans, viruses, and archaea collectively called as gut microbiota. Gut microbiome (GM) modulates a variety of physiological responses ranging from immune and inflammatory responses, neuronal signalling, gut barrier integrity and mobility, synthesis of vitamins, steroid hormones, neurotransmitters to metabolism of branched-chain aromatic amino acids, bile salts, and drugs. Type 2 diabetes mellitus (T2D) is a highly prevalent metabolic disorder that is featured by imbalance in blood glucose level, altered lipid profile, and their deleterious consequences. GM dysbiosis a major factor behind the incidence and progression of insulin resistance and is responsible for altering of intestinal barrier functions, host metabolic, and signaling pathways. The GM of type 2 diabetes (T2DM) patients is characterized by reduced levels of Firmicutes and Clostridia and an increased ratio of Bacteroidetes:Firmicutes. Endotoxemia stimulates a low-grade inflammatory response, which is known to trigger T2DM. Xenobiotics including dietary components, antibiotics, and nonsteroidal anti-inflammatory drugs strongly affect the gut microbial composition and can promote dysbiosis. However, the exact mechanisms behind the dynamics of gut microbes and their impact on host metabolism are yet to be deciphered. Interventions that can restore equilibrium in the GM have beneficial effects and can improve glycemic control.

Keywords: type 2 diabetes, inflammation, immune response, gut microbiome, xenobiotics

1. Introduction

Our quality of life and health status are modulated by our food habits and lifestyle. Hence several metabolic disorders and are the greatest global health issues are influenced by improper diet and lifestyle [1]. The other factors that are involved in the development of metabolic disorders and diseases are environmental factors, maternal health, and host genetic makeup. The resident microorganisms in our gastrointestinal tract are collectively collected as the gut microbiota (GM). GM consists of bacteria, fungi, Archaea, protozoa, and viruses. In case of mammals, GM comprises of four main phyla: Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%), and Actinobacteria (3%). These phyla are important for the

regulation of host metabolism and physiology [2]. The total number of both prokaryotic cells and host eukaryotic cells in the gut is approximately 100 trillion, which is three times that of the total number of human body cells [3]. Hence, our unique gut environment is considered as a functional and measurable organ [4]. However, the composition of GM varies along the gastrointestinal tract, and differs within and between individuals depending on the gestational age, mode of delivery, breastfeeding, antibiotic exposure, dietary lifestyle and nutritional status of the individual status of [5, 6]. The colonization of GM is limited in stomach and small intestine, but quite dense and diverse in the colon owing to the absence of digestive secretions, slow peristalsis, and rich nutrient supply [7]. This variety in composition of GM and its function is influenced by the consumption of improper diet, which in turn affects the health condition of the host. GM regulates the energy homeostasis, intestinal integrity and immunity against invading pathogens by participating in the digestive process and energy production, hampering pathogen colonization, and modulating the immune system; hence GM can modulate the overall health status of the host. Gut microbiome also influences an individual's metabolic status such as calorie derived from indigestible dietary substances and storage of calories in adipose tissue, which regulates incidence of obesity in an individual. Studies from germ-free and wild type mice showed alteration in homeostasis in kidney, liver, and intestine in germ-free mice depicting the fact that GM influences whole body metabolism [8–13]. GM also plays a vital role in vitamin production, energy harvest and storage, fermentation and absorption of undigested carbohydrates. The distribution of GM is determined by diet to a large extent as evident from individuals who follow a diet high in animal fat have dominance of Bacteroides in GM, whereas those who follow a carbohydrate-rich diet have a *Prevotella* dominant GM (**Table 1**) [14–16]. According to conventional theories the relationship between genetic and environmental factors such as high-calorie diet and lack of physical activities was considered as the major main contributor to obesity but recently GM has attracted much attention in relation to human health and disease. Recent scientific investigations have shown that GM can be considered as an important endogenous factor controlling obesity [17, 18].

2. Host-gut microbiota metabolite interaction

Several reports have shown that the metabolites derived by GM from fermentation of food play a key role in maintenance of the host metabolism. Clostridium and Eubacterium from our GM break down bile acid in the intestine to its secondary metabolites like deoxycholic acid and lithocholic acid. These metabolites bind to Takeda G protein coupled receptor-5 TGR5 receptor (G-protein-coupled bile receptor) present in the endocrine glands, adipocytes, muscles, immune organs, spinal cord and enteric nervous system, and stimulates the secretion of incretin hormone GLP-1 and insulin. Hence these metabolites in turn promote energy expenditure (**Table 1**) [19]. Long chain fatty acids, for example linoleic acid produced by the GM regulates our lipid profile finally resulting in obesity [20]. Short chain fatty acids (SCFs) another secondary metabolite of gut microbial fermentation is formed by the digestion of indigestible polysaccharides and oligosaccharides that are neither digested nor absorbed in the proximal jejunum [21]. SCFs mainly acetate and propionate contributed by Bacteroidetes and butyrate produced by Firmicutes balance the host metabolism by influencing energy homeostasis, lipid accumulation and appetite [22]. SCF produced in the gastrointestinal tract are also known to control the pH of the lumen by increasing the absorption of nutrients. SCFs also act as a source of nutrition for GM due to high carbon content [23]. Butyrate is the main source of energy for colonocytes. It aids in the proliferation, maturation,

Gut microbiota	Facts and effects
Bifidobacteria	Population reduces in high fat-fed mice gut increasing endotoxemia [14]
Bacteroidetes	Population high in the gut of people consuming animal-based food rich diet [15]
Prevotella	Population high in the gut of people consuming plant-based food rich diet [16]
Clostridium and *Eubacterium*	Break down bile acid in the intestine to its secondary metabolites like deoxycholic acid and lithocholic acid. These metabolites bind to TGR5 receptor (G-protein-coupled receptor) present in the endocrine glands, adipocytes, muscles, immune organs, spinal cord and enteric nervous system, and stimulates the secretion of incretin hormone GLP-1 and insulin [19]
Lactobacillus reuteri GMNL-263	They are capable of reducing T2D markers like serum glucose, glycated hemoglobin and c-peptide in high-fructose-fed rats along with reduction in inflammatory cytokines IL-6 and TNF-α in adipose tissue and down-regulated forms of GLUT 4 and PPAR-γ [58]
Lactobacillus casei Shirota	They can increase lipopolysaccharide-binding protein expression in plasma and diminishes endotoxemia [63]
Bifidobacterium animalis subsp. lactis	They can restrict bacterial translocation in intestine alleviating bacteremia in early stages of T2D [64]
L. casei Zhang	Oral administration can ameliorate impaired glucose tolerance in hyperinsulinemic rats induced by high-fructose [65]
Lactobacillus	Oral administration is positively correlated with expression of CB2 receptor [76]
Clostridium	Oral administration is negatively correlated with CB2 expression probiotics control GM through CB2 receptor expression [76]
Bifidobacterium infantis	Impairs inflammation by altering the intestinal permeability [80, 81]
Bacteroidetes:Firmicutes ratio	Low in GM of obese patients [112, 113]
Butyrate-producing bacteria (*Roseburia* species and *Faecalibacterium prausnitzii*)	Low population in GM of T2DM patients [113]
Firmicutes (Gram-positive) and Bacteroidetes (Gram-negative)	90% of the bacterial species present in gut [15, 16]
Proteobacteria and particularly *Escherichia coli*	High in T2D patients [113, 121]
Enterobacteriaceae	Population elevated by T2D drugs [122]
Clostridium and *Eubacterium*	Population lowered by T2D drugs [122]
Akkermansia sp. *Akkermansia muciniphila*	Metformin increases the populations of *Akkermansia* sp. in high-fat diet-fed mice, hence improving glucose metabolism. Oral administration of *Akkermansia muciniphila* also improves metabolic dysfunctions like endotoxemia and adipose tissue inflammation [122]

Table 1.
Facts and effects of various types of bacteria present in GM

maintenance of colonocytes and also protects the colon by enhancing mucin expression and immune response [24]. Acetate and propionate can cross the liver epithelium, and propionate gets metabolized in the liver, whereas acetate stays in the peripheral circulation [25]. SCF also regulates epithelial barrier integrity by maintaining the tight junction proteins like claudin-1, occludin, and Zonula Occludens-1. Suppression of these proteins leads to invasion of bacteria and lipopolysaccharides (LPS) stimulating an inflammatory response [26]. Hence SCF acts as energy source and also regulates host biological responses including inflammation, oxidative

stress, and immune response toward Crohn's disease, ulcerative colitis, and colorectal cancer [27, 28]. Host metabolism is activated by SCFs by direct stimulation of G-coupled receptors like free fatty acid receptors 2 and 3 (FFAR2/GPR41 and FFAR3/GPR41) occurring mainly in the gut epithelial cells. They also activate host metabolism by inhibiting nuclear class I histone deacetylases (HDACs) present in the epithelial cells [27]. FFAR2 acts as the receptor for acetate and FFAR3 is the receptor for butyrate and propionate. Activation of these receptors regulates the level of satiety hormones like ghrelin (orexigenic peptide), glucagon like peptide-1 (GLP-1), and peptide YY (PYY) (anorexigenic peptide) [29]. Ghrelin secretion occurs pre-meal, while GLP-1 and PYY are secreted post-meal, which in turn stimulates insulin production in the pancreatic β cells. GLP-1 and PYY also reduce food intake, normalizes weight loss and maintain the balance of energy intake. Increase in the production of SCFs enhances the secretion of PYY and GLP-1 but decreases secretion of ghrelin, which ultimately leads to increased satiety and reduction in food intake [30]. The other factors inducing reduced appetite is mediated by butyrate and propionate by (i) enhanced expression of leptin in adipocytes, direct regulation of body weight and energy homeostasis by decreased food intake and upregulated energy expenditure [31], (ii) promoting gluconeogenesis in the intestinal cells [32] and (iii) inhibition of histone acetyltransferase and deacetylases which exhibit anti-inflammatory responses, epigenetic modification necessary for proliferation and differentiation of immune cells, activated AMP-activated protein kinase (AMPK) pathway synchronised adiponectin secretion, induction of mitochondrial biogenesis and fatty acid oxidation [33]. In healthy subjects SCF regulates integrity of gut, secretion of hormones, and immune responses, while in metabolically unhealthy subjects SCF implements protection from diabetes, ulcerative colitis, colorectal cancer, and neurodegenerative disorders [24, 34].

2.1 Gut microbiota composition

Recent studies targeting metagenomics have disclosed that approximately 90% of the bacterial species in the GM of adult humans are Bacteroidetes (Gram-negative) and Firmicutes (Gram-positive) [35, 36]. A healthy person fosters 500–1000 bacterial species at a single time and almost 1012–1014 colony-forming units (CFU) with a total mass weight of about 1–2 kg in the total gut [37] with 109–1012 CFU/ml in the colon, 101–103 CFU/ml in jejunum and 104–108 CFU/ml in the ileum [38]. Transfer of microbiota from mother to embryo takes place in utero or during birth and attains strength by the 2 years. Composition of GM is shaped by host genetics, environmental factors and early exposure to microbes during birth. The other factors that regulate formation of a stale GM are exposure to vaginal microbiome during normal delivery, skin microbiota during cesarean sections, breast-feeding and antibiotics in neonatal or early childhood.

2.2 Role of gut microbiota in carbohydrate metabolism

Normal diet of a healthy human contains a considerable percentage of carbohydrates comprising of monosaccharides, disaccharides and complex polysaccharides. The difference lies in the absorption of the sugars, for example common sugars like cane sugar and fruit sugars are readily absorbed in the intestine, disaccharides like maltose, lactose and sucrose and complex polysaccharides like pectin, starch and hemicellulose are broken down into monosaccharides in the ileum with the help of bacterial enzymes like glycosidases before being absorbed [39]. After food intake consisting of carbohydrate-rich diet, glucose levels in the blood rise, and later are strongly regulated and kept at a homeostatic level by the help of two hormones,

insulin and glucagon. Carbohydrate digestion and absorption occurs in the upper digestive tract via glucose transporters called GLUTs (glucose transporters) located on the epithelial cells [40]. GLUT proteins uptake glucose into the pancreatic β-cells. Metabolization of glucose stimulates insulin secretion due to increased ATP/ADP ratio, membrane depolarization and closure of potassium channels, resulting in calcium dependant exocytosis of insulin [41].

The role of gut environment and gut associated lymphoid tissue plays a pivotal role in T2D [42]. T2D is a chronic metabolic disorder characterized by fasting serum hyperglycemia, non-responsiveness of insulin and insulin insufficiency [43]. Insulin resistance or non-responsiveness occurs in the liver and skeletal muscle cells when they undergo failure to sense insulin. Other factors in T2D are non-responsiveness or deficiency of incretins, amplified lipid catabolism, increased glucagon levels in circulation and increased salt and water renal retention [43, 44]. High-fat-diet-fed germ-free mice, wild type mice and standard diet fed mice exhibit different metabolic and immunological characters depending on diet and GM [45, 46]. Also mice belonging to same genotype and diet exhibit different metabolism of glucose depending on their GM [47].

2.3 Role of gut microbiota and its association with diet

In the earlier sections it has been discusses that our GM plays a key role in digestion and absorption of food. Increased population of Bacteroidetes lead to increase in energy production. The population of Bifidobacteria reduce in high fat-fed mice gut increasing endotoxemia. Prebiotic supplementation can restore Bifidobacteria levels in the mouse gut [48, 49]. Bacteroidetes are more widespread in the gut of people consuming animal-based food rich diet. *Prevotella* is prevalent in people consuming plant-based food rich diet. In case of people consuming plant-based foods, the GM produce more SCFAs and increased synthesis of amylase, glutamate and riboflavin [50, 51]. On the contrary, people consuming animal-based foods have GM modified for increased catabolic processes as for example degradation of glycans and amino acids [52]. SCFAs like butyrate, propionate and acetate along with some gases like hydrogen are produced by the breakdown of these polysaccharides, are further used in colonic fermentation and yield energy [53]. Butyrates can decrease calorie intake of an individual by inducing satiety via production of GLP-1 and gastric inhibitory peptide-1 [54]. Butyrates are also involved in maintenance of gut integrity by supplying energy for regulating the survival and proliferation of enterocytes.

Low-grade inflammation is a key pathophysiological factor behind the progression of type 2 diabetes (T2D), and incidence of hyperglycemia and insulin resistance [55]. Progression of T2D occurs along with reduced GM diversity and increased gut inflammation. Gut inflammation includes innate immune responses via toll-like receptors, (TLRs) secretion of proinflammatory cytokines and increased endotoxemia. Also during high-fat diet induced obesity, intestinal Gram-negative bacteria translocates in the circulatory system, adipose tissue and cause endotoxemia [56].

2.4 Role of probiotics upon gut microbiota

Probiotics enhance production of interleukin-10 (IL-10) an important regulatory and anti-inflammatory cytokine in diabetic mice. Increased IL-10 down-regulates proinflammatory cytokines like interferon-γ (IFN-γ) and interleukin-2 (IL-2)/interleukin 1-β (IL-1β) preventing inflammation and incidence of diabetes [56, 57]. *Lactobacillus reuteri* GMNL-263 reduces T2D markers like serum glucose, glycated hemoglobin and c-peptide in high-fructose-fed rats along with reduction

in inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in adipose tissue and down-regulated forms of GLUT 4 and peroxisome proliferator activated receptor-γ (PPAR-γ) (**Figure 1** and **Table 1**) [58]. Methodical consumption of probiotic yoghurt reduces inflammatory markers such as high-sensitivity C-reactive protein levels in pregnant women and T2D [59, 60]. Probiotic strains decrease oxidative stress in pancreatic tissue, reducing inflammation and apoptosis of pancreatic cells [61]. Probiotic strains also lessen LDL cholesterol and total cholesterol in serum by regulating lipid metabolism, reducing the risk of T2D [62]. Consumption of *Lactobacillus casei* Shirota increase lipopolysaccharide-binding protein expression in plasma and diminishing endotoxemia (**Table 1**) [63]. *Bifidobacterium animalis* sub sp. lactis can restrict bacterial translocation in intestine alleviating bacteremia in early stages of T2D (**Table 1**) [64]. Oral administration of *L. casei* can also ameliorate impaired glucose tolerance in hyperinsulinemic rats induced by high-fructose (**Table 1**) [65].

2.5 Role of gut microbiota in maintaining intestinal integrity and metabolic conditions

Increased gut permeability provides the relation between high-fat diet and LPS by causing LPS entry into circulation via the portal system in T2D patients [66]. Animal model studies have provided evidence between increased intestinal permeability and progression of obesity and insulin resistance [67, 68]. Consumption of prebiotics increase gut microbiota, rectify intestinal permeability, diminish inflammation, alleviate endotoxemia and ameliorate glucose tolerance [68]. High-fat diet induce decrease in tight junction proteins regulating epithelial integrity of gut lining and gut permeability such as zonula occluden-1 (ZO-1) and occludin. Dietary fatty acids activate toll-like receptor 2 (TLR-2) and toll like receptor 4 (TLR-4) signaling pathways. TLR-4 leads to LPS translocation into intestinal capillaries and induces insulin resistance in mice [69–71]. Altered gut permeability and plasma LPS levels are related with distribution of ZO-1 and occluding and

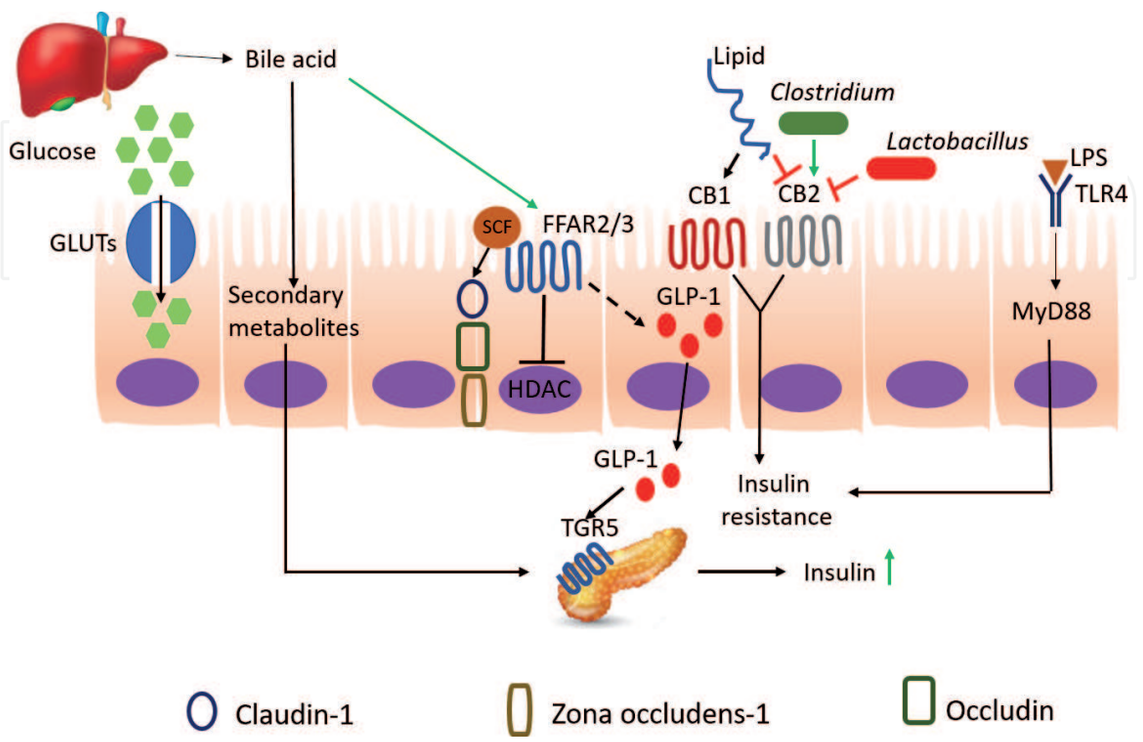

Figure 1.
Influence of gut microbiota in various physiological responses [80, 81, 83, 84, 110, 111].

endocannabinoid (eCB) system. Gut microbes selectively modify expression of the cannabinoid receptor 1 (CB1) in colon also affecting zona occluding ZO-1 and occludin [72]. Administration of probiotics changes the gut microbiota resulting in reduced gut permeability in obese mice. Antibiotic exposure induces metabolic endotoxemia in mice fed with high-fat diet, along with increased gut permeability, secretion of proinflammatory cytokines, and incidence of diabetes and obesity (**Figure 1**). Modulation of the eCB system is connected with inflammation and diabetes [72, 73]. Moderation of GM controls eCB expression in gut, thereby regulating gut permeability and plasma LPS levels through the CB1 receptor [72]. Changes in the gut microbiota due to prebiotic feeding reduce gut permeability in obese mice. Modulation of gut permeability occurs through the distribution of tight junction proteins through eCB systems [55]. Activation of cannabinoid CB2 receptor and blocking of CB1 receptor improves glucose tolerance [74, 75]. *Lactobacillus* administration is positively correlated with expression of CB2 receptor, and *Clostridium* spp. is negatively correlated with CB_2 expression (**Table 1**) [76]. Also probiotics control GM through CB2 receptor expression [77].

3. Gut microbiota and obesity mediated type 2 diabetes

GM has a close association with host obesity, since the increase in total body fat in wild type mice is high when compared to germ free mice consuming more food. Transplanting of cecum-derived microbiota induced an increase in body fat mass and insulin resistance, adipocyte hypertrophy, and increased level of circulating leptin and glucose [78]. Germ free mice when fed with a diet rich in fat and sugar content showed lean phenotype however wild type mice who were fed with the high sugar and high fat diet turned obese. Also the germ free mice showed enhanced insulin sensitivity, leading to improved glucose tolerance and altered cholesterol metabolism diminishing cholesterol storage and increasing cholesterol excretion via fecal route. GM alters intestinal permeability, causes endotoxemia, enhances calorie provision, stimulates endocannabinoid system (eCB), regulates lipid metabolism by increasing activity of lipoprotein lipase and lipogenesis resulting in host obesity. Lipopolysaccharides (LPS), present in the cell membrane of Gram-negative bacteria, stimulate low-grade inflammation and incidence of insulin resistance (IR). LPS reaches the circulation from gut by diffusion either by enhanced intestinal permeability or absorption after association with chylomicron [79]. LPS acts as a ligand for toll-like receptors TLR-4 occurring in immune cells, liver and adipose tissue. LPS activated TLR-4 prompts conformational changes recruiting adapter molecules like myeloid differentiation primary factor MyD88 protein, IL-1 receptor associated kinase IRAK, TNF receptor associated factor TRAF6, and NF-κB inducing kinase NIK, phosphorylating and degrading inhibitor of nuclear factor kappa B kinase IKKB, inhibitor of nuclear factor kappa light chain enhancer of activated B cells NF-κB. Activated NF-κB translocates to the nucleus triggering expression of inflammatory proteins and various pathways like janus kinase JNK, p38 microtubule associated protein kinase MAPK, and extracelluar signal regulated kinase ERK finally resulting in insulin resistance (**Figure 1**). Colonization of *Bifidobacterium infantis* can impair inflammation by altering the intestinal permeability. Excess of lipid in diet enhances exposure to free fatty acids and their derivatives, facilitates endotoxin absorption and increases plasma LPS level termed as "metabolic endotoxemia" (**Table 1**) [80, 81]. Interaction between endogenous lipid and cannabinoid receptor (CB1 and CB2) stimulates adenylate cyclase and MAPK, ERK, and NF-κB pathways, triggering inflammation, insulin resistance and obesity [82]. On the whole GM stimulates the eCB system, enhances intestinal permeability, triggering

LPS entry into circulatory system resulting in endotoxemia. Rise in LPS, modulates the integrity of the tight junctions of the intestinal membrane increasing LPS in circulation. Therefore, GM is a complex system having both advantageous and dangerous microbes, and understanding the GM and host integration system provides a generalized idea about the function of each unit of the GM-host system [83, 84].

3.1 Gut microbiota and carbohydrate metabolism during type 2 diabetes

Bile acids affect glucose homeostasis via activation of nuclear farnesoid X receptor (FXR) and the membrane-bound G protein coupled receptor, TGR5. These receptors are expressed in liver, ileum and pancreas [85]. Some bile acids act as agonists for FXR, and others are FXR antagonists [86–88]. Known FXR agonists are CDCA, lithocholic acid, deoxycholic acid, and cholic acid [89]. The antidiabetic effects exhibited by vertical sleeve gastrectomy, bariatric surgery, occurs through FXR [90]. Also, intestinal FXR agonist treatment can improve insulin sensitivity [91]. In the ileum, activation of FXR leads to the production of fibroblast growth factor-19, a hormone that affects glucose tolerance through mechanisms that are largely independent of insulin [92, 93]. Activation of TGR5 produces glucagon-like peptide-1 (GLP-1) from ileum improves both energy and glucose homeostasis [94]. Activation of FXR in pancreas regulates insulin transport and secretion [95], and protects the islets from lipotoxicity [96]. FXR activation in liver improves insulin sensitivity in T2D patients [97]. The GM can modulate the amount and type of secondary bile acids produced via FXR and TGR5 signaling. GM enzymes such as bile salt hydrolase for deconjugation, 7-alpha dehydroxylase for dihydroxylation and 7α-hydroxysteroid dehydrogenase for epimerization of bile acids are reduced in T2D patients compared to healthy controls [98]. Bile acid concentrations in the circulation show a diurnal pattern since they increase after food intake [99].

3.2 Gut microbiota and lipid metabolism during type 2 diabetes

Our body metabolism, inflammatory processes and innate immune system are regulated by dietary lipids [100]. The dietary lipids can also act as (proinflammatory) ligands which can bind to nuclear receptors [101]. The nuclear receptors are peroxisome-proliferator-activated receptors (PPAR) and liver X receptors (LXR) which regulate metabolic and inflammatory pathways. Hence the dietary lipids can improve insulin action and down-regulate secretion of pro-inflammatory cytokines [102, 103]. Lipids can also activate G-protein coupled receptors (Gpcr) such as Gpr43 when activated by dietary-metabolite acetate lipolysis in adipocytes is decreased leading to reduced plasma-free fatty acids. Gpr43 can be considered as a potential target for regulation of lipid metabolism [104]. Inflammation and lipid accumulation are characteristic features of atherosclerosis [105]. Recent evidences provide sufficient link between atherosclerosis and GM variety [106]. Short-term antibiotic administration can alter the composition of GM which can convert dietary choline and L-carnitine to trimethylamine (TMA). TMA is later oxidized into TMAO by the action of hepatic Flavin monooxygenases [107]. Dietary choline is highly available in foods rich in lipid phosphatidylcholine, lecithin, such as in eggs, red meat, milk, poultry, liver, and fish [108]. Bile acids are key modulators of lipid and cholesterol metabolism, and they facilitate intestinal absorption and transport of nutrients, vitamins, and lipids. Production of bile occurs in the liver and 95% of bile acids are reabsorbed in the ileum. Later the bile acids are re-absorbed in liver, entering the enterohepatic circulation. GM converts primary bile salts to secondary bile salts by bile acid de-hydroxylation [109]. Bile acids can also result in the release of GLP-1 from enteroendocrine L cells via activation of Takeda G protein coupled receptor-5

(TGR5) (**Figure 1**). This phenomenon affects insulin secretion sensitivity [110]. Bile acids have another receptor called farnesoid X receptor (FXR) present in liver, intestine, and pancreatic beta cells [111]. Hence, bile acids improve our metabolism in the long term after bariatric surgery by enhancing intestinal hormone secretion.

3.3 Gut microbiota composition during type 2 diabetes

The GM of T2D patients exhibit low population of Firmicutes and Clostridia and high ratio of Bacteroidetes:Firmicutes (**Table 1**) [112, 113]. However, the GM of T2DM and obese patients are not always identical because the GM of obese patients show decreased Bacteroidetes:Firmicutes ratio [113–115, 118]. GM of T2DM patients also show low population of butyrate-producing bacteria. Short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate are fermented from dietary fiber in large intestine by GM. SCFAs regulate energy metabolism, immune responses and tumorigenesis in gut. Butyrate is the energy source for colonic epithelial cells. Butyrate perpetuates intestinal integrity and thereby avert translocation of Gram-negative intestinal bacteria across the lumen of the gut. This phenomenon ultimately leads to endotoxemia triggering a low-grade inflammation during T2D [15, 113, 115].

The major risk factors behind T2D are genetic predisposition, less physical activity, fetal programming, obesity and altered GM [114, 116]. Total weight of GM in the distal gut is about 1.5 kg and it is considered as a microbial organ. The GM consists of embers from Bacteria, Archaea, Eukarya and viruses, but a large part of the population includes anaerobic bacteria. 90% of the bacterial species present in gut are grouped into the two bacterial phyla Firmicutes (Gram-positive) and Bacteroidetes (Gram-negative) (**Table 1**) [15, 16]. An average adult fosters a minimum of 160 bacterial species and a set of genes in the GM is obligatory for proper functioning of the GM [15]. The GM gives protection from disease causing pathogens and facilitates the immune system. GM also help in production of vitamin K and many B-vitamins like folate, vitamin B12. Metagenomic studies about sequencing of T2D patients exhibit dysbiotic GM and less butyrate-producing bacteria (*Roseburia* species and *Faecalibacterium prausnitzii*). Metabolic disorders like obesity and impaired glucose metabolism are related with an altered ratio of Firmicutes and Bacteroidetes [118–120]. Populations of Proteobacteria and particularly *Escherichia coli* are also high in T2D patients (**Table 1**) [113, 121]. Gram-negative bacteria contribute to inflammatory lipopolysaccharides (LPS) stimulating pro-inflammation, during T2D and obesity. Oral administration of metformin, a widely used drug for T2D elevates populations of Enterobacteriaceae and lowers populations of *Clostridium* and *Eubacterium*. Metformin also increases the populations of *Akkermansia* sp. in high-fat diet-fed mice, hence improving glucose metabolism [122]. Oral administration of *Akkermansia muciniphila* also improves metabolic dysfunctions like endotoxemia and adipose tissue inflammation (**Table 1**) [122, 123]. Hence metformin can be used as a potent drug in improvising the GM content in T2D patients, managing glucose tolerance and inflammation.

4. Modulation of gut microbiota to cure type 2 diabetes

4.1 Antibiotics

Antibiotics have become very popular for elimination of pathogenic bacteria. However, antibiotics are also harmful to the local population of beneficial GM. Hence excess use of antibiotics must be prevented for healthy maintenance of

GM. Bacterio-therapeutic use of antibiotics in farm animals has increased increase growth and food production, but has taken a toll of their metabolic pathways [115]. Excess of usage of antibiotics in early infancy show chronic effects on GM diversity, overweight in infants, obesity in adults. For example, excess of bacterio-therapy with vancomycin has increased the incidence of obesity in adults. Even, short-term treatment with vancomycin impeded peripheral insulin sensitivity and other related metabolic syndromes affecting GM (**Table 2**) [115]. Hence, even short-term treatment with oral antibiotics harness intense and chronic damage to GM diversity and function.

4.2 Prebiotics and probiotics

Recently prebiotics and probiotics have gained a lot of popularity among individuals as a healthy substitute for antibiotics. Prebiotics are actually indigestible carbohydrates that improve the growth and function of colonic bacteria boosting host health. Prebiotics include oligosaccharides which cannot be digested in the upper GI tract. These oligosaccharides are fermented, producing SCFAs in the colon and result in stimulation of growth of colonic. Prebiotics can be obtained from a large number of dietary elements like barley, garlic, asparagus, wheat bran and onions and both prebiotics and probiotics can be obtained from pickled and fermented foods like sauerkraut, kimchi, miso, yogurt [15, 16]. Probiotics obtained from food and supplements contain some very popular strains like bifidobacteria and lactobacilli. These bacteria alter the composition and function of GM as well as host system activity. The prebiotics and probiotics compete with pathogenic

Types of cure	Effects
Antibiotics	• Affect GM diversity • Overweight in infant • Obesity in adult • Vancomycin impede insulin sensitivity [115]
Prebiotics and probiotics	• Compete with pathogenic bacteria • Intensify intestinal barrier by secreting some antimicrobial substances • Enhances immune system [15, 16, 115]
Dietary modulation	• Increase GM ecosystem diversity • Enhances SCFA • Reduces fasting and postprandial glucose, A1C, serum cholesterol, insulin resistance, BMI, waist and hip circumferences [124]
Metformin	• Increases levels of butyrate-producing bacteria • Decreases levels of Lactobacillus [125]
Fecal microbiota transplant	• Allogenic infusion from lean donors lead to significant rise in GM diversity, enhanced levels of butyrate producing bacteria and improved insulin sensitivity [114, 115]
Bariatric surgery	• Proteobacteria rises and Firmicutes and Bacteroides lowers • BMI reduces by 15–32% • C-reactive protein decreases • T2DM is attenuated [112, 115]

Table 2.
Types of treatments for T2D involving modulation of GM and their effects.

bacteria, intensify the intestinal barrier by secreting some antimicrobial substances and enhances the immune system (**Table 2**) [15, 16, 115].

4.3 Dietary modulation

Changes in diet plan can modulate activity of GM and host metabolism. A fat and carbohydrate restricted diet increased the ratio of Bacteroidetes to Firmicutes in obese patients with T2D [118]. Also calorie deficient diet plans or diet plans rich in high-fiber macrobiotics like complex carbohydrates, legumes, fermented products, sea salt, and green tea and free of animal protein fat, and added sugar improved dysbiosis, increased GM ecosystem diversity, and enhanced SCFA producers in T2D patients. Macrobiotic diet can more efficiently reduce fasting and postprandial glucose, A1C, serum cholesterol, insulin resistance, BMI, waist and hip circumferences than the control diet. Also macrobiotic diet could effectively reduce pro-inflammatory bacterial strains (**Table 2**) [124].

4.4 Metformin

Metformin, already a well-established drug for T2D, has recently been known to have bacterio-therapeutic effects on microbial composition and production of SCFA. Several recent reports have shown that metformin affects GM of T2D patients like increasing the levels of butyrate-producing bacteria. Metformin can also decrease the levels of Lactobacillus which remains high in T2D patients (**Table 2**) [125].

4.5 Fecal microbiota transplant

Fecal microbiota transplant, or stool transplant also called bacteriotherapy, which is the process of replacing fecal bacteria from a healthy individual into a host individual has been quite effective in restoring GM composition. Fecal microbiota transplant is used in treating recurrent *Clostridium difficile colitis* recharging useful bacteria in the GI tract along with usage of antibiotics. Autologous infusion is reinfusion of one's collected feces and allogenic infusion is infusion with feces from a donor. Insulin resistant adults when autologously transplanted did not alter the GM composition but when transplanted with allogenic infusion from lean donors exhibited significant rise in GM diversity, enhanced levels of butyrate producing bacteria and improved sensitivity to insulin (**Table 2**) [114, 115].

4.6 Bariatric surgery

Bariatric surgery, or Roux-en-Y gastric bypass (RYGBP), is removal of a portion of stomach and re-routing the small intestine to a small stomach pouch. It is performed on people as an efficient tool to treat obesity. After bariatric surgery huge changes occur in the GM, Proteobacteria rises and Firmicutes and Bacteroides lowers, BMI reduces by 15–32%, C-reactive protein decreases and T2DM is attenuated. However, increase in some bacteria are highly significant than the normal levels in lean controls, which means these alterations are linked with GM modification, and not body weight (**Table 2**) [112, 117, 118].

5. Conclusion

The GM makes one of the largest organs in human body and remains the reason behind various metabolic disorders such as obesity, atherosclerosis, type 2 diabetes

and so on. The alterations in GM is very susceptible to changes in our diet and environment which makes them vulnerable and ultimately ends in the incidence of diseases. Reversal of the GM alterations can restore the normal physiological functions and health. Hence further investigation is required in order to get a detailed scenario of the composition of various GM and their detailed function. Scrutiny of the composition of the GM and the change in their population in various metabolic disorders can create new avenues in finding out the treatment for those diseases. Deeper insights in the composition and function of GM can also provide more ideas for development of various techniques and drugs for the enhancement of the GM for better physiological responses and treatment of diseases.

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Conflict of interest

The authors declare no conflict of interest.

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