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The Intricate Relationship between Diabetes, Diet and the Gut Microbiota

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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 led 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 ($\geq 6.5\%$), 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 I A 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 I B 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 hyperglycaemic 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/height² in: (i) Overweight—BMI 25–29.9 kg/m²; (ii) Grade I obesity—BMI 30–34.9 kg/m²; (iii) Grade II obesity—BMI 35–39.9 kg/m²; and (iv) Grade III obesity—BMI > 40 kg/m². 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].

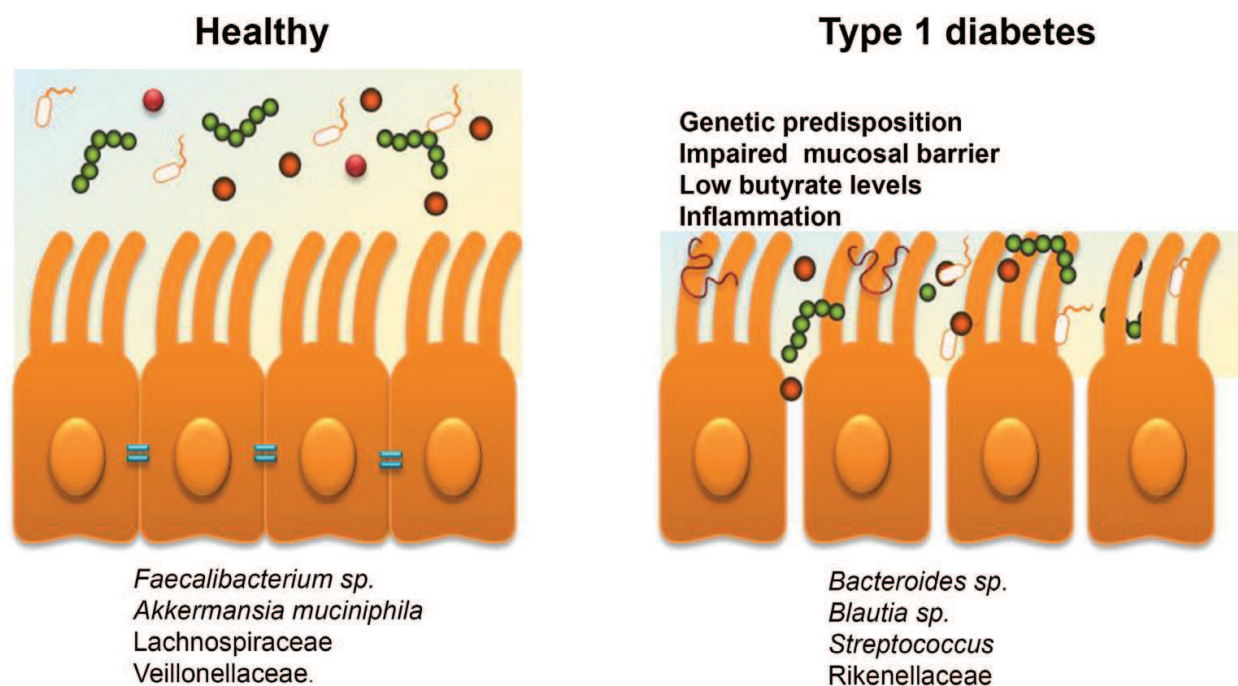


Figure 1. The microbiota in type 1 diabetes. Individuals with type 1 diabetes have an impaired gut barrier function with a thinner mucus layer and increased intestinal permeability. Their microbiota is enriched in *Bacteroides*, *Blautia*, *Streptococcus* and *Rikenellaceae* but low in butyrate producers such as *Faecalibacterium prausnitzii* and mucin degraders such as *Akkermansia muciniphila*.

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 glycosylated 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 led to reductions in *Ruminococcus bromii* and *Roseburia faecis* and an increase in *Viverruaceae* 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 trimethylamine 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

crucial impact on the microbiome. The role of dietary protein in shaping the microbiota has been described since 1977 when individuals who consumed a diet rich in beef harboured elevated levels of *Bacteroides* and *Clostridia* and low levels of *Bifidobacterium adolescentis* compared to those who had a meatless diet [63]. Several studies have recently used different forms of protein including vegetarian pea protein, whey protein and animal protein (meats, eggs and cheese) and correlated protein consumption with microbial diversity [61]. Conversely, the consumption of animal-based protein positively correlated with the abundance of bile-tolerant anaerobes such as *Alistipes*, *Bacteroides* and *Bilophila* [64]. Even though it may promote a greater weight loss, a protein-rich diet can also be detrimental. Thus, individuals on a high protein/low carbohydrate diet had a microbiota with diminished levels of *Roseburia* and *Eubacterium rectale* and low levels of butyrate in their feces [65]. Similarly, patients with inflammatory bowel disease (IBD) had a similar microbiota signature, with low levels of *Roseburia* and decreased butyrate levels [66]. In addition, elevated intake of red meat has been linked to elevated levels of the proatherogenic trimethylamine-N-oxide (TMAO) [62]. Animal studies have shown that high protein consumption increases the levels of insulin-like growth factor 1 (IGF-1), which are known to be correlated with a high risk of diabetes and overall mortality. Indeed, proteins of vegetarian origin have been linked to a lower mortality in comparison with animal-derived proteins [67].

In addition to high protein content, animal-based diets are also high in fat. The well-known Western diet, which is nowadays the main culprit for obesity and diabetes development, is high in saturated and trans fats and low in mono and polyunsaturated fats [61]. While consumption of high saturated and trans fat diets increases cholesterol levels and is associated with a risk of cardiovascular disease, mono and polyunsaturated fats decrease the risk of chronic disease [68]. Human studies have revealed that a high-fat diet increases the abundance of total anaerobic microorganisms and the levels of *Bacteroides* as well [19, 57]. The consumption of different types of fat has different effects on the microbiome. Consumption of a low fat diet promotes the overabundance of *Bifidobacterium* and leads to a reduction of fasting glucose and total cholesterol. Conversely, a high saturated fat diet determined the establishment of a microbiota enriched in *Faecalibacterium prausnitzii*, and a diet high in monounsaturated fat was correlated to a reduced total bacterial load and reduced cholesterol [69].

Animal studies revealed that a high fat diet promotes a microbiota with less *Lactobacillus intestinalis* and with more *Clostridiales*, *Bacteroides* and *Enterobacteriales*. In addition, the abundance of *L. intestinalis* was negatively correlated with fat mass and body weight [70]. Studies in mice compared the effects of different type of lipids on the microbiota. Thus, lard-fed mice harboured elevated *Bacteroides* and *Bilophila* whereas mice fed with fish oil had increased lactic acid bacteria (*Lactobacillus* and *Streptococcus*), increased *Verrucomicrobia* (*A. muciniphila*) and *Actinobacteria* (*Bifidobacterium* and *Adlercreutzia*). In addition, lard-fed mice had white adipose tissue inflammation and impaired insulin sensitivity compared to fish oil-fed mice [71].

Among all the dietary macronutrients, carbohydrates are the most studied. Based on their ability to be degraded enzymatically in the small intestine, carbohydrates are either digestible (i.e., starch and sugars including glucose, lactose, fructose and sucrose) or non-digestible (resistant starch and fibre). Upon degradation, digestible carbohydrates release glucose into the bloodstream and lead to an insulin response [61]. Humans who were fed high levels of glucose, fructose and sucrose in the form of dates had a microbiota enriched in *Bifidobacteria*, and low in *Bacteroides* [72, 73]. Moreover, the addition of lactose to the aforementioned diet replicated the same bacterial shifts but it also decreased the levels of *Clostridia* species [74].

Recently, a subject of debate in the field of carbohydrates and their role in shaping the microbiota is represented by the use of artificial sweeteners. Artificial sweeteners such as saccharin, sucralose and aspartame were intended to be a healthier, no-calorie food additive for replacing natural sugar. However, recent work by Suez et al. showed that artificial sweeteners are more prone to induce glucose intolerance than consumption of sucrose or glucose. The effects exhibited by artificial sweeteners were attributed to the induction of microbiota changes characterized by increased abundance of *Bacteroides* and decreased *Lactobacillus reuteri* [75]. Conversely, the use of natural sugars such as fructose, sucrose and glucose promoted microbiota shifts exactly opposed the ones induced by the use of artificial sweeteners.

Unlike digestible carbohydrates, non-indigestible carbohydrates are not digested in the small bowel but rather reach the colon where they undergo fermentation by commensal microbiota leading to SCFAs production such as butyrate, propionate and acetate. Butyrate is an important energy source for intestinal epithelial cells and a modulator of enterocyte differentiation, proliferation and restitution. Loss of microbial producers of SCFA can alter the communication between host epithelium and resident bacteria, thus contributing to the development of colitis. For instance, *F. prausnitzii* is depleted not only in IBD patients [66] but also in diabetics.

Dietary fibres are essential for intestinal health and have been designated as prebiotics, that is non-digestible dietary constituents that benefit host health via selective stimulation of the growth and/or activity of certain microorganisms [76]. Prebiotics can originate from a multitude of sources including inulins, unrefined wheat, unrefined barley, raw oats, soybeans and non-digestible oligosaccharides such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), fructans, polydextrose, xylooligosaccharides (XOS) and arabinooligosaccharides (AOS) [77]. A low fibre diet has been associated with a reduced bacterial abundance [78] and high consumption of these non-digestible carbohydrates resulted in an increase in microbiota gene richness in obese patients [79]. Many studies revealed that a diet rich in non-digestible carbohydrates targets the microbiota by increasing probiotic bacteria such as bifidobacteria and lactic acid bacteria. Indeed, diets rich in whole grain and wheat bran led to an increase of intestinal *Bifidobacteria* and *Lactobacilli* [80, 81]. FOS-, polydextrose- and AOS-based prebiotics were shown to reduce *Clostridium* and *Enterococcus* species. In addition, resistant starch and whole grain barley increased the abundance of *Ruminococcus*, *E. rectale* and *Roseburia* [61].

8. The microbiota in type 2 diabetes

Genetics, lifestyle and increased bodyweight all contribute to the development of type 2 diabetes. Around 80% of individuals with T2D are overweight thus suggesting an important role of diet and microbiota in the pathophysiology of this disease. The link between microbiota and T2D first became evident in studies on germ-free mice. Thus, colonization of germ-free animals with microbiota harvested from conventionally raised mice lead to a significant increase in body fat and insulin resistance [82]. A following study showed that germ-free mice were resistant to diet-induced obesity [83].

Subsequently, several studies have documented the microbiota shifts associated with T2D. After analysing a cohort of Chinese patients with T2D, Qin et al. showed that the diabetic microbiome is low in butyrate-producing bacteria such as *Clostridiales* sp., *F. prausnitzii*, *Roseburia intestinalis* and *E. rectal* [84]. Moreover, the T2D intestinal niche contained opportunistic pathogens including the sulfate-reducing *Desulfovibrio*, *Bacteroides caccae* and *E. coli*. In line with these findings, a study in Scandinavian post-menopausal women revealed decreased levels of *F. prausnitzii* and *R. intestinalis* in T2D compared with individuals having impaired glucose tolerance. In addition, both Chinese and Scandinavian T2D cohorts exhibited elevated *Lactobacillus* levels. Obesity and impaired glucose metabolism were reported to have an altered ratio between Bacteroidetes and Firmicutes [85]; however, neither the Chinese nor the Scandinavian study found this microbiota change.

The Chinese study revealed an increase of *E. coli* in T2D patients and another Danish study showed that Proteobacteria levels were elevated in T2D [86]. These Gram-negative bacteria could potentially be involved in the pathophysiology of T2D. Specifically, the lipopolysaccharides (LPS) released by these bacteria could promote a subclinical proinflammation, which is typical to both diabetes and obesity. Recent studies revealed that T2D is characterized by elevated endotoxemia. Indeed, mice receiving high fat (HF) diet until they developed diabetes had endotoxemia, increased intestinal permeability and a distinct microbiota [87]. In addition, the term of metabolic infection has emerged in order to describe the role of the microbiome in endotoxemia-associated inflammation together with insulin resistance in T2D. Endotoxin of microbial origin could play a role in the insulin resistance associated with T2D since blood levels of bacterial DNA (mostly Proteobacteria) were shown to be increased in prediabetes.

One caveat of the currently available human studies is the lack of information regarding the role of antidiabetic medication in altering the microbiota. The first-line drug of choice for type 2 diabetes treatment is represented by metformin. In the Swedish study, the diabetic patients received metformin treatment and their microbiota was enriched in Enterobacteriaceae and had low levels of *Eubacterium* and *Clostridium*. In mice-fed a high-fat diet, metformin was shown to affect both the host glucose metabolism as well as the microbiota by increasing the levels of *Akkermansia* [88]. Recently, metformin treatment has also been shown to alter the microbiota composition in T2D patients by increasing *Escherichia* sp. and decreasing the abundance of *Intestinibacter* sp. (**Figure 2**) [89].

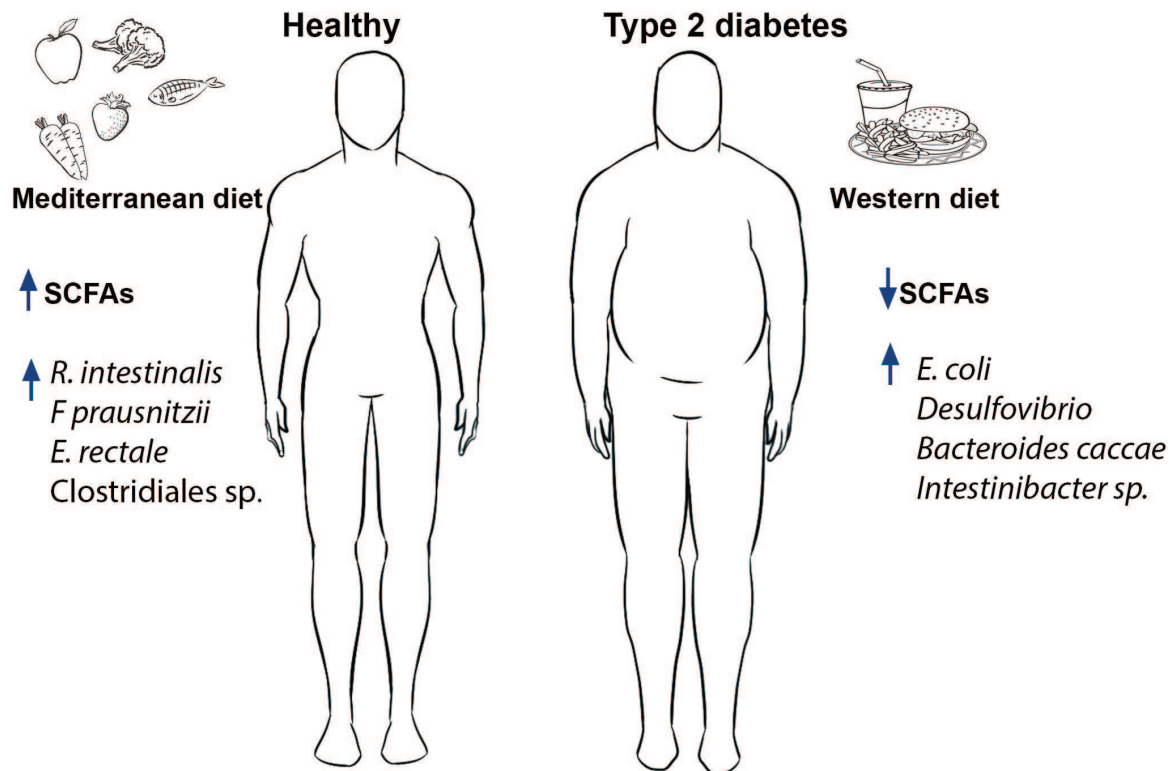


Figure 2. The microbiota in type 2 diabetes. Overweight and obese individuals consuming an unhealthy diet such as a Western diet are prone to develop type 2 diabetes. While healthy individuals consuming a balanced diet with a high content of monounsaturated and polyunsaturated fatty acids, elevated vegetable protein content, and high levels of antioxidants and fibre harbour a microbiota rich in *R. intestinalis*, *F. prausnitzii*, *E. rectale*, *Lactobacillus* sp. and Clostridiales, individuals with type 2 diabetes have a microbiota characterized by higher levels of *Desulfovibrio* sp., *Bacteroides* sp. and *Intestinibacter* sp.

9. Probiotic interventions

Due to their anti-inflammatory, hypoglycaemic, insulinotropic, antioxidative and satietogenic properties, probiotics can be employed as a treatment for T2D. The insulinotropic effect of genetically engineered *Escherichia coli* Nissle 1917 for GLP-1 was investigated in Caco-2 cells; it was observed that the probiotic strain stimulated the epithelial cells leading to the secretion of insulin corresponding to blood insulin concentration of 164 pmol/ml to 164 nmol/ml [90]. In addition, Paszti-Gere et al. reported that oxidative stress causing damage to insulin-secreting β -cells was counteracted by metabolites of *Lactobacillus plantarum* 2142. Specifically, the spent culture supernatant of *L. plantarum* 2142 decreased the oxidative stress-induced overexpression of pro-inflammatory cytokines IL-8 and TNF- α in IPEC-J2 cell line [91]. The multiple mechanisms of probiotics in T2D treatment have emerged from studies by using animal models. Oral administration (0.05%) or diet supplementation (0.1%) of heat-killed *L. casei* in different mouse models including KK-Ay mice, NOD mice and Alloxan-induced diabetic mice reduced the plasma glucose level and diabetes development [92, 93]. Feeding neonatal STZ-induced diabetic (n-STZ) rats with a diet containing *Lactobacillus rhamnosus* GG for a period of 9 weeks determined a lower blood haemoglobin level and an improved glucose tolerance in comparison to the control group

receiving a conventional diet. The *L. rhamnosus* GG treatment group had a serum insulin level significantly higher than the control group at 30 min after glucose loading [94]. Furthermore, feeding VSL#3 lowered β -cell destruction and inflammation in NOD mice, and this effect was accompanied by increased IL-10 secretion in pancreas, Peyer's patches and spleen. In a separate study, the feeding of a probiotic containing *Lactobacillus acidophilus* NCDC14 and *L. casei* NCDC19 significantly lowered free fatty acids, the blood glucose and glycosylated haemoglobin, and triglycerides in fructose-induced diabetic rats [95]. The feeding of the same probiotic to STZ-induced rats suppressed the STZ-induced oxidative damage in pancreatic tissues by inhibiting lipid peroxidation, generation of nitric oxide and improved the antioxidant potential of glutathione, superoxide dismutase, and catalase and glutathione peroxidase. These data suggest that oral administration of the probiotic significantly ameliorated the risk factors such as dyslipidemia, hyperglycemia and oxidative stress in diabetic rats [96]. Probiotic pre-treatment with a mixture containing *Bifidobacterium lactis*, *L. acidophilus* and *L. rhamnosus* lowered the blood glucose and improved the bioavailability of gliclazide, a second-generation sulphonyl-urea used for treating non-insulin dependent diabetes mellitus T2D in alloxan induced diabetic rats [97]. The antidiabetic effects against insulin resistance of different probiotics can also be due to increased liver natural killer T (NKT) cells. NKT cells are involved in regulating the inflammatory process in the liver which is the main organ responsible for inflammation-mediated insulin resistance. Depletion of liver NKT enhanced the production of pro-inflammatory cytokines, and HFD was known to induce depletion of hepatic NKT cells leading to insulin resistance. HFD-induced depletion of NKT cells in male C57BL-6 mice was significantly improved by administration of the VSL#3 probiotic. This probiotic treatment also leads to weight loss, and improved insulin resistance and inflammation by modulating TNF- α expression and reducing NF- κ B binding activity [98]. Treatment with *L. plantarum* DSM 15313 and *L. reuteri* GMNL-263 was reported to lower the blood glucose and glycosylated haemoglobin, in HFD-fed C57BL/6 J mice and STZ-induced diabetic rats [99, 100]. DCs from NOD mice were stimulated with three different strains of lactobacilli including *L. casei*, *L. reuteri* and *L. plantarum* for a period of 24 h. Out of the strains tested, *L. casei* was found to induce DCs to generate the highest level of IL-10 and the lowest level of IL-12 expression. When the *L. casei*-stimulated DCs were transferred to NOD mice, they showed a significant delay in diabetes incidence [101]. *Bifidobacterium longum* CGMCC NO. 2107 added as a supplemented in HFD was shown to reduce the metabolic endotoxin (LPS) plasma concentrations and to improve intestinal inflammation [102]. Amar et al. analysed the effect probiotic treatment has on mucosal dysbiosis, bacterial translocation and glucose metabolism [103]. The results obtained revealed that the bacterial translocation was prevented in mice lacking the microbial pattern recognition receptors Nod1 or CD14. Nevertheless, it was increased in Myd88 deficient mice and ob/ob mouse under the same conditions. In addition, the administration of *Bifidobacterium animalis* subsp. *lactis* 420 reduced the bacterial translocation to mesenteric adipose tissue, decreasing the expression of major pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 in mesenteric adipose tissue, liver and muscle. In addition, *B. animalis* subsp. *lactis* 420 also improved the insulin sensitivity and fasting hyperinsulinaemia in HFD fed mice [103].

Since there are a few reports in this area, the knowledge regarding the efficacy of probiotic administration in diabetic human subjects is quite limited. Consumption of probiotic yoghurt

was shown to improve the antioxidant status and lipid profile in T2D patients. Several randomized, double blind, placebo-controlled clinical trials evaluated the effects of probiotic administration on antioxidant status, blood glucose and lipid profile in T2D. The patients with T2D mellitus enrolled in these studies were divided into two groups: the probiotic intervention group consumed 300 g/d of probiotic yoghurt containing 10^6 cfu/mL *L. acidophilus* La5 and 10^6 cfu/mL *B. lactis* Bb12, whereas the control group consumed 300 g/d of conventional yoghurt during a period of 6 weeks. The probiotic treatment cohort exhibited a significant decrease in fasting blood glucose as well as an increase in the activities of the erythrocyte superoxide dismutase and glutathione peroxidase. In addition, the total cholesterol: high-density lipoprotein (HDL)-C and LDL-C: HDL-C ratios were decreased in the probiotic-treated patients compared to the control [104, 105]. Another randomized, double-blind, placebo-controlled study was performed on 20 elderly diabetic volunteers aged 50–60 years, over for a period of 30 days to study the effect of a symbiotic drink (a preparation with a combination of both probiotics and prebiotics) on glycaemia and cholesterol levels. The symbiotic group that consumed 10^8 cfu/mL *Bifidobacterium bifidum*, 10^8 cfu/mL of *L. acidophilus*, and 2 g oligofructose harboured a significantly increased HDL cholesterol, and a decrease in fasting glycemia but, importantly, no significant changes were observed in the placebo group [106]. Recently, in a study by Shao et al., 67 diabetic patients with gastrointestinal cancer were randomized into the probiotic treatment group (33 patients receiving enteral nutrition with probiotics, glutamine and fish oil) and the control group (34 patients receiving regular enteral nutrition). Fasting blood glucose and insulin were recorded on the day before surgery and post-operative days 3 and 7. Insulin resistance index (HOMA-IR) was calculated as well by using the homeostasis model assessment (HOMA) for both groups, and the supplementary data on incidence of nosocomial infections, intestinal function recovery time and length of hospitalization were also recorded [107].

The enteral nutrition with probiotics, glutathione and fish oil was associated with a low fasting insulin and insulin resistance index compared to the control group. The length of hospital stay was significantly decreased from 21 to 17 days in the treatment group. Nevertheless, no significant differences in nosocomial infection and intestinal function recovery were observed between the two groups. The role of maternal probiotic-supplemented dietary counseling during pregnancy on colostrum adiponectin concentration in neonatal nutrition, metabolism and immunity was analysed in a randomized, placebo-controlled study by Luoto et al. [108]. Specifically, 256 pregnant women were randomized into three groups: dietary intervention with probiotics (diet/ *L. rhamnosus* GG and *B. lactis*), with placebo (diet/placebo) and a control cohort (control/placebo). Dietary intake was analysed by food records at each pregnancy trimester, and subsequently colostrum samples were collected after birth for the analysis of adiponectin concentration. An improved adiponectin concentration is a parameter of neonatal metabolic homeostasis and is also an indicator of reduced chances of gestational diabetes. Probiotic treatment increased the colostrum adiponectin concentration compared to the control (12.7 ng/ml vs. 10.2 ng/ml). Nevertheless, other studies state that probiotic use does not provide a benefit for the diabetic host. For instance, a randomized, double-blinded clinical trial using the commercial probiotic *L. acidophilus* NCFM in a group of 45 men for a timeframe of 4 weeks revealed that there were no changes in the expression of baseline inflammatory markers and in the systemic inflammatory response following probiotic treatment [109].

10. Prebiotics: a useful tool for the management of diabetes

Prebiotics were initially 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, and thus improves host health” [110]. Later, prebiotics were designated as selectively fermented ingredients that allow certain changes in the composition and/or activity of the gastrointestinal microbiota that confer benefits upon host well-being and health [111]. Prebiotic substances need to meet certain criteria such as: (i) fermentation by the commensal microbiota; (ii) selective stimulation of the growth and/or activity of probiotic bacteria; and (iii) resistance to gastric pH, hydrolysis by the host enzymes and gastrointestinal absorption [112]. The currently known prebiotics which achieve the aforementioned criteria include non-digestible carbohydrates, fructooligosaccharides, galactooligosaccharides and lactulose. Prebiotics, such as fructooligosaccharides and inulin, undergo digestion by probiotics such as bifidobacteria and stimulate their growth [113, 114]. Besides their involvement in stimulating the expansion of probiotics, prebiotics also stimulate immunity, inhibit pathogen growth and produce vitamins. In addition, prebiotics were suggested to promote cell differentiation, cell-cycle arrest and apoptosis of transformed colonocytes by epigenetic modifications and by decreasing the transformation of bile acids [110]. Prebiotics administration may have a regulatory role in modulating endogenous metabolism since the SCFAs obtained as an end product of the carbohydrate metabolism improve glucose tolerance. SCFAs also decrease glucagon levels and activate glucagon-like peptide1 (GLP-1), which can stimulate the elevation of insulin production and elevate insulin sensitivity [115, 116]. SCFAs were shown to have an important role in T2DM patients because they promote secretion of GLP-1, a hormone that inhibits glucagon secretion, decreases hepatic gluconeogenesis and improves insulin sensitivity [117].

Prebiotics were also suggested to lead to hypercholesterolemia by lowering cholesterol absorption and by the generation of SCFAs upon selective fermentation by commensal microbiota [118]. A daily intake of 20 g of the prebiotic inulin significantly lowered serum triglycerides compared to the control group. Inulin treatment also decreased serum LDL-cholesterol and increased serum HDL-cholesterol [119]. Moreover, normolipidemic individuals consuming 18% of inulin on a daily basis without any other dietary restrictions exhibited a decrease in total plasma cholesterol and triacylglycerols as well as an increased fecal concentration of *Lactobacillus*-lactate [120]. The inclusion of inulin in the diet of rats increased the excretions of fecal lipids and cholesterol compared to that of the control group due to a reduced cholesterol absorption [121]. Other prebiotics including resistant starches and their derivatives, oligodextrans, lactose, lactoferrin-derived peptides and N-acetylchitooligosaccharides were also shown to have hypocholesterolaemic effects in T2DM patients who are at high risk of developing cardiovascular complications [112]. A diet enriched with arabinoxylan and resistant starch consumed by adults with metabolic syndrome leads to a reduction in the total species diversity of the faecal associated intestinal microbiota and an increase in *Bifidobacterium* and butyrate levels [122].

Clinical trials reported that dietary polyphenols increase the population of *Bifidobacterium* sp. in the gut [123]. Daily consumption of red wine polyphenols for a period of 4 weeks significantly increased the levels of *Bifidobacterium*, *Prevotella*, *Bacteroides*, *Bacteroides uniformis*, *Eggerthella lenta*, *Enterococcus*, and *Blautia coccoides*-*E. rectale* groups compared with baseline, but there

was no control drink for comparison [124]. Meta-analyses of acute or short-term, randomized controlled trials revealed that chocolate or cocoa-reduced insulin and fasting insulin after glucose challenge and improved insulin resistance with no effect on fasting glucose and glycated haemoglobin (HbA1c) [125].

Consumption of dark chocolate containing 500 mg polyphenols for a period of 4 weeks reduced blood pressure (BP), fasting glucose and insulin resistance in lean and overweight females compared to 20 g of placebo dark chocolate with negligible polyphenol content [126]. Drinking cocoa flavanols (902 mg) for 12 weeks also improved insulin sensitivity in overweight and obese individuals compared to a low-flavanol cocoa drink [127]. In contrast, daily consumption of 25 g dark chocolate for 8 weeks did not ameliorate fasting glucose, insulin and HbA1c levels in hypertensive diabetic subjects compared to those consuming 25 g of white chocolate [128]. Given the conflicting results obtained, current data are insufficient to use cocoa polyphenols for glycaemic control.

Cinnamon contains several polyphenols such as procyanidin, cinnamtannin trans-cinnamic acid and flavones (cinnamaldehyde and trans-cinnamaldehyde) and catechin, and several studies have shown the positive effects of cinnamon on glycaemic control [123]. Two clinical studies reported positive effects of cinnamon on fasting blood glucose levels, but no significant changes of HbA1c, LDL, HDL, total cholesterol or TG [129, 130]. Other studies reported no significant changes in fasting glucose, lipids, HbA1c, or insulin levels in 43 subjects with T2D receiving 1 g of cinnamon daily for 3 months [131], 25 postmenopausal women with T2D taking 1.5 g of cinnamon daily for 6 weeks [132], in 11 healthy subjects taking cinnamon (3 g) daily for 4 weeks [133], and in 72 adolescents with T1D taking 1 g of cinnamon daily [134]. A randomized, placebo-controlled, double-blind clinical trial of 58 subjects with T2D found that intake of 2 g daily of cinnamon for 12 weeks significantly reduced HbA1c, systolic blood and diastolic blood pressure [135]. Whole grains including wheat, soy, rye and flaxseed and nuts such as almonds, pecans and hazelnuts are an important source of polyphenols [136]. Whole grain intake is associated with a reduced risk of T2D, but the mechanism of the protection is not well understood [137]. Extra virgin olive oil and olive leafs are another source of polyphenols such as oleuropein and hydroxytyrosol, and they are suggested to have beneficial effects in T2D [138]. The Mediterranean diet supplemented with virgin olive oil or nuts harboured anti-inflammatory effects by decreasing chemokines, interleukin-6 (IL-6) and adhesion molecules, and T-lymphocytes and monocytes [139]. A study of 3541 patients with high cardiovascular risk revealed that a Mediterranean diet rich in extra virgin oil leads to a 40% reduction in the risk of T2D compared with the control group [140].

Supplementation with olive leaf polyphenols improved insulin sensitivity and pancreatic β -cells secretory capacity after oral glucose challenge in overweight, middle-aged men at the risk of developing metabolic syndrome [141, 142]. Supplementation with a 500 mg olive leaf extract tablet for 14 weeks in subjects with T2D significantly lowered HbA1c and fasting insulin but had no effects on postprandial insulin levels [142, 143].

Red wine, berries, grape skins, rhubarb roots, red wine and peanuts, and the roots of rhubarb are sources of resveratrol, a polyphenol naturally synthesized by plants in response to infection and injury. Resveratrol supplementation in obese men for a period of 30 days reduced

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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