Chapter 2

The Microbiome and the Epigenetics of Diabetes Mellitus

Lissé Angarita Dávila, Valmore Bermúdez Pirela, Waldo Díaz-Vasquez, Nadia Reyna Villasmil, Silvana Cisternas León, Ma Cristina Escobar Contreras, Kristian Buhring Bonacich, Samuel Durán Agüero, Paula Carrasco Vergara, Rodrigo Buhring Bonacich, Constanza Bugman, Virginia Céspedes, Marcell Gatica, Marion Guerrero Wyss, Jorge González Casanova and Francisco Valdebenito

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http://dx.doi.org/10.5772/intechopen.76201

Abstract

Gut microbiota (GM) in the epigenetic mechanisms of diabetes mellitus and the reprogramming of the cells is a novel and emerging concept. The purpose of this chapter is to describe the modification of the GM and its relation with DM2. The increased risk of this disease is associated with changes in the amount of *Bacteroides*/*Clostridium* in the *Firmicutes*/*Bacteroidetes* ratio of people having DM. A dysbiosis state associated generates low-grade inflammation with similar characteristics that occur under metabolic syndrome, whose pattern is recognized by Toll-like receptor that recognizes important patterns of immunity. The synthesis of butyrate generated by intestinal microorganisms inhibits the metabolic pathway of histone deacetylase, promoting cellular differentiation, proliferation, and insulin resistance. On the other hand, the direct relationship between the neuroendocrine system and the GM has been demonstrated through the production of serotonin by enterochromaffin cells, whose action could influence the etiopathogenic factors of DM2.

Keywords: diabetic, epigenetics, diet, microbiome

1. Introduction

Diabetes *mellitus* type 2 (DM2) is a global pandemic; although genetic factors can predispose subjects to suffer from it, external factors such as socioeconomic changes and cultural and eating habit changes have more contributions to increasing world prevalence [1], where overweight and obesity are considered as the main mediators of the disease. The number of cases of DM2 according to the International Diabetes Federation is 415 million adults by 2015. The risk death of subjects with DM is significantly higher than those without the disease, doubling it when we refer to cardiovascular death reason [2]. It has been determined that the gut microbiota (GM) is altered in subjects with type 2 diabetes, so studying its role in the development of pathology is essential to determine new approaches to treatment; it permits the identification of those bacteria beneficial to humans, from the bacterial genome recognition. The so-called microbiome correspond to the entire GM genome; it exceeds the size of the human genome, having about 500 times more genes that complement our coding; this bacterial ecosystem has evolved in a symbiotic relationship with human [3]; GM exerts nutritional, metabolic, and immunological functions that affect the human being. During the last decade, several studies have been reported on the effect of the GM on glycemic control [4]. In this context, GM in the epigenetic mechanisms of diabetes mellitus and the reprogramming of the cells is a novel and emerging concept. It is known that products derived from diet along with intestinal bacteria can change the epigenome of the host with favorable metabolic effects [5]. These microorganisms are essential for the biosynthesis of vitamins and hormones, as well as for the degradation of nondigestible dietary fibers and mucin in simple sugars and short-chain fatty acids [6]. Changes in the composition and function of the predominant GM are associated with an increased risk of DM2 and are linked to an increase in the number of *Bacteroides* [7] and *Clostridium* [8]. Specifically, the increase of *Firmicutes*/*Bacteroidetes* ratio in the distal bowel, as well as the number of opportunistic pathogens, and in the production of endotoxins of Gram-negative bacteria is capable of modifying intestinal permeability. The metabolic syndrome is associated with changes in the framework of the GM that lead to low-grade inflammations, since the increased permeability of the intestinal membrane damaged by bacteria induces inflammation, through the epigenetic alteration of inflammatory molecules such as Toll-like receptors [9]. Mucus and glycocalyx layer mainly produced by *Bacteroides thetaiotaomicron*, *Akkermansia muciniphila*, and *Escherichia coli* cause chronic low-level inflammation, insulin resistance, and, lastly, DM2 [10]. Evidence demonstrates the link between diabetes and histone deacetylase (HDA), because the microorganisms producing butyrate, an HDA inhibitory molecule that promotes differentiation and cellular proliferation and insulin resistance [11], are decreased in diabetics [5]. On the other hand, it has been recognized that the microbiome has a direct effect on the immune and neuroendocrine system, constituting a new brain gut axis [12], in which the circadian rhythm plays a fundamental role [13]. The production of colonic serotonin [14, 15] by the microbiome, through the effect of short-chain fatty acids on enterochromaffin cells [13, 16, 17], would allow to relate this neurotransmitter to the metabolic processes as one of the possible etiopathogenic factors of DM2. The next challenges are focused on integrating the transcriptomic, epigenetic, proteomic, and metabolic information of the human genome and the microbiome into the nutritional treatment [2].

2. Microbiome, epigenetics, and diabetes interactions (metabolic pathways)

The human intestinal microbiota (HIM) is composed of a complex community of microorganisms; more than 1000 species have been identified, where only a few are cultivable [18]. The gut microbiome corresponds to a total set of genes present in the HIM (about 3 million genes), approximately 150-fold human genome [19]. This microorganism participates as a counterpart of gut enzymatic activities by a diverse metabolic repertoire becoming an important contributor to the metabolism of the host [20]. Exploratory studies have been shown that play an important role in the etiology and development of many diseases, being considered as markers of the course of the disease. Some chronic illnesses in which HIM has been regarded are the inflammatory bowel disease (IBD), the irritable bowel syndrome (IBS), diarrhea, obesity, diabetes, and inclusive cancer. The recent role attributed to the microbiome and health has promoted the research to study the microorganism characteristics and the design of strategies to restore damage microbiome to a normal "state" by using a microbe inoculation strategy or by using dietary modification to feed specific species and help their development or otherwise consume foods or other substances that induce the extinguishment of some species in the intestine. The abundance and diversity of the intestinal bacteria are located mainly in the large intestine where it exerts its principal metabolic role. Bacteria are capable of hydrolyzing carbohydrates, lipids, and proteins principally; *saccharolytic* bacterial fermentation produces generally beneficial metabolites such as short-chain fatty acids (SCFAs) and gases. The three most abundant SCFAs detected in feces are acetate, propionate, and butyrate, in molar ratios of 3:1:1 to 10:2:1 [21]. Butyrate is recognized as the most important SCFA for human health and is absorbed by the epithelial cell of the colon in the proximal colon via passive diffusion and by active transport mechanisms. Some properties have been attributed to butyrate, for instance, being able to be used by colonocytes as energy source, the potential anticancer activity inducing apoptosis of colon cancer cells, its ability to regulate gene expression in host by inhibiting histone deacetylases [22], and the beneficial effects in glucose regulation by activation of gluconeogenesis in the gut via cAMP-dependent manner [23].On the other hand, propionate exerts a dual action in intestine and liver regulation of gluconeogenesis and is considered an important molecule for satiety signaling because of an interaction with G protein-coupled receptors GPR 41, GPR 43 receptors, and fatty acid receptors FFAR2 and FFAR3. The net effect of the conversion of propionate to glucose is the decrease of gluconeogenesis in the liver; this generates a reduction in the production of adiposity [23]. Acetate is the most abundant SCFA and is considered as essential metabolite for bacteria growth. *Faecalibacterium prausnitzii* will not grow in pure culture in the absence of acetate [24]. Acetate participates in the cholesterol metabolism and lipogenesis in the host [25].

2.1. Microbiota metabolism

A cross-feeding effect has recently been described, for instance, *Bifidobacterium longum* growing in fructooligosaccharides (FOS) produces a conversion into lactate and promotes the growth of *Eubacterium hallii* that could not grow in the presence of FOS alone and converts it to butyrate [26]. Another example of cross feeding occurs when *Roseburia intestinalis* increases its growth in co-cultures with—the acetate contributor—*B. longum* [27, 28]. Two main routes of butyrate

production [29] and three pathways for propionate production have been identified in bacteria; noteworthy peptide and amino acid can be used to form propionate and butyrate from some species of *Bacteroidetes* and *Firmicutes*. The main sources of propionate are aspartate, alanine, threonine and methionine, instead glutamate, lysine, histidine, cysteine, serine and methionine for butyrate production [30]. Sequencing targeted gene instead of 16S rRNA genes indicates that most bacteria had the capability to produce exclusively propionate or butyrate but not both. Conversely, bacteria change their fermentation depending on growth conditions and produce different SCFAs. *Roseburia inulinivorans* produces butyrate normally, but it can change its gene expression pattern in the presence of fucose producing propionate and propanol [31]. *Ruminococcus obeum* produces acetate, formate, and lactate on glucose growth and also produces propionate in the presence of fucose. *Bacteroides thetaiotaomicron* in the presence of fucose also increases fucosylated glycan to be used in absence of nutrients; it has been described that it is also important in early colonization of the infant gut [32]. By decreasing the carbohydrate content of the diet significantly reduced both fecal butyrate concentrations and numbers of the *Roseburia/E. rectale* group [33]; wheat bran has >70% arabinoxylan oligosaccharides (AXOS) that increase the SCFA content [34]. Unfortunately, the increased SCFA content causes reduced transit time and thus a decreased colonic absorption of SCFA. Excluding those vegetables rich in short fermentable carbohydrates such as oligosaccharides, monosaccharides, and polyol (FODMAP diet) reduces bacterial fermentation, showing a decrease in the total numbers of bacteria, and the fecal concentration of different SCFAs is similar to the control diet [35].

2.2. Gas production and the microbiome

HIM generates hydrogen, carbon dioxide, and methane, all of them odorless gases; odoriferous gases constitute less than 1% of total flatus and include NH_3, hydrogen sulfide, indole, skatole, and volatile amines. There are many bacteria that do not produce gas [36] such as lactobacilli and bifidobacteria, so they can be used as probiotic able to reduce the gas content in colon. Gases can be excreted by flatus (several liters per day in a healthy human) [37]. Hydrogen is produced by *Bacteroides* and *Clostridium* [38] and produces a high energy yield, and it can be used by other bacteria from the gut to produce lactate, succinate, and ethanol and sulfate-reducing bacteria (SRB), where *Desulfovibrio* is the principal [39]. In the methanogenesis CO_2 is converted to CH_4, and in the acetogenesis dioxide and hydrogen are converted into acetate both use hydrogen [38]. Carbon dioxide is between 5 and 50% of the total flatus volume, and it is produced by acidification of bicarbonate in the upper gastrointestinal tract, and bacterial metabolism [40], *C. sporogenes*, *C. butyricum*, and *C. perfringens*, produces hydrogen and CO_2.

2.3. Proteins

HIM has an important role converting protein metabolism, enzymes, mucin in short peptides, fatty acids and gases (H_2, NH_4, CO_2 and H_2S), Clostridia, Streptococci, Staphylococci, *Bacillus* and species of *Bacteroides* and *Propionibacterium* as the predominant proteolytic characteristics in fecal samples [41]. A preference for amino acid fermentation at higher ranges of colonic pH and a reduction in quantity when fermentable carbohydrate was available are observed [42]. The proximal colon was predominantly saccharolytic by nature; whereas protein fermentation increased distally, the fermentation was associated with the presence of phenol, indole, ammonia, and branched-chain fatty acids [21]. Aromatic amino acids phenylalanine, tyrosine,

and tryptophan can be fermented to phenylpropanoid, phenylacetic acid, and 4-hydroxyphenyl-acetic acid by *Bacteroides*, *Eubacterium hallii*, *and Clostridium bartlettii* [43].

2.4. Vitamin synthesis and the microbiome

Gut microbiome can synthesize certain vitamins, such as vitamin K, biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine of B group [44]. For instance, subjects having low vitamin K diet showed an important decrease in plasma prothrombin when treated with broad-spectrum antibiotic [45]. Explored genomes in gut showed presence of eight vitamin B synthesis pathways. The most represented were riboflavin [46] and niacin with 162 genomes. *Bacteroidetes* is the phylum with larger B predicted vitamin generators. In the same line, bacteria can complement the biosynthesis of vitamins. In sum, GM can contribute with 25% of total dietary vitamin intake [47].

2.5. Bile acids and the microbiome

Gut microbiota can modify the structure of bile acid in the colon, because bile acids have antimicrobial activity causing membranes and DNA damage [48]. Deoxycholic acid produced by microorganisms is tenfold greater than cholic acid producing a feedback to control bacteria population [49]. Bile salt hydrolase enzyme has been recognized in *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Lactobacillus*, and *Listeria* [50]. It can deconjugate bile acids reducing its toxicity [51]. Microbial dehydroxylation by *Clostridium and Eubacterium* transforms chenodeoxycholic acid and cholic acid into lithocholic acid and deoxycholic acid, it can produce a cytotoxic effect on enterocytes, and it can be associated with colon cancer. On the other hand, bile acids are also a ligand for nuclear receptor farnesoid X receptor (FXR) and plasma membrane-bound GPR TGR [52] that regulates their synthesis and affects the lipid and glucose metabolism [53]. Bacteria deconjugate bile acids reducing the efficacy of lipid emulsification showing a downstream effect in metabolic processes.

2.6. Gut microbiota and diabetes type 2

Diet plays an important role in obesity. There are preliminary studies suggesting that the consumption of probiotic bacteria found in yogurt and other fermented milk products can beneficially alter the composition of the gut microbiome. Yogurt, a fermented dairy product containing a variety of probiotic bacteria, is found to be associated with a reduction in inflammation markers and weight loss [54]. Yogurt consumption is involved in energy balance and/or energy homeostasis, which in turn controls body weight and reduces the risk of the development of DM2 [55]. One of the causes of dysbiosis is diet, and studies have shown that diet may change the gut microbiota and contribute to obesity and diabetes [56]. Obesity and DM2 are characterized by an altered gut microbiota, inflammation, and gut barrier disruption [57]. Studies in germ-free animals have shown that shifts in the composition of the gut microbiome may play an important role in disease development, specifically obesity and diabetes [58]. There is evidence demonstrating that the composition of the gut microbiota also influences metabolism and can affect energy balance [59], gut permeability [60], and inflammation [61], all of which are associated with obesity and associated disorders, including DM2 [62]. The evidence for the role of the HIM in metabolism of dietary components and the impact on health has been obtained from

comparative studies in germ-free animals, by using conventional microbiome, or by animals with human microbiome-associated, and from *in vitro* studies using human fecal incubations. In this sense, gastric bypass surgery leads to a substantial shift in the gut microbiota, which may contribute to weight loss in part by HIM modifications [63]. One of the most important situations is that the immune system faces microbiome continuously and it affects the host immunity and inflammation control. In this line, GM can affect the immune system by metabolites like SCFAs [64] and toxin production, such as LPS [61], modifying the adipogenesis and influence in the insulin resistance. LPS induces generation of pro-inflammatory cytokines by the immune system and adipocytes. Acetate, butyrate, and propionate (SCFA) modulate the gene expression in host, modifying the infant microbiome and stimulating white blood cells [65]. Some studies suggested that infants born by cesarean section are at greater risk of developing obesity and/or diabetes than those born vaginally [66]. Other studies with preschool children showed overweight or obesity in children born by cesarean [67], while in other showed the opposite [68]. On the other hand, infant feeding is also important to develop GM because mother milk is not sterile and is the first bacteria to colonize the gut [69]. Breast milk is a source of probiotics and other bacteria [71] containing more than 700 species [70]. The median bacterial load is 10^6 bacterial cells/Ml [71]. *Streptococci* and *Staphylococci* are predominant bacterial genera in human milk [69]. *Weissella*, *Leuconostoc*, *Staphylococcus*, *Streptococcus*, and *Lactococcus* are predominant in colostrum and are thought to modify the lactation to increase *Veillonella*, *Leptotrichia*, and *Prevotella* for over 6 months [71]. In this line, milk from obese mothers contains less-diverse bacteria than normal-weight mothers and has pro-inflammatory properties [72, 73, 74]. Another import issue is the infection of virus or bacteria pathogens. For instance, *Clostridium difficile* patients and asymptomatic carriers with the use of 16S ribosomal RNA gene pyrosequencing found that both had reduced microbial richness, diversity, and dysbiosis state compared with healthy subjects [75]. Gut microbiota transplants can help to increase the richness and diversity of GM [76]. For example, clearance of hepatitis B virus infection requires the reestablishment of the gut microbiota. Drugs also affect the microbiome including the drugs used to treat DM2 [77]. But also in the opposite direction. Broad-spectrum antibiotics reduce bacterial diversity and provoke the augmentation of some species like opportunistic pathogens [78], predisposing to inflammatory bowel disease [79]. *Clindamycin* produces a prolonged effect of modifying the microbiome in infants [80]. Studies in both mice and humans have found that the use of antibiotics early in life could promote obesity later in life, mediated by the alteration of the gut microbiota [81]. In the same line, antibiotics can reduce body weight and increase insulin sensitivity [82]. *Berberine* is recognized for its antidiabetic effect by modulating the gut microbiota and diminishing glucose and insulin resistance [83]. Metformin increases the insulin sensitivity in fat cells and hepatocytes and also reduces the overproduction of glucose in hepatocytes. Recent studies showed that metformin alters the GM [84, 85]. In obese mice, metformin caused the increase of mucin-degrading *Akkermansia* [85]. In human GM, altered gut microbiota can be the cause of common metformin side effects and could have a role in drug efficacy. There is a link between high-calorie diets contributing to obesity and DM2 and GM [55]. Dietary changes can result in substantial and rapid changes in the GM [86]. High-fat diet reduces the α diversity in GM. For instance, *A. muciniphila* decreased in obese mice and DM2, and it can be normalized by prebiotic consumption [62]. Treatments with *A. muciniphila* reduced fat mass, inflammation, and insulin resistance induced/caused by high-fat diet [62]. An enterotype is a classification of living organisms based on their bacteriological ecosystem in the gut microbiome. Changes in GM enterotypes were strongly associated with long-term diets, *Bacteroides* with protein and animal fat, and

Prevotella with carbohydrates; gut microbiota composition depends on diseases and long-term dietary interventions. GM alterations can be observed within 24 h after high-fat and low-fiber or low-fat and high-fiber diet [87]. Type 1 is characterized by high levels of *Bacteroides*, type 2 has few *Bacteroides* but *Prevotella* are common, and type 3 has high levels of *Ruminococcus* [18].

3. Metagenomic, metatranscriptomic, metaproteomic, and metabolomic approaches to mimic the gut ecosystem

Metagenomics is used to study differences in microbiome composition having diseases and compared with healthy people. Recently a technique was developed (Ecemble; enzyme classification using ensemble approach) to predict enzymes from protein sequences in gut microbiome from metagenomic samples and study the role of GM in metabolism; 48 pathways having at least one bacteria-encoded enzyme were found [88]. The carbohydrate active enzymes are important due to their role in dietary fiber and non-absorbed carbohydrate metabolism; 81 families of glycoside hydrolases have been identified. On the other hand, single-cell genomics uses isolated colonies to shotgun sequencing and put in phylogenetic context to complement metagenomic analysis. Is important to note that the presence of a gene does not mean it amounts to their expression; in this sense, metatranscriptomics, metaproteomics, and metabonomics are needed. Metatranscriptomics involves the generation of cDNA by reverse transcription and permits to identify noncoding RNAs and small RNAs that control quorum sensing and stress response [89]. Metatranscriptomics of fecal microbiome analysis of the 16S rRNA transcripts showed *Firmicutes* (49%) and *Bacteroidetes* (31%) are the main source of RNA and smaller proportion of *Proteobacteria* (3.7%), *Actinobacteria* (0.4%), and *Lentisphaerae* (0.2%) and *Lachnospiraceae* and *Ruminococcaceae* are the major proportion of *Firmicutes*, whereas *Bacteroidaceae, Prevotellaceae*, and *Rikenellaceae* for *Bacteroidetes phylum* [90]. Other transcripts were compared with COG database to obtain a functional distribution. Results showed similar behavior for carbohydrate transport, energy production, and synthesis of cellular components. Nevertheless acid and lipid metabolism, motibily, and secondary metabolite biosynthesis were underregulated. Unfortunately, short half time of bacteria RNA makes the detection of all RNAs in fecal samples difficult. Metaproteomics permits to determine gene translation and post-transductional modifications and permits to classify microorganism to a specific catalytic function [91, 92]. Temporal stability of the fecal metaproteome was assessed, and it was determined that glutamate dehydrogenase showed high level of redundancy in *Lachnospiraceae*, *Bacteroidaceae*, *Ruminococcaceae*, and *Bifidobacteriaceae*. Ten percent of total proteome is involved to ABC sugar transport and glycolytic enzymes; the main functional categories were metabolism of carbohydrates, nucleotides, energy, amino acids, and cofactors and vitamins (especially B12 and folic acid) [87]. Finally, metabolomic approach allows to determine low-molecular-weight compounds in fecal sample and can be influenced by environmental inputs and metabolic interactions between host and environment. For example, SCFA content in the gut can be modified by diet; after that, absorption from the gut initiates the metabolism of the host and results in downstream metabolic perturbations and the generation of microbial-host co-metabolites [93]. For instance, intake of choline (meat and eggs) can form trimethylamine and dimethylamine by GM, trimethylamine is toxic and should be converted to trimethylamine-*N*-oxide (TMAO), and the latter is an electron acceptor for anaerobic metabolism *of E. coli* and is implicated in cardiovascular disease (CVD) [94–98]. Genomic

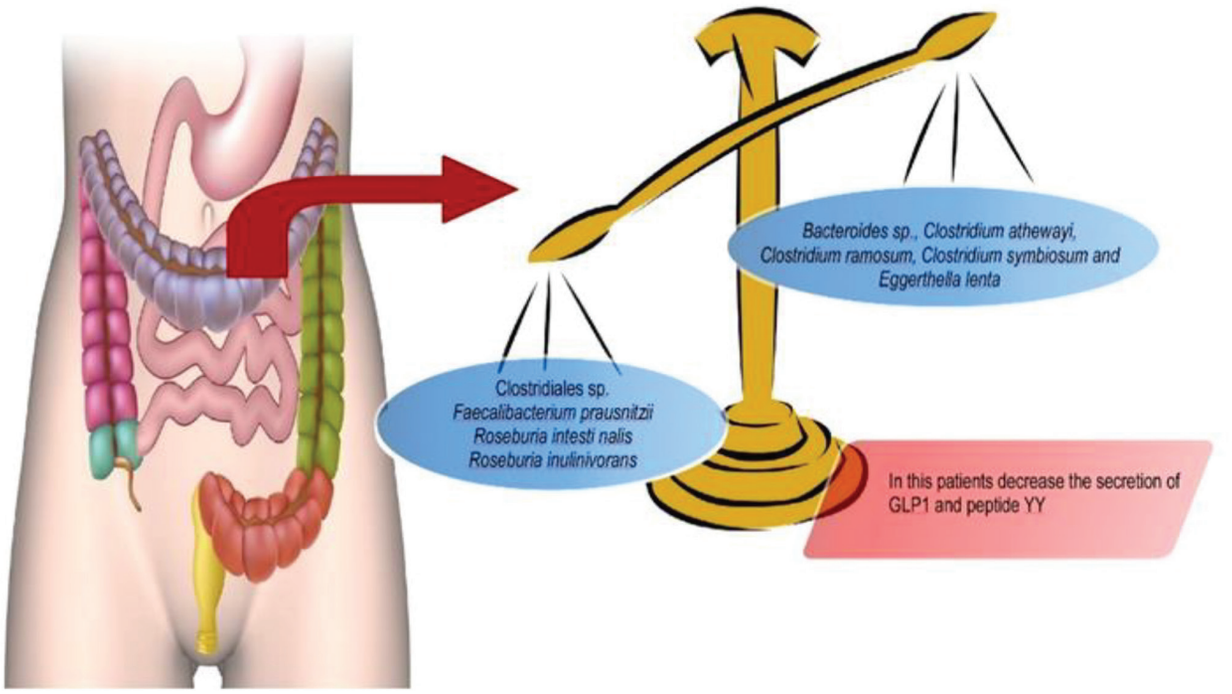

Figure 1. Changes in the composition of the gut microbiome are associated with an increased risk of DM2: In patients with DM2, the intestinal dysbiosis causes a decrease of short-chain fatty acid content, molecules that stimulate the secretion of peptide similar to glucagon type 1 (GLP1) and YY peptide by intestinal cells, proteins that control glucose homeostasis and regulate the intake of nutrients in intestinal cells.

analyses of the GM of subjects suffering from DM2 allowed to identify bacterial genes that are differentially expressed in those subjects; these changes in the gene expression of microbiome are related to the metabolic dysfunction and inflammation that these patients suffer from [99]. Bacterial genes including *Clostridiales* sp. SS3/4, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Roseburia inulinivorans* are decreased in patients with DM2, whereas genes corresponding to *Bacteroides* sp., *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, and *Eggerthella lenta*, are increased in these subjects [100]. Functional analyses suggest enriched genes in samples of DM2 patients are involved in plasmatic membrane sugar transport, branched-chain amino acids transport, methane metabolism, xenobiotic degradation and metabolism, biosynthesis of hydrogen sulfide, and oxidative stress. In contrast, decreased genes are related to functions such as chemotaxis, flagellum assembly, butyrate biosynthesis, and the metabolism of cofactors and vitamins [100]. The depletion of bacterial strains producing butyrate in patients with DM2 may be related to the ability of this fatty acid to increase secretion of peptide similar to glucagon type 1 (GLP1) and peptide YY, whose function is to promote intestinal gluconeogenesis, which leads to a better control of glucose homeostasis and cellular energy (**Figure 1**) [101, 102].

4. Nutrigenomics and the microbiome

In most chronic pathologies, environmental and genetic factors are involved because of a polygenic behavior. Recent research investigate the mechanisms involved in the dysfunction of a healthy phenotype to another with chronic dysfunction, explaining how gene expression

and dietary components regulate genetic information. Nutrigenomics involves understanding how diet components affect gene expression, meaning which genes are induced and which are repressed against a particular nutrient [103]. Chronic diseases, such as obesity, DM2, and cancer, are expressed from complex polygenic reactions with the environment. The most influential environmental interaction in the development of these diseases is given by the consumed nutrients. Evidence of gene-nutrient interaction is substantially demonstrated, estimating that a balanced healthy nutrition reduces the overall incidence of cancer by 35%. On the other hand, polymorphisms that predispose to certain diseases have been identified under unhealthy diet; this is the case of DM2, osteoporosis, vascular disease, and others, which can be prevented by modifying the diet [104]. The regulation of gene expression is performed through specific proteins that interact with DNA through posttranscriptional or posttranslational modifications. Regulation can occur at the level of mRNA during splicing; it would result from the interaction of certain molecules with specific nutrients, whose result could be potentially preventive [104]. The diet and the GM composition have also been associated with different characteristics of the metabolic syndrome (MS) (obesity, DM2, cardiovascular diseases, and nonalcoholic steatohepatitis). Increasing evidence suggests that the GM contributes to the onset of its characteristic low-grade inflammation, through mechanisms associated with intestinal barrier dysfunction [105]. The GM of an obese person in comparison with a normal-weight person presents a greater percentage of *Firmicutes* and smaller percentage of *Bacteroidetes*, causing dysbiosis in most of the obese and/or diabetic patients (**Figure 2**). Due to its physiological impact, GM is now recognized as an organ and can be transplanted from one individual to another [106]. Recent evidence suggests that the intestinal microbiome affects nutrient acquisition, energy storage, and metabolic pathways of the host [10]. *Bacteroidetes* have been shown to easily assimilate dietary carbohydrates. In a study in mice lacking Toll-like receptors (TLRs), which are receptors that recognize important patterns of inflammation and immunity, it is shown that these mice present hyperphagia and obesity and develop metabolic syndrome, when intestinal microbiome of these

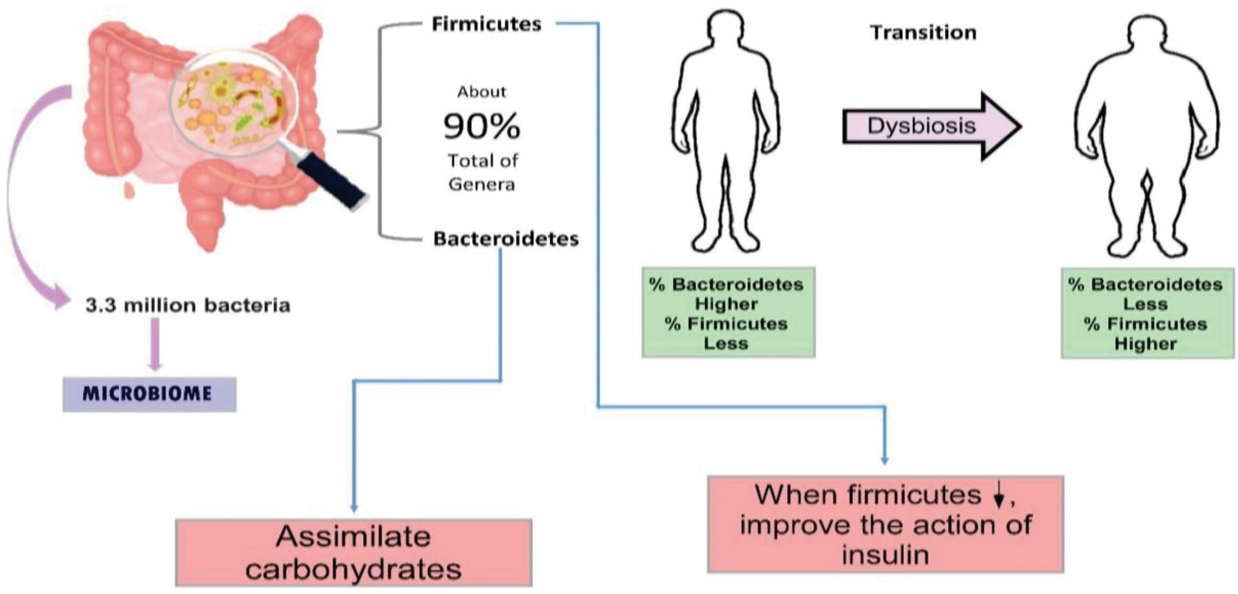

Figure 2. The GM of an obese person in comparison with a normal-weight person presents a greater percentage of *Firmicutes* and smaller percentage of *Bacteroidetes*, causing dysbiosis in most of the obese and/or diabetic patients.

mice is transplanted to germ-free mice with the TLR5 gene intact; they also developed the *Bifidobacterium* strain similar to the metabolic syndrome, suggesting that the GM was the determinant factor of this disease phenotype [107]. Another study showed that mice deficient in TLR2 presented greater amount of *Firmicutes* and *Actinobacteria* and smaller amount of the genus *Bifidobacterium* [10, 107]. Administration of an antibiotic cocktail eliminated many of the *Firmicutes* and resulted in improved insulin action and increased glucose tolerance [107].

5. New brain gut axis, serotonin production, and its relationship with DM

Some studies have shown the clear connection between immune system and neuroendocrine system highlighting the effect of the GM, which allows a new focus for research on the so-called brain gut axis [12]. The mechanisms of enteric neuroprotection were recently been described; enteric neurons have one of their own signaling molecules to this propose. In the adult intestine, serotonin acts like a paracrine signal hormone and neurotransmitter [108]. However, it is also a neuronal growth factor during development and a major promoter of mucosal epithelium growth by stimulating submucosal cholinergic neurons [109]. This neurotransmitter may even stimulate neurogenesis in the growing enteric nervous system, and in adults, this hormone promotes neurogenesis and neuroprotection through the activation of 5-HT4 receptors. It is interesting to mention that mucosal serotonin is not a direct neuroprotective agent to enteric neurons. Mucosal serotonin behaves as a pro-inflammatory factor, and this ability constitutes a threat to neuronal survival [110]. According to these facts, this hormone has received the name of "sword and shield" of the intestine. Mucosal serotonin is the pro-inflammatory "sword," while neuronal serotonin is the anti-inflammatory "shield" [111]. It has been demonstrate that DM1 is related with an excess of pro-inflammatory cytokines close to B pancreatic cells, while DM2 is caused due to an excess of pro-inflammatory cytokines in systemic circulation, which could be related to intestinal serotonin secretion. Gershon et al. have established that neurodegenerative/neuroprotective actions of 5-HT4 receptor complex may be vital for the normal enteric nervous system's maintenance [12]. Bianco et al. show the mechanisms through the 5-HT4 agonist participate in protection of enteric neurons against oxidation [112]. This sentence is relevant because the enteric neurons lost during inflammation strongly depend on the released forces throughout oxidative stress (**Figure 3**) [113, 114]. Bhattarai et al. suggest that the "sword" function is manipulated by the microbiome [115]. The intestine has a variety of regulatory mechanisms that contrast the actions of 5-HT for transport maintenance; conversely, Chang and Rao incorporate the GM as a homeostasis influence factor evading the alteration of 5-HT during diarrhea and intestine inflammatory diseases. Recently, observations have been made about the possible mechanisms by which dysbiosis of the microbiome alters the function of 5-HT [14]. The HIM plays a key role in enhancing the serotonin biosynthesis in enterochromaffin cells. This increased serotonin content stimulates the intrinsic projections of the primary afferent neurons and in turn activates interneurons, which activate the peristaltic reflex promoting intestinal motility and besides accelerate the gastric emptying, which is augmented when 5-HT receptor is antagonized [111]. The intestinal speedup promotes the production of several gastrointestinal hormone secretions that mediate glucose metabolism, unleashing

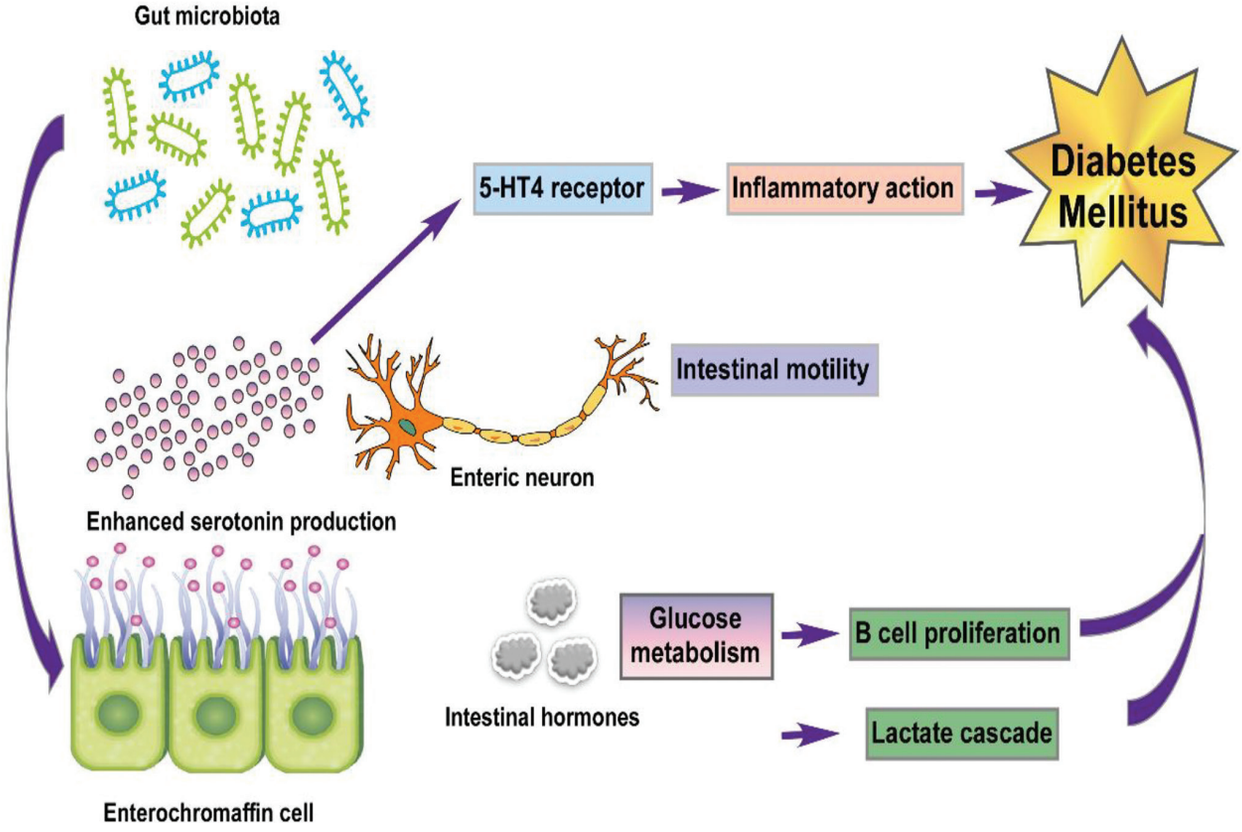

Figure 3. The hypothesis of the alteration of the GM by serotonin and the metabolic pathway that generates insulin resistance it could be considered as one of the possible etiopathogenic factors of DM2.

insulin synthesis such as β-cell proliferation or glucagon release [116]. On the other hand, it has been shown that serotonin participates during lactate signaling cascade to stimulate β-cell proliferation [117]. Under this premise, there is a hypothesis of a possible relation between the alteration of the GM by serotonin and the metabolic pathway that generates insulin resistance, and it could be considered as one of the possible etiopathogenic factors of DM2.

6. Conclusions

The interaction of the diet in the modification of HIM, in addition to its potential effect on the microbiome and the development of DM, has been positively affected by the evolution of nutrigenomics as a science discipline. Diets rich in carbohydrates and fats, favor the development of bacteria capable of causing intestinal dysbiosis of low degree of inflammation; affecting the permeability of the intestinal mucosa. It has been shown that intestinal production of serotonin by enterochromaffin cells participates in the cascade of stimulation of the proliferation of pancreatic β cells, via the lactate pathway, suggesting the hypothesis of a possible link between serotonin, insulin resistance, and DM2. Finally, the advances reflected in this chapter demonstrate a small part of the future projection around nutrigenomics and its effect on the composition of the

microbiome in diabetic subjects; it would be interesting to carry out more specific studies of this area, associating it with the effect of satiety and the alteration of the microbiome in patients with obesity and/or metabolic syndrome, as an integral part in the prevention of DM2.

Acknowledgements

This work team is composed of Carrera de Nutrición y Dietética, Universidad Andres Bello, Concepción, Chile; Centro de Investigaciones Endocrino - Metabólicas. Facultad de Medicina, Universidad del Zulia. Maracaibo - Venezuela. Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia. Facultad de Ciencias para el Cuidado de la Salud, Escuela de Nutrición y Dietética, Universidad San Sebastián, Santiago, Chile; Departamento de Salud Pública, Universidad Católica de la Santísima Concepción, Concepción, Chile; and Hospital 12 de Octubre, Madrid, España.

Author details

Lissé Angarita Dávila[1], Valmore Bermúdez Pirela[2,3]*, Waldo Díaz-Vasquez[4], Nadia Reyna Villasmil[3], Silvana Cisternas León[1,9], Ma Cristina Escobar Contreras[1], Kristian Buhring Bonacich[1], Samuel Durán Agüero[4], Paula Carrasco Vergara[1], Rodrigo Buhring Bonacich[6], Constanza Bugman[1], Virginia Céspedes[7], Marcell Gatica[1], Marion Guerrero Wyss[5], Jorge González Casanova[8] and Francisco Valdebenito[1]

*Address all correspondence to: v.bermudez@unisimonbolivar.edu.co

1 Facultad de Medicina, Carrera de Nutrición y Dietética, Universidad Andres Bello, Concepción, Chile

2 Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia

3 Centro de Investigaciones Endocrino - Metabólicas, Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela

4 Escuela de Nutrición y Dietética, Facultad de Ciencias para el Cuidado de la Salud, Universidad San Sebastián, Santiago, Chile

5 Escuela de Nutrición y Dietética, Facultad de Ciencias para el Cuidado de la Salud, Universidad San Sebastián, Valdivia, Chile

6 Departamento de Salud Pública, Universidad Católica de la Santísima Concepción, Sede Concepción, Chile

7 Servicio de Rehabilitación y Fisiatría. Hospital 12 de Octubre, Madrid, España

8 Facultad de Ciencias de la Salud, Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile, Santiago, Chile

9 Area Salud. Universidad Tecnológica de Chile, Inacap, Chile

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