Chapter 11

New Insights into Alleviating Diabetes Mellitus: Role of Gut Microbiota and a Nutrigenomic Approach

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Abstract

The scientific literature has shown that diet is able to modify the gut microbiota and contribute to obesity and diabetes development. This process—characterized by inflammation and gut barrier disruption—can affect the immune system and alter the adipogenesis and insulin resistance. This chapter describes the advances in nutrigenomics and Human Intestinal Microbiota (HIM) modification, and its relation with diabetes mellitus type two (DM2). In context where health and feeding are the main concerns of the human being, food innovation takes a special interest to people that look for a healthy diet or demand a functional aliments, such as nutraceutical. Some products derived from diet and interaction with HIM module the expression of many genes on the host, the so-called epigenome, with favorable effects. Novel functional fiber like low-glycemic oligosaccharides and sweeteners shows a potential prebiotic activity giving a new focus of nutritional guidelines for control and prevention of DM2. The use of prebiotics derived from functional fiber sources, such as fructo-oligosaccharides and beta-glucans as well as lignin and keffir, can contribute to the development of a healthy HIM by promoting the growth of specific bacteria, some of them associated with the prevention of obesity and diabetes.

Keywords: human intestinal, diet, fiber, prebiotic, carbohydrates, diabetes

1. Introduction

Diabetes mellitus type two (DM2) is a complex pathology, it depends of the interaction of genetic, epigenetic, environmental, and lifestyle factors [1]. This disease has generated an epidemiological worldwide impact, with a current report of 425 million adults having the disease according to the International Diabetes Federation (IDF). Currently, the last report of the year 2017, the epidemiological data showed an increment of 10 million cases diagnosed respect to 2015 [2]. According to the IDF, projection for 2045 is 650 million subjects with DM2. North America and the Caribbean have the highest prevalence of this disease (11%), where an increase of 62% is expected for the same period [3].

In the multidisciplinary treatment of this pathology, dietotherapy has been specifically considered as a critical control point in the international guidelines for DM2 [4, 5]. Recently, important advances in nutrition management have been developed associated to nutritional genomics, whose objective focuses on the interaction between the bioactive components of food and the human genome, this approach includes studies of nutrigenetics, nutrigenomics, and epigenetic modifications caused by nutrients [6].

Some investigations have used nutrigenomics to illustrate the modulation mechanism of specific fatty acids on gene expression, producing an impact on human metabolism [7, 8]. A common approach is the examination of individual levels of mRNA in relation to nutrient intake [9]. Tests with carbohydrates and dietary components such as fiber show a relationship between specific polymorphisms and the effect on insulin resistance [10]. In this sense, in a recent review, the effectiveness of the supply of fermentable carbohydrates on human metabolism is explained [11].

Furthermore, new advances in study of the composition of the human microbiota have shown an evident relationship between Human Intestinal Microbiota (HIM) and DM2 [12]. In this context, a significantly greater association of Firmicutes/Bacteroidetes in DM2 has been observed when is compared with normal weight and obese subjects [13].

New focus of nutritional treatment and its potential epigenetic effect constitute a panacea in the modification of the diabetic patient's microbiota [14]. The HIM is affected by the ingestion of bioactive compounds, showing prebiotic or probiotic effects, whose action can help to generate the growth of beneficial bacteria, such as *Bifidobacterium* and Bacteroidetes. The development of personalized nutritional methods considering the genomic information, use of prebiotics from novel sources of functional fibers (Fructo-oligosaccharides FOS, beta-glucans) [15], consumption of carbohydrates with low-glycemic index (GI), as well as the use of monosaccharide sweeteners with potential prebiotic activity, such as (tagatose) [16], would allow to generate a new therapeutic orientation for the control and prevention of this pathology. These dietary practices are important as part of the near future and will be analyzed in this chapter. Finally, a description in nutrigenomics advances and the effect of prebiotics consumption on modification of HIM are shown and its relationship with DM2 will be discussed.

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2. Nutritional treatment and new perspectives

2.1. Prebiotics derived from functional fiber sources

A prebiotic is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" [17]. Modification encouraged by prebiotics on the composition of HIM leads to the predominance of a few of the potentially health-promoting bacteria, especially, but not exclusively, *Lactobacilli* and *Bifidobacteria* [18]. Some prebiotics pass by the small intestine to the lower gut and become accessible for probiotic bacteria without being utilized by other intestinal bacteria [19]. Lactulose, galacto-oligosaccharides, fructo-oligosaccharides, inulin, and its hydrolysates, malto-oligosaccharides, and resistant starch are prebiotics normally used in the human diet [20, 21].

The definition used at present was given by the Food and Agriculture Organization of the United Nations World Health Organization, according to which probiotics are redefined as "live microorganisms which when are administered in adequate amounts confer a health benefit on the host." In relation to foods, the definition can be adjusted to beneficial effect exerted by microorganisms "when are consumed in adequate amounts as part of food" [17, 21].

2.1.1. Betaglucans

2.1.1.1. Cereal β-glucans

Functional properties of β-glucans have been particularly attributed to the fact that these create viscous solutions in aqueous solution, as occurs in the digestive tract [22, 23]. This viscosity causes β-glucans to delay gastric emptying and interfere with the contact between pancreatic enzymes and their substrates in the intestinal lumen, slowing the digestion and absorption processes of nutrients [24]. This property could explain the effect of β-glucans on the reduction of plasma cholesterol concentrations and the glycemic index [25, 26].

2.1.1.2. Yeasts and fungi β-glucans

Another pivotal property of fungi/yeasts β-glucans is the modulation of the immune system [27, 28]. This effect could be due to the ability of β-glucans to stimulate receptors of the innate immune system present in the membrane of enterocytes, M cells and dendritic cells, improving the phagocytic activity of macrophages and antimicrobial activity of mononuclear cells and neutrophils [29–31]. This type of β-glucans would also prevent the promotion and progression of certain types of cancer, acting synergistically with monoclonal antibodies and chemotherapy [32, 33]. This stimulation of immunity would be achieved by increasing the secretion of pro-inflammatory cytokines and chemokines [34]. The main receptor involved in the effect of B-glucans immunity is Dectin-1, even though there is also a role for the receptor 3 of the complement, TLR-2, TLR-6 and the "scavengers" receptors [35, 36]. Dectin-1, known in human beings as β-glucans receptor (βGR), is a member of the pattern recognition receptors (PRR)

which fulfill an essential role in the innate immune response against viruses, bacteria, yeasts, and fungi, contributing to the recognition and elimination of pathogens [34]. This receptor is highly expressed in immune cells such as dendritic cells, neutrophils, eosinophils, and monocytes as well as in some populations of T and B cells and, to a lesser extent, in macrophages and enterocytes [31, 34, 35]. Dectin-1 acts through signal transduction activating Syk and RAF-1 [14]. It can also act synergistically with TLR which mediates the production of pro-inflammatory cytokines, such as IL-12 and TNF-α [33, 35].

2.1.2. Fructo-oligosaccharides

Inulin is a non-digestible carbohydrate present in many vegetables, fruits, and cereals [36]. Currently, at the industrial level it is extracted from the chicory root *(Cichorium intybus*) and is widely used as an ingredient in functional foods. Inulin and its derivatives (oligofructose, fructo-oligosaccharides) are generally called fructans, basically composed of linear chains of fructose [37]. The maximum dose allowed to be added to food formulated with inulin is up to 20 g/day for a simple dose and up to 10 g/day for multiple doses. At higher doses it can cause intolerances after consumption, such as osmotic effects (diarrhea), intestinal noises and flatulence as a result of the fermentation process [38]. Oligofructose is obtained by the partial enzymatic hydrolysis of inulin, composed of linear chains of glucosyl-fructosil. GP ranges between 2 and 8, with an average value of approximately [37]. It is present in foods such as cereals, onions, garlic, banana, and corn [38, 39]. There are promising evidences of its performance in the regulation of lipid parameters, reduction of the risk of cancer, reinforcement of the immune response and protection against intestinal disorders [40]. In a wide variety of food products, inulin and its derivatives are used as: thickener, emulsifier, gelling agent, sugar and fat substitute, moisturizer, depressor of the freezing point [37, 39].

2.1.3. Lignin's: mucilage's (flaxseed)

2.1.3.1. Lignans

Plant lignans are phenolic compounds with a skeleton of 2,3-dibenzylbutane [40]. Flaxseed is the richest food source in the precursors of lignans, secoisolariciresinol diglucoside (SDG), and materesinol, which are phytoestrogens that by action of gastric acid and bacterial glucosidase (facultative aerobics of Clostridia class) of the digestive tract transform into enterolactone and enterodiol, respectively, known as lignans of mammals [41]. These have more antioxidant capacity than their predecessors. Other lignans, such as lariciresinol, hinoquinina, arctigenin, divanillyl tetrahydrofuran nordihydroguaiaretic acid, isolariciresinol, and pinoresinol, are also present in flaxseed but the most abundant is SDG [40]. The health benefits of flaxseed lignans rely in their antioxidant capacity as retainers of hydroxyl radicals, and as estrogenic and anti-estrogenic compounds due to their structural similarity to the 17-β-estradiol [37, 41]. The antioxidant activity of flaxseed lignan (SDG) is related to the suppression of the oxidizing conditions of oxygen reactive species [41]. Secoisolariciresinol diglucoside and its aglycone secoisolariciresinol show a high antioxidant capacity and protective effects to the damage of the DNA and liposomes, especially in the epithelial cells of the colon exposed to these

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compounds, during the metabolism of the colon bacteria that transform them into lignans of mammals [42, 43].

2.1.3.2. Mucilage

Mucilage is water-soluble polysaccharide present in many seeds, capable of absorbing 60–100 times their weight in water forming gels. They are formed by ramified arabinoxylans chains [44]. The mucilage is similar to the gums, composed of galactose, mannose, xylose, and other sugars [45]. One of the best known mucilage is psyllium (psyllium) or also called plantain, coming from the seeds of Plantago genus [42, 44]. The mucilage extracted from algae contains sugars somewhat different from terrestrial vegetables, such as agarobiose in the agar and sulf-sugar in the carrageenan, used in food technology [44]. Flaxseed mucilage is a complex polydisperse hydrocolloid and the different rheological behaviors observed in cultivars are caused by the differences in the ratio between neutral and acid polymers and by the molecular weight and structural conformation of polysaccharides [45, 46].

2.1.3.3. Flaxseed

Even though flaxseed is much known, it is not widely used in the formulation of food [47]. This seed has significant amounts of bioactive compounds, such as alpha-linolenic acid, lignans and dietary fiber, with potential effects in the prevention of some chronic diseases such as reducing the risk of cardiovascular diseases, mitigating the effects of diabetes, renal pathologies, obesity, colon and rectum cancer, reducing serum cholesterol level, and promoting the intestinal evacuation [46, 47]. These characteristics make flaxseed an attractive source of ingredients to be used in the elaboration of different functional foods [48].

2.1.4. Kefirs

Different *in vitro* and *in vivo* studies have demonstrated the ability of kefir to promote health through the presence of bioactive peptides. Multiple bioactivities of this beverage such as antihypertensive, antimicrobial, immune-modulating, mineral-carrying, antithrombotic, opioid, and antioxidant have been the most reported [49]. These characteristics of kefir, along to the pre- and probiotic properties, hypocholesterolemic, the bioavailability of milk components with biological activity and the presence of metabolites such as organic acids and bacteriocins, situate it as functional food [50]. This is a food that beyond the nutritional contribution of its components has been proven to benefit one or more physiological functions of the organism, improving the health, well-being, and/or reducing the risk to suffer diseases [51–53]. Additionally, there are bioactivities that have been poorly studied as the mineral fixing properties and the antithrombotic activity. There are some studies about the substrate-microorganism-metabolite-bioactivity inter-relationships based on metagenome studies [54, 55]. It would be important to carry out more investigations to determine the different bioactivities more deeply and the effective dose by trying to reach the intestinal level in sufficient quantity to implant and colonize its surface [56].

2.2. Low-glycemic index of carbohydrates and inflammatory state intestinal mucose

2.2.1. Historic context glycemic index and glycemic load

One of the major dietary changes of the modern world has been the high consumption of processed foods rich in carbohydrates and low in fiber; highly related to the increasing rates of obesity and diabetes [49]. In this sense, pharmacological approaches focused on large clinical trials have been useful for improving glycemic control in patients with type 2 diabetes (DM2) [51]. Similarly, a positive effect in the control of diabetes has been associated with the consumption of diets low in GI [52], these indicator determines the effect of the available carbohydrates in food on the average concentration of glucose in blood, this value is defined as the relation between the area under the curve of 50 g of available carbohydrates in a food, with the area under the curve of same amount of carbohydrates of a reference food [53].

White bread and glucose, which has been assigned a GI of 100, are considered reference foods rather than a high value for this indicator [54]. Different entities worldwide, such as the American Diabetes Association (ADA) [55], the European Association for the Study of Diabetes [56], the Canadian Diabetes Association [57], and the UK Diabetes Nutrition Sub-Committee [58] have prioritized dietary treatment with a relevant approach to carbohydrate quality for the glycemic control, with special emphasis on reducing the digestion rate, absorption and metabolism of carbohydrates from foods [59].

Therefore, this indicator expresses the potential glycemia of a meal, representing the quality of foods with predominance of carbohydrates [60]. Foods with carbohydrates capable of digesting, absorbing and metabolizing quickly are considered food with high GI (GI ≥ 70 in the glucose scale). Those between GI = 55 and 70 are considered in an intermediate value, while those digested, absorbed and metabolized slowly are classified as foods with low GI (GI ≤ 55 in the glucose scale) [53, 60]. There are international tables with the published values of this indicator for a large number of products on the market. The first table was published in 1981 and was later updated in 1994 and 1995 [61, 62]. There is a marked controversy over the use of this indicator in the decade of the 80, due to an inadequate interpretation of the evidence for its determination [60, 63]. Criticism has focused on the methodological validity of the process to quantify it since a large number of factors had influenced the results [60, 64]. The position of the latest consensus of glycemic index experts in 925 held in Europe has determined that most of the current critics are not valid, and that these reflect a failure of the knowledge translation [60]. In this context, it is important to consider that important entities such as the International Diabetes Federation have recognized the relevance of post-prandial regulation of glucose in order to achieve the objectives of HBA1C by developing specific guidelines, whose management is related to the GI concept [64].

2.2.2. Glycemic load, glycemic index, and insulin response

The value of glycemia and the insulin response depends on the quantity and quality of carbohydrate and the mix of food ingested, the so-called glycemic load (GL). The GL represents a relationship between the quantity and quality of carbohydrate [54, 60], and is defined as the total carbohydrate content available in an amount of food (GL = GI × available carbohydrates/specific amount of food) [60], and is the result of multiplying the amount of carbohydrate

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ingested in food by the value of its GI. The GL should be interpreted as a measure in the demand for insulin, this value is a good indicator of the levels of post-prandial glycemia, associated to the amount of calories in a particular portion of food or diet [65]. Thus, foods with high GL and high GI have a direct effect on the development of hyperinsulinemia [66], insulin resistance and risks to develop DM, which also have been linked to high-IG foods [67].

2.2.3. Insulin response and inflammation mucus and glycocalyx layer

Several studies have determined a clear link between the glycemic index and the glycemic load of food and the insulin response [52, 68, 69]. Studies suggest that carbohydrates can modify the microbiota, depending on their ability to increase glycemic and insulin response values according to glycemic and insulinemic index [70, 71]. In this sense, several studies in rodents have reported oligofructose as a recognized prebiotic, capable of modulating IM and improving insulin sensitivity [72, 73]. Similarly, inulin-type fructans have been tested to determine their ability to modulate lipid metabolism and carbohydrate in various animal models [73, 74]. It has been reported that oligofructose (OFS) decreases the intake of food, the development of fat mass and hepatic steatosis in normal and obese rodents. In addition, OFS exerts an antidiabetic effect in rats treated with streptozotocin and mice treated with high content of fat [72]. Chang et al. demonstrated that the addition of OFS also caused changes in the IM, specifically for *Bifidobacterium* and *Clostridium leptum* [75] content. These results suggest that OFS may be an effective therapeutic complement in the treatment of diabetes type 1 (DM1) by improving insulin sensitivity and beta cell function, leading to better glycemic control [76]. OFS reduced body weight, energy intake and fat mass in both phenotypes ($P < 0.05$) [76]. In another study carried out in two different groups of rodents, OFS did not modify ghrelin in plasma, but plasma levels of GIP were reduced and PYY were elevated ($P < 0.05$) [76] by OFS, reducing body weight and adiposity in prone obese phenotypes and in those insulin-resistant [76].

The changes induced by this saccharide in the profiles of IM of these animals, along with the changes of intestinal hormone levels probably contribute to lower body weights sustained [76, 77]. Milk prebiotic oligosaccharides have been reported to alter the IM and may influence the metabolism of the host. In a study performed in rats comparing diets with 15% of glucose, fructose, galactose, and methylcellulose content, daily intake of 15% galactose improved the sensitivity to hepatic insulin compared with glucose and fructose, producing an increase in the content of hepatic glycogen in the feeding state and a positive change in the IM populations; unlike the intake of galacto-oligosaccharides [78], which improved the IM profile without any effect on the insulin sensitivity. The GI of lactose, fructose and isomaltose is (=43), (=20), and (=2), respectively [62]. Further studies on these indicators are required in monosaccharides and their effect on the human microbiome.

3. New perspectives in biotechnology of foods, low-glycemic index and the microbiota

In context where health and feeding are the main concerns of the human being, food innovation takes a special interest to people that look for a healthy diet or demands a greater number

of functional products, such as nutraceutical, that often generates more contribution than nutrients, helping to improve the prevent of different diseases [79].

A functional food has been defined as a: (i) natural food, (ii) food which a component with some technology or biotechnology has been added or removed, (iii) food where the nature of one or more components has been varied, (iv) food which the bioavailability of one or more of its components has been modified, and/or (v) any combination of the above possibilities [80]. The world commercialization for functional foods and beverages have grown from $ 33 billion in 2000 to 67.7 billion pesos in 2013, that mean the 5% of the global food commercialization, and the growth of investment in food industry as a whole. Latin America is currently a potential producer and consumer of functional foods, because of its large natural resources, a wide biodiversity of flora and fauna having a variety of plants and edible fruits with potential and beneficial effects for health [78].

Bioactive molecules works mainly modifying cellular signaling and causing changes in expression of certain genes, for instance producing a defensive response to harmful processes like differentiation and cell proliferation, inflammation, it is the base of the understanding for most prevalent diseases. New technology applied for food and nutrition sciences are closely related to the biomedical area, researchers require strong training in molecular biology, genetics and nutritional biochemistry, among others disciplines [81]. The current "omics" technologies, such as genomics, transcriptomics, proteomics, metagenomics, metatranscriptomics and metabolomics, have introduced important strides in the fields of health, biotechnology, ecology, and food [81]. The increase of the importance of (I + D) from academy, where food and pharmaceutical industry have worked together to promote healthy feeding, functional foods and nutraceuticals developing, those products when are consumed in a regular way, contribute to the prevention and/or treatments of certain diseases [82]. Genetic engineering plays an important role in the improvement of functional foods, which involves biological and technological research and also normative and ethical communication [83]. New probiotic strains isolated from natural niches and other produced by genetically engineered organisms (GMOs) have broadened the spectrum of organisms with improved probiotic properties for incorporation into functional foods [84]. More than 500 probiotic food products have been introduced into the world stores over the last couple of decades [81]. The contribution of biotechnology to production of prebiotics is remarkable. Prebiotic such as inulin and fructose polymer are produced by extraction of natural products (mainly chicory for fructose polymer), other prebiotics are produced by bioprocesses involving microorganisms or enzymes specifically conditioned for efficient synthesis of non-digestible oligosaccharides. On the other hand, inulin is the most used prebiotic, although it is probably not the most effective, actually, in the formulation of functional foods, also providing textural and rheological properties to the food matrix [83]. Another example of innovation is the design and development of product with intestinal microbiota and/or GI control effects, such as powdered additive, that incorporates also beneficial bacteria to the food. This development, achieved by researchers from National Institute Food Technology in Chile and Conicet Argentina, incorporated as an additive to certain foods—cold or lukewarm liquids—enriches the digestive system, balances the intestinal microbiota with a positive impact on the immune system [85].

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3.1. Non-caloric sweeteners and gut microbiota

Non-caloric sweeteners (NCSs) are food additives widely used as sugar substitutes; these sweeteners enhance tastes and simultaneously reduce calories consumption. Some epidemiological studies have shown that artificial sweeteners are beneficial for weight loss, principally for subjects having glucose intolerance and type 2 diabetes [86]. Historically, the consumption of NCSs was restricted to people who have diseases such as diabetes; however, their consumption has increased in recent decades for general population. For their approval for human consumption, there are rigorous procedures required to consider them safe, however, today a controversy exist in its safety and it has been noted the possibility that the NCSs alter intestinal microbiota (IM). IM is involved in the metabolism of the host and plays a crucial role in food digestion and energy homeostasis. However, multiple environmental factors, such as diet, antibiotics and heavy metals, can disrupt the ecological balance of microbiota in the intestine [87]. A study in male Sprague-Dawley rats who were subjected to oral probe of 100, 300, 500, or 1000 mg/kg of Splenda for 12 weeks showed at the end of the treatment period, the number of total anaerobes, *Bifidobacteria*, *Lactobacilli*, *Bacteroides*, *Clostridia* and total aerobic bacteria decreased significantly. These changes occurred in Splenda doses containing sucralose at 1.1–11 mg/kg (FDA's acceptable daily intake for sucralose is 5 mg/kg) [88]. Other study realized in 8 weeks old C57B1 mice, two experiments were performed. Experiment 1, 4-week-old male mice were divided into three groups (n = 8 x group) and treated for 8 weeks as follows: mice in control group received distilled water; mice in the low dose sucralose group (LS) a sucralose solution of 1.5 mg/kg body weight per day were given; and mice in the high-dose sucralose group (HS) received a sucralose solution of 15 mg/kg body weight per day, which is equal to the maximum IDA. In Experiment 2, 4-week-old male mice were divided into two groups and treated for 8 weeks as follows: Mice in control group received distilled water (n = 8); and acesulfame-K mice were given an acesulfame-K solution of 15 mg/kg body weight per day, which is equal to the ADI (n = 9), resulting that consumption of sucralose, but not of acesulfame-K, reduced the relative amount of *Clostridium cluste*r XIVa in feces. Meanwhile, sucralose and acesulfame-K did not increase food intake [89]. Acesulfame k is genotoxic, and can inhibit the fermentation of glucose by intestinal bacteria [90]. A study in CD-1 mice (~8 weeks of age), were given a dose of 37.5 mg/kg body weight/day of acesulfame-K during 4 weeks, in males *Bacteroides* showed increased instead in females mice drastically decreased the relative abundance of multiple genres, including *Lactobacillus*, *Clostridium*, Ace-K disrupts the composition of the intestinal microbiome in a sex-dependent manner [90]. Another study in adult male C57B1/6 WT mice, gave two groups of mice a high in fat diet (60%) and commercial saccharin (equivalent to one human IDA) or glucose [91], resulting in an alteration in the glucose tolerance, the authors concluded that glucose intolerance was mediated by change in the microbiota (increase of *Bacteroidetes* and *Clostridium*). To corroborate the latter, a fecal transplantation to germ-free mice w performed, after 6 days an altered glucose tolerance was present in these mice. A similar study was carried out this time in seven humans (five men and two women), who were given 5 mg/kg/weight of saccharin (IDA equivalent) for 7 days, four of whom had altered glycemic responses. Other study, carried out in 31 humans that evaluated the consumption of aspartame and acesulfame k, showed that the consumers of these NCSs presented a different bacterial diversity to those who did not consume these

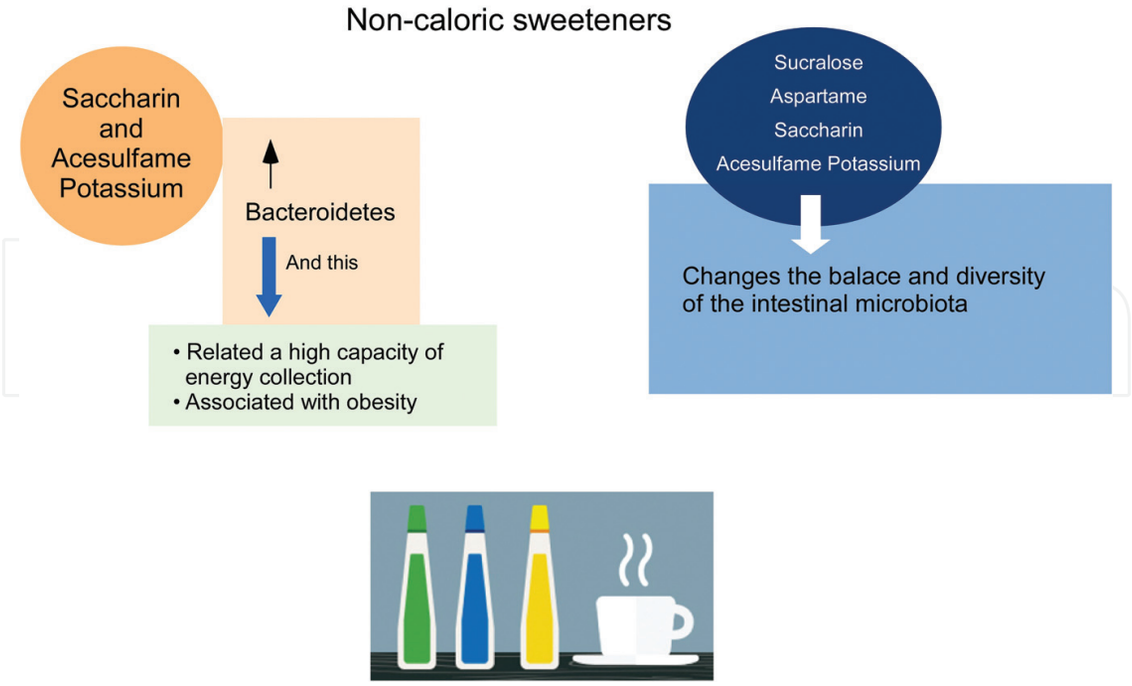

Figure 1. NCSs: sucralose, saccharin and acesulfame-K have been found to modify the balance of the HIM, either by decreasing or increasing the number of Bacteroidetes.

NCS [92]. This group also performed a smaller trial of seven healthy volunteers (five males, two females, and ages 28–36) who did not normally consume NCS and who received saccharin for 1 week at a dose of 5 mg/kg, IDA for these sweeteners. Most of these (4/7), known as "NCSs responders" developed lower glucose tolerance and altered IM compared to "non-responders of NCS" [92]. Microbiome of "NCS responders" showed changes in composition by 16S rRNA analysis. Due this control group was not included in the design, it is unclear whether some healthy individuals exposed to seven consecutive tests of oral glucose tolerance (daily intake of 75 g of glucose) would have developed changes in glucose metabolism in the absence of saccharin. Palmnas et al. [107], demonstrated that 8 weeks of exposure to aspartame (at an equal dose to subjects consuming approximately 2–3 sodas/day) disrupted the intestinal microbiota; aspartame + high fat diet vs. water + high fat diet increased total bacteria; *Entero-bacteraceae*, *Clostridium leptum*, and *Roseburia* spp. reduced *Bifidobacterium* sp. On the contrary, when the diet was low fat + aspartame or low-fat + water, *Clostridium leptum* increased, resulting in elevated levels of fasting glucose and insufficiency tolerance to insulin in rats [51]. However, the mechanism by which aspartame disrupted the IM is unclear, as aspartame is metabolized before it reaches the colon by intestinal esterases and peptidases in amino acids and methanol (**Figure 1**) [49].

3.2. Tagatose and prebiotic potential activity

D-tagatose (D-tag) is an isomer of fructose approximately 90% sweeter than sucrose. Only 20% of the oral intake of tagatose is completely metabolized, mainly in the liver [49]. The mayor part of this molecule is not digested or absorbed and passes through colon where water is absorbed and D-tag is fermented by colonic bacteria. This natural sweetener can be artificially

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obtained from lactose. This sweetener with natural origin can be obtained artificially from lactose. Through food technology, glucose is separated and galactose is extracted, whose molecule is transformed into D-tagatose through an isomerization process [43].

D-tag would have an antihyperglycemic potential through its beneficial effects increasing postprandial serum glucose and hyperinsulinemia. Recent studies indicate that D-tag has a potent anti-diabetic effect and could be eventually associated with significant benefits for the treatment of obesity. The hypothesis regarding the mechanism of action proposed for this hypoglycemic effect would consider the interference with carbohydrates absorption by inhibition of intestinal disaccharidases and glucose transport, an also a mechanism of inhibition of hepatic glycogenolysis [37]. Another important characteristics of the D-tag is it low GI, considering white bread and glucose as reference foods, the D-tag GI is 3 and 4, respectively [63]. The potential applications of D-tag in the pharmaceutical industry and in food industry have reached a great boom [41]. However, the use of D-tag is limited by its high cost of production [36]. Another characteristic of D-tag is its potential prebiotic activity, and in order to preserve this effect the processing and storing of the food must ensure the maintenance of the chemical structure of the sweetener [35]. It has been determined that D-tag can be used for the formulation of diabetic beverages with minimal chance of degradation and very low loss of prebiotic activity [31, 33, 36], maintaining adequate thermal stability. Preliminary results suggest that D-tag would have an effect on the reduction of total cholesterol, VLDL, and LDL compared to sucrose in diabetic patients [53]; the contribution of D-tag to increase levels of HDL cholesterol has also been shown [54]. These clinical studies and wonderful advances in food technology make this molecule an ideal sweetener in functional products for patients with diabetes [62–64], with the ability to positively affect the intestinal microbiota of these patients, making its consumption more interesting and useful in a little explored area [85, 87]. On the other hand, the incorporation of novel functional sources of fiber, as well as oligosaccharides of potential prebiotic activity, has generated great scientific interest in the formulation of healthy foods aimed at diabetics. This new direction of science could be the anticipation of a new line of research that is beginning to emerge. Finally, future projection of personalized nutrigenomics foresees a great challenge toward the integration of different sciences as transcriptomics, epigenetics, proteomics, and metabolomics, with the purpose of positively modifying the microbiome, generating impact in the gene expression of the human organism, and avoiding manifestation of chronic diseases such as DM2.

4. Conclusions

The use of prebiotics obtained from functional fiber sources such as fructo-oligosaccharides and beta-glucans, as well as lignin and prebiotics such as keffir, can contribute to the development of a healthy HIM by promoting the growth of bacterial species that have been associated with obesity and diabetes prevention. On the other hand, it has been described that some low GI monosaccharides can positively modify the composition of the HIM in animal models, by regulating the mechanism of insulin sensitivity. More investigations are needed to evaluate the effect of saccharides, such as fructose, lactose and isomaltose in the human microbiome. Although, some NCS such as sucralose, saccharin, and acesulfame-K can modify the balance of HIM, mainly through the alteration in the number of *Bacteroidetes* species. Nevertheless, more studies in humans are required. In this sense, a new caloric sugar called D-tag has proposed

as possible hypoglycemic and probiotic effects. Finally, the new information presented in this chapter allows us to map out the near future where the integration of nutrigenomics and nutritional treatment focused on the microbiota modification will be plausible. Futhermore, the use of bioactive compounds that alter gene expression and/or affects immunity of pancreatic beta cells represent a projection toward the treatment and/or prevention of DM2.

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