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The Intricate Relationship between Diabetes, Diet and the Gut Microbiota

Gratiela G. Pircalabioru, Ariana Picu, Laura Petcu, Marcela Popa and Mariana Carmen Chifiriuc

Abstract

The most recent World Health Organization report revealed that the number of adults suffering from diabetes has almost quadrupled since 1980 to 422 million, thus drawing attention to the urgent need to step up prevention and treatment of this disease. This chronic ailment is often associated with serious complications such as increased risk of heart disease, stroke and kidney failure. In 2012 alone, diabetes lead to 1.5 million deaths. This dramatic rise is mainly due to the increased prevalence of type 2 diabetes and factors driving it include overweight and obesity. Novel studies in this area have advanced our understanding regarding the complex relationship between diet, gut microbiota and diabetes. Despite no clear microbiota signature is associated with diabetes, patients harbour a reduction of butyrate-producing species (Faecalibacterium prausnitzii, Roseburia intestinalis) as well as an increase in opportunistic pathogens. Furthermore, the functions of the gut microbiome (i.e., vitamin metabolism, transport of sugars, carbohydrate metabolism, short chain fatty acid (SCFA) synthesis, etc.) are also different in patients with type 2 diabetes, a fact that may significantly alter the course of disease. Diet is one of the most decisive factors that have an impact on the gut microbiome. Nutritional interventions using prebiotics (i.e., inulin-type fructans), polyphenols and arabinoxylans have been employed for the treatment of diabetes. Besides the shifts produced by these dietary components in the microbiome composition, it is worth mentioning their impact on host physiology through modulation of gut peptide production and glucose metabolism. The information presented within this chapter summarizes the most recent advances in the study of the microbiome-diet-diabetes interplay and analyses how these novel findings can be used in order to establish new therapeutic approaches for those with diabetes.

Keywords: diabetes, obesity, microbiota, diet, prebiotics, gut physiology
1. Diabetes: the “silent killer”

Diabetes mellitus (DM) is defined as “a heterogeneous syndrome characterized by a complex disorder in regulating the body’s energy metabolism, which also affects the use of carbohydrates, lipids and proteins” [1]. Several processes are involved in the evolution of diabetes pathology ranging from autoimmune pancreatic β cells destruction that induces insulin deficiency, up to anomalies, which causes insulin resistance. Increased blood glucose levels (≥126 mg/dL), blood glucose at 2 h after 75 g oral glucose (≥200 mg/dL), HbA1c (≥6.5%), or all of them characterize diabetes mellitus simultaneously. The American Diabetes Association (ADA) has classified diabetes mellitus into several types: (i) type 1 DM (T1D)—characterized by the destruction of pancreatic β cells; (ii) type 2 DM (T2D)—characterized by a progressive deficiency of insulin secretion on a background of pre-existing insulin resistance; (iii) gestational DM—diabetes diagnosed during pregnancy; and (iv) other specific types of diabetes due to other causes such as genetic defects of β pancreatic cells, genetic defects in the action of insulin, diseases of exocrine pancreas, endocrinopathies, diabetes induced by drugs or chemicals, etc. Type 1 diabetes (T1D) also known as juvenile diabetes or insulin-dependent diabetes mellitus is a very common autoimmune disorder in children and adolescents, and it is caused by the cellular-mediated autoimmune destruction of pancreatic β-cells, leading to an absolute insulin deficiency, which interferes with glucose metabolism [2]. T1D has two variants: (i) type IA is due to the destruction of the pancreatic cells under the influence of immune factors, in which case autoantibodies to islet cells can be detected in serum and (ii) type IB in which the pancreatic β-cell lysis occurs in the absence of an obvious anti-pancreatic mechanism [3]. Patients with this type of diabetes are usually young (under 30 years), have normal weight and require continuous insulin administration for survival. T1D symptoms are usually present with the onset of hyperglycaemia and include polyphagia, polydipsia, polyuria, weight loss, paraesthesia, recurrent infections and ketoacidosis tendency. The T1D prevalence of 1:300 is increasing worldwide, and it represents 5–10% of all diabetes mellitus cases [4]. The main cause of T1D is genetic predisposition with the human leucocyte antigen (HLA) DR3-DQ2 and DR4-DQ8 haplotypes as the most prevalent variants involved, which are common for other autoimmune diseases such as celiac disease [5]. Besides genetic predisposition, other factors such as infections, birth delivery mode, diet and the use of antibiotics have all been linked to T1D development [6], but the mechanisms linking them to T1D development are not clear.

DM type 2 (T2D) comprises a heterogeneous group of conditions characterized by varying degrees of insulin resistance or inappropriate insulin secretion and elevated plasma glucose (hyperglycaemia). Hyperglycaemia of this type of diabetes is due to genetic or metabolic defects of insulin synthesis and/or secretion, which once identified have become particularly important in discovering new effective therapeutic means. Pre-diabetes stages (IFG and IGT) typically precede T2D [7]. T2D appears at the age of 40 or above and is not associated with autoimmune aetiology but with metabolic syndrome involving hypertension, atherosclerotic cardiovascular disease, low high density lipoprotein cholesterol (HDLc), high circulating level of low density lipoprotein cholesterol (LDLc), decreased fibrinolysis, increased plasma lipopolysaccharide (LPS) due to alteration of mucosal permeability, obesity and especially...
visceral or abdominal type of obesity (visceral fat tissue is more metabolically active than the subcutaneous adipose tissue), producing pro-inflammatory adipokines and peripheral insulin resistance. According to the ADA guidelines of 2016: “Standards of medical care in diabetes” (Diabetes Care), the criteria for the diagnosis of T2D refer to: (i) Glucose concentration in venous blood (fasting plasma glucose) ≥126 mg/dL (7.0 mmol/L) in at least two consecutive determinations, measured after at least 8 h of fasting; (ii) Glucose concentration in venous blood 2 h after oral glucose tolerance test—OGTT—(ingestion of 75 g of anhydrous glucose dissolved in water) ≥200 mg/dL (11.1 mmol/L); (iii) HbA1C ≥48 mmol/mol determined in the medical laboratory by the National Glycohemoglobin Standardization Program (NGSP) and standardized by DCCT (Diabetes Control and Complications Trial); and (iv) Glucose concentration in venous blood ≥200 mg/dL (11.1 mmol/L) randomly determined in hyperglycemic individuals. Some potential risk factors for T2D are family history and race. Specifically, Hispanic, Asian American, or Indian Americans are at greater risk to develop T2D. Age is another risk factor worth considering, as individuals who are 40–45 years old or older have a greater risk for developing the condition. Diabetic patients have an increased incidence of cardiovascular disease, atherosclerosis, peripheral arteriopathy and cerebrovascular disease. Long-term complications of diabetes include retinopathy with possible loss of vision, nephropathy followed in time by renal insufficiency, peripheral neuropathy with risk of leg ulceration and amputation. Neuropathy autonomously induces gastrointestinal, genitourinary, cardiovascular and sexual dysfunction. Like most other conditions, the earlier that diabetes is detected, the more successfully it can be managed. There is no cure for type 2 diabetes, but it can be very well managed if identified early. The latest data released by a group of WHO experts provide an alarming prognosis of the diabetes epidemic. It is estimated that by 2025, there will be 324 million people with diabetes. Thus, the prevalence will increase from 2.8% (2000) to 4.3% (2025). The T2D epidemic is considered one of the worst in the history of humankind. What is alarming, however, is that at the time of T2D diagnosis, a large percentage of people already have chronic complications and/or morbid associations. The WHO predictions for 2030 place T2D as the seventh cause of death worldwide. Epidemiological data revealed an increased prevalence for both obesity and T2D in developed countries, suggesting the role of diet and lifestyle in the pathogenesis of these two diseases [1]. Recently, it has been shown that overeating saturated fats and refined sugars can lead to dyslipidemia and insulin resistance. Thus, T2D prevalence is directly proportional to the energy intake of saturated fatty acids [8]. Currently, type 2 diabetes is most commonly encountered in most cases associated with overweight or obesity in adults. WHO classifies obesity grades by the formula: Body Mass Index (BMI) = weight/height$^2$ in: (i) Overweight—BMI 25–29.9 kg/m$^2$; (ii) Grade I obesity—BMI 30–34.9 kg/m$^2$; (iii) Grade II obesity—BMI 35–39.9 kg/m$^2$; and (iv) Grade III obesity—BMI > 40 kg/m$^2$. In T2D, the most common type of obesity is the central or abdominal type [9]. An increased prevalence of T2D in the predominantly abdominal distribution of adipose tissue was reported independent of the degree of obesity [10]. On the other hand, there are studies that show that obesity is not sufficient or mandatory for the appearance of T2D. In support of this hypothesis, there are several arguments: the presence of T2D in a normal weight phenotype, the existence of populations with high prevalence of obesity, but the low prevalence of T2D, the predominance of obesity in females, in contrast to that of T2D that does not differ between genders and finally data according to which in most
populations studied most obese individuals do not have T2D [1]. Cross-sectional studies have failed to determine a causal relationship between T2D and obesity or a common factor triggering both diseases, but prospective and longitudinal studies have provided some evidence of the direct role of obesity in T2D pathogenesis. Prospective studies on the populations of Japan, Sweden and the Pima Indians show that the central distribution of body adiposity is a major risk factor for the emergence of T2D, regardless of the degree of obesity [11]. However, these studies only suggest that insulin synthesis or deficiency obesity and defects predispose to T2D but offer little data on the duration of these anomalies or their interaction [1]. There is increasing evidence that adipose tissue has a limited capacity to store the energy surplus [12] and that overstressed adipocytes suffer a process of apoptosis or necrosis, precipitating an inflammatory response which contribute to the development of insulin resistance [13].

The specificity of obesity in T2D is also the infiltration of adipose tissue with monocytes and activated macrophages leading to the synthesis of pro-inflammatory cytokines (IL-6 and TNF-α). Because of changes induced in the adipose tissue (lipolysis and lipids products), hepatic lipid synthesis (especially of very low-density lipoproteins-VLDL and triglycerides) occurs. Due to the changes in lipid metabolism, T2D is also characterized by dyslipidemia (elevated triglycerides, LDL-C levels and low HDLc) [14].

2. The gut microbiota-evolution, composition and functions

The gut microbiota is a dynamic system composed of tens of trillions of microorganisms, which carry out essential functions for the human host. The first composition of the microbiota is acquired at birth when microorganisms from the mother and the environment rapidly colonize the neonatal gastrointestinal tract. Thus, the delivery mode is a keystone factor which determines whether the newborn is colonized by Lactobacillus, Prevotella or Sneathia spp. from the birth canal or by Staphylococcus sp. and Propionibacterium spp. coming from the skin of the mother and other participants in the caesarean section [15].

Subsequently birth, diet becomes the main modulator of the microbiota composition. In line with this, breastfeeding babies harbour a distinct microbiota from formula-fed babies. While breastfeeding enhances the prevalence of lactic acid bacteria, infant formulas promote the enrichments of species like Staphylococcus aureus and Bacteroides spp. Until 3 years of age, the microbiota is highly influenced by diet and disease and, in time, its composition becomes very similar to one of the adults [16]. At around 7 years old, 90% of the microbiota is composed of bacteria from the phyla Bacteroidetes and Firmicutes, while the remaining 10% is made of Proteobacteria, Tenericutes and Cyanobacteria [17]. A study by Arumugam et al. proposed the existence of three gut enterotypes for the entire world population: Bacteroides, Ruminococcus and Prevotella [18]. Furthermore, these enterotypes were linked to dietary patterns [19]. For instance, the Prevotella enterotype was found to be more prevalent in case of individuals that had a diet rich in fibre and low in fat, whereas the Bacteroides enterotype was characteristic for people eating a diet dominated by animal fat and protein. In addition, recent studies have investigated school-age children from different regions of the world and highlighted the role of age, diet, geographical localization and traditions in shaping the microbiota. Children from Mexico,
Indonesia, Thailand and Malawi have a diet with a low level of animal protein and fat and a high content of plant polysaccharides and fibre, which translate into a microbiota rich in *Prevotella*. Conversely, children from Japan, the United States, Italy and China have a Western diet rich in fat, animal protein and low in fibre and thus have a microbiota dominated by *Bacteroides* [17]. However, the enterotype hypothesis was recently challenged by Knights et al. who showed that enterotypes can vary widely and continuously over time within an individual [20].

The gastrointestinal (GI) tract of a healthy host is home to 10^12 microbial cells within the stomach into the duodenum and jejunum, whereas the distal ileum harbours around 10^8 microbial cells. However, the highest microbial level (around 10^12 cells) resides in the highly anaerobic environment of the colon. Since most of these microbes are not cultivatable, the advent of culture-independent sequencing has provided a valuable insight into the composition of the microbiota in health and disease conditions. Despite the large volume of data generated by sequencing technologies, our understanding of the functional properties of these microorganisms comes from germ-free animals. Thus, animals, which were born and reared under sterile conditions, have provided strong evidence regarding the role of microbiota in shaping immunity, host metabolism and even social development. Unlike animals reared under specific pathogen-free (SPF) conditions, germ-free animals were shown to have a defective development of the immune system with impaired development of the gut-associated lymphoid tissue, with fewer and smaller Peyer’s patches [21].

3. The immunity-diet-microbiota interplay in type 1 diabetes

The microbiota modulates the immune response of the host even before birth as suggested by the fact that the intrauterine environment is not completely sterile. Indeed, there is evidence that the placenta harbours a low-abundance commensal microbiota similar to the oral microbiota [22]. Thus, the foetus is exposed to antigens against which it has to develop immunological tolerance. Following birth, diet represents the crucial factor guiding microbiota composition as well as immunity. Dietary antigens correlated with T1D are modulated by feeding regimens (breast milk vs infant formula) and the introduction of solid foods (particularly of wheat). While infant formula has been historically associated with T1D, breast milk has beneficial immunomodulatory effects in the neonatal gut. Within this line of thought, studies in mice showed that sIgA transferred passively in breast milk promotes gut homeostasis and prevents bacterial translocation [23].

Studies in Finnish and American children revealed that fat and protein intake from milk products promote a risk of advanced β-cell autoimmunity and consequently progression to T1D [24]. Patients with T1D and latent autoimmune diabetes of adults were shown to have elevated titres of anti-β-casein antibodies. Several bovine β-casein variants have a Pro-Gly-Pro-Ile-Pro motif in their sequence, which is also present in the glucose transporter GLUT2. Hence, a plausible explanation for pancreatic damage is a cross reactivity of the immune system initially targeted against the dietary antigen in milk.

T1D is similar in terms of its genetic HLA-associated risk with celiac disease and T1D children have an altered T-cell reactivity against wheat antigens in the gut [25]. Consequently, diets
high in gluten are considered an important culprit for microbiota changes and T1D development [26]. Thus, introduction of gluten-containing foods between 3 and 7 months of age can significantly decrease the risk of T1D autoimmunity [27].

Gluten is a well-known trigger for celiac disease and recently for T1D due to its effects on gut permeability. As a consequence of the impaired gut barrier, gliadin peptides move across the epithelium into the lamina propria where they are detected by dendritic cells. Dendritic cells recognize gliadin peptides and migrate to other sites including the pancreatic lymph nodes where they activate autoreactive T cells [27].

4. The microbiota in type 1 diabetes

The involvement of the intestinal microbiota in the pathophysiology of T1D was highlighted by several animal studies. Valuable insights into the role of microbiota in diabetes pathogenesis were obtained using diabetes prone animals, specifically non-obese diabetic (NOD) mice and bio-breeding diabetes prone (BB-DP) rats.

Initial studies showed that NOD mice with chronic viral infection were characterized by a lower diabetes incidence [28]. Mycobacteria infection and stimulation with bacterial antigens lowered the incidence of diabetes development in NOD mice suggesting that a germ-free niche augments the risk of diabetes development [29]. However, this is not the case since recent studies suggested that rather certain microbes (i.e., *Bacillus cereus*) were modulating the risk of diabetes development [30].

Within a study by Brugman et al., the use of BB-DP rats and fluorescence in situ hybridization targeted against the 16S rRNA of *Clostridium*, *Lactobacillus* and *Bacteroides* showed that rats that developed diabetes harboured higher levels of *Bacteroides* [31]. Further investigations revealed that BB-DP rats had a microbiota with lower levels of *Lactobacillus* and *Bifidobacterium* when compared to diabetes-free rats. More recently, Patterson et al. used the streptozocin (STZ)-induced T1D rat model to offer information regarding diabetes onset and progression in terms of microbial shifts [32]. Thus, T1D was linked to a shift in the Bacteroidetes/Firmicutes ratio, whereas later T1D progression was characterized by an enrichment of lactic acid bacteria (i.e., *Lactobacillus*, *Bifidobacterium*). In addition, STZ-induced T1D rats exhibited a reduced microbial diversity 1 week after disease onset, and this diminished diversity was maintained throughout the study.

Importantly, the integrity of the intestinal epithelium plays a pivotal role in the functioning of the immune system by regulating the passage of antigens to dendritic cells. A compromised barrier epithelium is associated with increased gut permeability, which favours the exposure to antigens and may subsequently lead to autoimmunity. T1D prone rats were shown to have increased gut permeability and diminished levels of the tight junction protein claudin [33]. Furthermore, upregulation of the protein zonulin which regulates tight junctions increased intestinal permeability and the prevalence of diabetes in BB-DP rats [34]. Within this line of thought, a study using the BB-DP rat model hypothesized that administration of *Lactobacillus*...
*johnsonii N6.2* delayed diabetes development via regulation of gut integrity, specifically by increasing the tight junction protein claudin-1 [35].

MyD88 is an adapter protein downstream of multiple toll-like receptors involved in sensing of microorganisms. The knock out of this protein in the NOD mouse was shown to protect against diabetes. Importantly, heterozygous MyD88KO/+ NOD mice, which normally develop disease, are protected from diabetes when colonized from birth with the intestinal microbiota of a MyD88-KO NOD donor mouse [36]. Thus, disease progression in the NOD mouse is partially determined by an exacerbated innate immune response to commensal microbiota, and changes in the composition of the microbiota may diminish this response and counteract disease.

Considerable effort has been made in the last years in order to provide more information regarding the composition of the diabetogenic microbiota in humans. As expected, the pattern of bacterial abundance is distinct between different studies due to variations caused by ethnicity, geography and age. Despite these variations, all studies have shown *Bacteroides* as a main driver for T1D-associated dysbiosis. Indeed, there is a direct relation between the abundance of *Bacteroides* and T1D-associated autoantibodies [37, 38]. However, another study found no difference in *Bacteroides* levels when analysing children with anti-islet cell autoimmunity versus healthy controls [39].

Dysbiosis was linked to autoimmunity and subsequent progression to T1D. Importantly, the appearance of β-cell autoimmunity precedes the onset of hyperglycemia for over 15 years [40]. Therefore, targeting the microbiota could potentially postpone T1D development in children with β-cell autoimmunity.

Recently, Kostic et al. highlighted specific features of the T1D microbiome [38]. The study investigated 33 infants from Finland and Estonia who were genetically predisposed to diabetes and observed a relative 25% reduction in alpha-diversity in T1D patients compared to non-converters and seroconverters (positive for at least two of the autoantibodies analysed including insulin autoantibodies, islet cell antibodies, islet antigen-2 antibodies and glutamic acid carboxylase antibodies). Microbiota shifts were evident in T1D children but not in the seroconverters without disease. T1D subjects were shown to harbour an enrichment of “pathobionts that is of commensal bacteria able to become pathogens such as Rikenellaceae, *Blautia* and the *Ruminococcus* and *Streptococcus* genera.” Furthermore, the authors observed a depletion of bacteria such as *Lachnospiraceae* and *Veillonellaceae*, which are commonly under abundant in inflammatory conditions (Figure 1).

A healthy gut microbiota is enriched with butyrate producers (i.e., *Faecalibacterium*) which determine elevated production of mucin and increased tight junction assembly which all determine an elevated epithelial integrity (Figure 1). A niche with high mucin production favours the enrichment of mucin degrading bacteria such as *Akkermansia muciniphila*. T1D subjects were reported to be colonized by lower levels of butyrate producing microorganisms such as *Roseburia* and *Faecalibacterium* and of mucin degrading bacteria such as *Akkermansia* and *Prevotella* [37, 41, 42]. In addition, the Bacteroidete: Firmicutes ratio was proposed as an early marker for autoimmune diseases since a higher level of Bacteroidetes was evident in children who developed T1D [43].
5. Diet and type 2 diabetes

Food intake has been strongly associated to diabetes and obesity not only in terms of quantity but also in terms of quality of diet. The food shortage and famine during the two World Wars has significantly decreased the diabetes mortality in countries around Europe. However, in countries like the United States of America and Japan, where there was no shortage of food, there was no change in diabetes mortality [44]. Almost two decades ago, the role of diet in T2D was suggested by the observation that diabetes was prevalent among rich people who had an easier access to food such as refined sugar, flour and oil [45]. While in the past it was considered a disease of the rich, nowadays T2D is more prevalent among those with a lower income. Many studies have shown a strong correlation between high intake of sugars and development of T2D. A study by Ludwig et al. analysed 500 ethnically diverse children for a period of 19 months and reported that the frequency of obesity increased for each additional serving of carbonated soft drinks consumed [46]. Several prospective studies revealed link between fat intake and subsequent risk of developing T2DM. A diabetes study involving more than a thousand subjects without a prior diagnosis of diabetes which were investigated for a period of 4 years reported a relationship among T2D, impaired glucose tolerance and fat intake [47, 48]. The high levels of fructose corn syrup used for the manufacturing soft drinks increase the blood glucose levels and the body mass index, thus suggesting that the intake of soft
drinks is linked with obesity and T2D [49]. In addition, diet soft drinks were reported to contain glycated chemicals, which significantly enhance insulin resistance [50]. Whereas high consumption of sweets, red meat and fried foods lead to an increased risk of insulin resistance and T2DM [51], a diet rich in fruits and vegetables may prevent disease development [52]. In addition, interventional studies revealed that high carbohydrate and high monounsaturated fat diets improved insulin sensitivity [53], whereas increased intake of white rice leads to an increased risk of T2D in Japanese women [54].

6. Popular diets and their impact on the microbiota

The most popular diets include omnivore, vegetarian, gluten-free, vegan, Western and Mediterranean. All of these dietary regimes have been studied regarding their role in shaping the microbiota. A gluten-free diet was associated with a decrease in *Bifidobacterium* and *Lactobacillus*, while populations of pathobionts (potentially unhealthy microbes), such as *Escherichia coli* and total *Enterobacteriaceae*, increased in parallel to reductions in polysaccharide intake after beginning the diet [55]. In another study by Bonder et al., a short-term gluten-free diet lead to reductions in *Ruminococcus bromii* and *Roseburia faecis* and an increase in *Victivallaceae* and *Clostridiaceae* [56].

The Western diet which is low in fibre but high in animal protein and fat was associated with a decrease in the total bacterial load and with lower levels of beneficial commensals such as *Bifidobacterium* and *Eubacterium* sp. [19, 57]. Importantly, consumption of a Western diet has also been linked with the generation of cancer-promoting nitrosamines [58]. Both vegan and vegetarian diets are high in fermentable plant-based foods. When comparing a vegan or a vegetarian diet to an omnivorous diet, it was reported that vegan and vegetarian individuals had lower abundance of *Bacteroides* and *Bifidobacterium species* [59].

The traditional Mediterranean diet consists of vegetables, olive oil, cereals, legumes, nuts, moderate consumption of poultry, fish and wine and a low consumption of dairy products, red meat and refined sugars [60]. Among the different diets, the Mediterranean diet is regarded as a healthy balanced diet due to its beneficial content of monounsaturated and polyunsaturated fatty acids, elevated vegetable protein content and high levels of antioxidants and fibre. The Mediterranean diet was associated with a high abundance of *Lactobacillus*, *Bifidobacterium* and *Prevotella*, and a decrease in *Clostridium* [61]. Furthermore, those consuming a Mediterranean diet exhibited increased levels of short chain fatty acids (SCFAs) and low urinary trim ethylamine oxide, which is associated with elevated cardiovascular risk [62]. The effects mediated by the Mediterranean diet include weight loss, improvement of the lipid profile and the decrease of inflammation.

7. Diet-microbiota interactions shape the risk of type 2 diabetes

Diet represents the main modulator of the composition and metabolism of the gut microbiota. The main macronutrients represented by proteins, carbohydrates and fats have a
glucose, insulin, insulin resistance index and leptin, and decreased inflammatory markers (TNF-α, leukocytes). Even though resveratrol supplementation also decreased adipose tissue lipolysis and plasma fatty acid and glycerol in the postprandial state [144], the study lacked some of the necessary controls therefore more investigations are needed in order to state that resveratrol has antidiabetic effects.

11. Conclusions and perspectives

The diet-microbiota-diabetes trio is a hot research topic at the moment, and it still requires further investigation. Even though several studies highlight the benefits associated to the consumption of probiotics in the management of diabetes, their use is hindered by the insufficient information regarding their mechanisms of action. Furthermore, additional human studies are still needed in order to get a better understanding of the role held by the ethnicity and diet in shaping the diabetic microbiome. Finally, future studies combining microbiota analysis, metabolomics, proteomics as well as treatment regimens will provide valuable information regarding the pathomechanisms of diabetes and potentially ways to prevent the onset of disease.

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The Intricate Relationship between Diabetes, Diet and the Gut Microbiota

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