We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 5

The Intricate Relationship between Diabetes, Diet and the Gut Microbiota

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

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70602

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

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

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 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/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*, *Rumincoccus* 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,

http://dx.doi.org/10.5772/intechopen.70602

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 10^2 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].

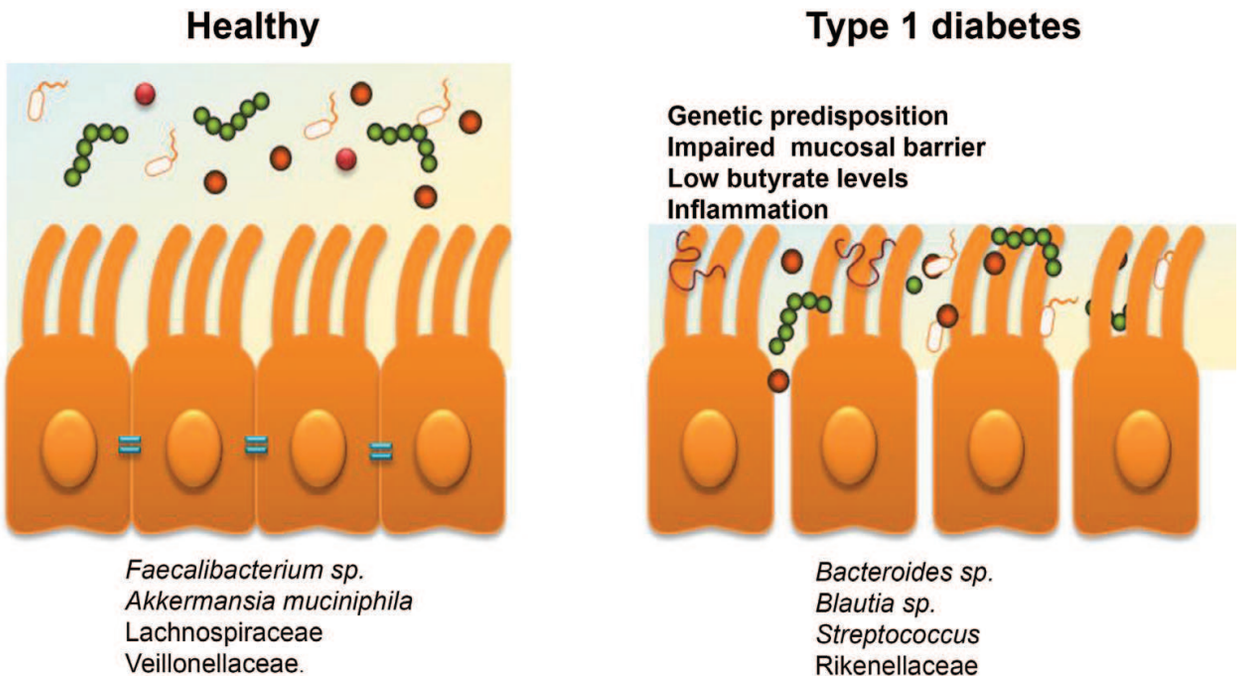


Figure 1. The microbiota in type 1 diabetes. Individuals with type 1 diabetes have an impaired gut barrier function with a thinner mucus layer and increased intestinal permeability. Their microbiota is enriched in *Bacteroides, Blautia, Streptococcus and Rikenellaceae* but low in butyrate producers such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

http://dx.doi.org/10.5772/intechopen.70602

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

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. prausnitz ii* 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. praunitzii* 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 microbiots [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].

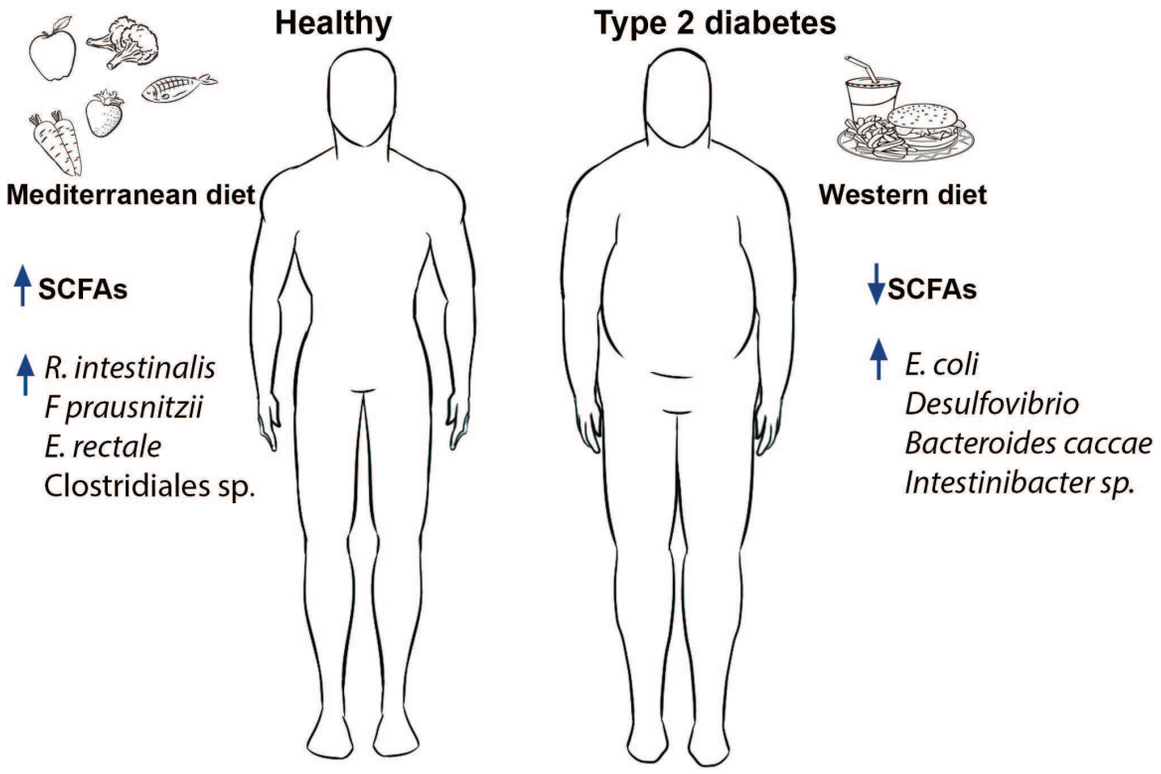


Figure 2. The microbiota in type 2 diabetes. Overweight and obese individuals consuming an unhealthy diet such a Western diet are prone to develop type 2 diabetes. While healthy individuals consuming a balanced diet with a high content of monounsaturated and polyunsaturated fatty acids, elevated vegetable protein content, and high levels of antioxidants and fibre harbour a microbiota rich in *R. intestinalis*, *F. prausnitz ii*, *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 satietogenis 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 ß-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 trigycerides 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 sulphonylurea 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-kB 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 supplemed 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-a, IL-1b 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.

Acknowledgements

This work was supported by the Research Grant PN III - P2-2.1-BG-2016-0369-116/2016.

Author details

Gratiela G. Pircalabioru[1]*, Ariana Picu[1,2], Laura Petcu[1,2], Marcela Popa[1] and Mariana Carmen Chifiriuc[1]

*Address all correspondence to: gratiela87@gmail.com

1 Research Institute of the University of Bucharest, ICUB, Bucharest, Romania

2 National Institute of Diabetes Nutrition and Metabolic Diseases (NIDNMD) "Prof. N.C. Paulescu", Bucharest, Romania

References

[1] Ionescu C. Tratat de Diabet Paulescu. Targoviste: Academiei Romane; 2004. p. 243-244, 734-750, 755-777, 895-1067

[2] A. D. Association. Standards of medical care in diabetes—2015: Summary of revisions. Diabetes Care. 2015;**38**(1):S4

[3] Grigore Mihaescu CC. Immunology and Immunopathology. Editura Medicala; Bucharest, Romania. 2015

[4] Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, Liese AD, Linder B, Mayer-Davis EJ, Pihoker C, et al. Prevalence of diabetes in U.S. Youth in 2009: The search for diabetes in youth study. Diabetes Care. 2014;402-408

[5] Kantarova D, Buc M. Genetic susceptibility to type 1 diabetes mellitus in humans. Physiological Research. 2007;**56**:255-266

[6] Atkinson MA, Eisenbarth GS. Type 1 diabetes: New perspectives on disease pathogenesis and treatment. Lancet. 2001;**358**(9277):221-222

[7] Kasper D et al. Harrison's Principles of Internal Medicine. McGraw-Hill; NewYork, USA. 2015

[8] Le Roith D, Taylor SI, Olefsy JM. Diabetes Mellitus. A Fundamental and Clinical Text. Lippincot, Williams and Wilkins; Philadelphia, Pennsylvania, United States. 2000

[9] Feldman R, Sender AJ, Siegelaub AB. Difference in diabetic and nondiabetic fat distribution patterns by skinfold measurements. Diabetes. 1969;**18**:478-486

[10] Hartz AJ, Rupley DC, Rimm AA. The association of girth measurements with disease in 32,856 women. American Journal of Epidemiology. 1984;**119**:71-80

[11] Lillioja S, Mott DM, Spraul M. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependant diabetes mellitus: Prospective studies of Pima Indians. The New England Journal of Medicine. 1993;**329**:1988-1992

[12] Gray SL, Vidal-Puig AJ. Adipose tissue expandability in the maintenance of metabolic homeostasis. Nutrition Reviews. 2007;**65**(6 Pt 2):S7-S12

[13] Cinti S, Mitchell G, Barbatelli G. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. Jounral of Lipid Research. 2005;2347-2355

[14] Longo DL, Fauci AS, Dennis L, Kasper LS, Hauser J, Jameson JL, Loscalzo J. Harrison's Principle of Internal Medicine. Vol. I. McGraw-Hill; New York City, New York, United States. 2011

[15] Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA. 2010;**107**(26):11971-11975

[16] Power SE, O'Toole PW, Stanton C, et al. Intestinal microbiota, diet and health. British Journal of Nutrition. 2014;**111**(3):387-402

[17] Mejía-León ME, de la Barca AM. Diet, microbiota and immune system in type 1 diabetes development and evolution. Nutrients. 2015;**7**(11):9171-9184

[18] Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. Nature. 2011;**473**(7346):174-180

[19] Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;**80**:105-108

[20] Knights D, Ward TL, McKinlay CE, Miller H, Gonzalez A, McDonald D, Knight R. Rethinking 'enterotypes'. Cell Host & Microbe. 2014;**16**:433-437

[21] Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. Nat Rev Immunol. 2004;**4**:1626-1632

[22] Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. Science Translational Medicine. 2014;**6**(237):237ra65

[23] Rogier EW, Frantz AL, Bruno ME, Wedlund L, Cohen DA, Stromberg AJ, Kaetzel CS. Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. Proc Natl Acad Sci USA. 2014;**111**:3074-3079

[24] Virtanen SM, Nevalainen J, Kronberg-Kippilä C, Ahonen S, Tapanainen H, Uusitalo L, Takkinen H-M, Niinistö S, Ovaskainen M-L, Kenward MG, et al. Food consumption and advanced β cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes: A nested case-control design. The American Journal of Clinical Nutrition. 2012;**95**:471-478

[25] Vaarala O. Is the origin of type 1 diabetes in the gut? Immunology and Cell Biology. 2012;**90**(3):271-276

[26] Davis-Richardson A, Triplett E. A model for the role of gut bacteria in the development of autoimmunity for type 1 diabetes. Diabetologia. 2015;**6**(10):1386-1393

[27] Larsen J, Weile C, Antvorskov JC, Engkilde K, Nielsen SMB, Josefsen K, Buschard K. Effect of dietary gluten on dendritic cells and innate immune subsets in BALB/c and NOD mice. PLoS One. 2015;**10**(3):e0118618

[28] Oldstone MB. Prevention of type I diabetes in nonobese diabetic mice by virus infection. Science. 1988;**80**:500-502

[29] Boerner BP, Sarvetnick NE. Type 1 diabetes: Role of intestinal microbiome in humans and mice. Annals of the New York Academy of Sciences. 2011;**1243**:103-118

[30] King C, Sarvetnick N. The incidence of type-1 diabetes in NOD mice is modulated by restricted flora not germ-free conditions. PLoS One. 2011;**6**(2):e17049-e17052

[31] Brugman S, Klatter FA, Visser JT, et al. Antibiotic treatment partially protects against type 1 diabetes in the bio-breeding diabetes-prone rat. Is the gut flora involved in the development of type 1 diabetes? Diabetologia. 2006;**49**(9):2105-2108

[32] Patterson E, Marques TM, O'Sullivan O, et al. Streptozotocin-induced type-1-diabetes disease onset in Sprague-Dawley rats is associated with an altered intestinal microbiota composition and decreased diversity. Microbiology. 2015;**161**(Pt 1):182-193

[33] Neu J, Reverte CM, Mackey AD, et al. Changes in intestinal morphology and permeability in the biobreeding rat before the onset of type 1 diabetes. Journal of Pediatric Gastroenterology and Nutrition. 2005;**40**(5):589-595

[34] Watts T, Berti I, Sapone A, et al. Role of the intestinal tight junction modulator zonulin in the pathogenesis of type I diabetes in BB diabetic-prone rats. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(8):2916-2921

[35] Valladares R, Sankar D, Li N, et al. Lactobacillus johnsonii N6.2mitigates the development of type 1 diabetes in BB-DP rats. PLoS One. 2010;**5**(5):e10507-e10516

[36] Wen L, Ley RE, Volchkov PY, et al. Innate immunity and intestinal microbiota in the development of type 1 diabetes. Nature. 2008;**455**(7216):1109-1113

[37] De Goffau MC, Luopajärvi K, Knip M, Ilonen J, Ruohtula T, Härkönen T, Orivuori L, Hakala S, Welling GW, Harmsen HJ, et al. Fecal microbiota composition differs between children with β-cell autoimmunity and those without. Diabetes. 2013;**62**(4):1238-1244

[38] Kostic AD, Gevers D, Siljander H, Vatanen T, Hyötyläinen T, Hämäläinen A-M, Peet A, Tillmann V, Pöhö P, Mattila I, et al. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Cell Host & Microbe. 2015;**17**(2):260-273

[39] Endesfelder D et al. Compromised gut microbiota networks in children with anti-islet cell autoimmunity. Diabetes. 2014;**63**:2006-2014

[40] Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, Winkler C, Ilonen J, Veijola R, Knip M, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. Journal of the American Medical Association. 2013; **309**(23):2473-2479

[41] Murri M, Leiva I, Gomez-Zumaquero JM, Tinahones F, Cardona F, Soriguer F, Queipo-Ortuno MI. Gut microbiota in children with type 1 diabetes differs from that in healthy children: A case-control study. BMC Medicine. 2013;**309**(23):2473-2479

[42] Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, Casella G, Drew JC, Ilonen J, Knip M, et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. PLoS One. 2011;**11**:e25792

[43] Giongo A, Gano KA, Crabb DB, Mukherjee N, Novelo LL, Casella G, Drew JC, Ilonen J, Knip M, Hyoty H, et al. Toward defining the autoimmune microbiome for type 1 diabetes. ISME Journal. 2011;**5**(1):82-91

[44] Lumey LH, Van Poppel FW. The Dutch famine of 1944-45: Mortality and morbidity in past and present generations. Social History of Medicine. 1994;**7**(2):229-246

[45] Seidell JC. Dietary fat and obesity: An epidemiologic perspective. The American Journal of Clinical Nutrition. 1998;**67**(3 Suppl):546S-550S

[46] Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: A prospective, observational analysis. Lancet. 2001; **357**(9255):505-508

[47] Lundgren H, Bengtsson C, Blohmé G, Isaksson B, Lapidus L, Lenner RA, et al. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in a population study of women in Gothenburg, Sweden. The American Journal of Clinical Nutrition. 1989; **49**(4):708-712

[48] Marshall JA, Hamman RF, Baxter J. High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: The San Luis valley diabetes study. American Journal of Epidemiology. 1991;**134**(6):590-603

[49] Nseir W, Nassar F, Assy N. Soft drinks consumption and nonalcoholic fatty liver disease. World Journal of Gastroenterology. 2010;**16**(21):2579-2588

[50] Amin TT, Al-Sultan AI, Ali A. Overweight and obesity and their association with dietary habits, and sociodemographic characteristics among male primary school children in Al-Hassa, Kingdom of Saudi Arabia. Indian Journal of Community Medicine. 2008;**33**(3): 172-181

[51] Panagiotakos DB, Tzima N, Pitsavos C, C. C, Papakonstantinou E, Zampelas A, et al. The relationship between dietary habits, blood glucose and insulin levels among people without cardiovascular disease and type 2 diabetes: The ATTICA study. The Review of Diabetic Studies. 2005;**2**(4):208-215

[52] Villegas R, Shu XO, Gao YT, Yang G, Elasy T, Li H, et al. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. Journal of Nutrition. 2008;**138**(3):574-580

[53] Krawagh AM, Alzahrani AM, Naser TA. Diabetes complications and their relation to glycemic control among patients attending diabetic clinic at king khalid national guard hospital in Jeddah, Saudi Arabia. Saudi Journal of Internal Medicine. 2012;**1**(1):29-33

[54] Nanri A, Mizoue T, Noda M, Takahashi Y, Kato M, Inoue M, et al. Rice intake and type 2 diabetes in Japanese men and women: The Japan public health center-based prospective study. The American Journal of Clinical Nutrition. 2010;**92**(6):1468-1477

[55] Sanz Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult humans. Gut Microbes. 2010;**1**(3):135-137

[56] Bonder MJ, Tigchelaar EF, Cai X, Trynka G, Cenit MC, Hrdlickova B, et al. The influence of a short-term gluten-free diet on the human gut microbiome. Genome Medicine. 2016;**8**:45. doi: 10.1186/s13073-016-0295-y

[57] Drasar BS, Crowther JS, Goddard P, Hawksworth G, Hill MJ, Peach S, et al. The relation between diet and the gut microflora in man. Proceedings of the Nutrition Society. 2007; **32**(2):49-52

[58] Park JE, Seo JE, Lee JY, Kwon H. Distribution of seven N-nitrosamines in food. Toxicology Research. 2015;**31**(3):279-288

[59] Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, et al. Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. Gut. 2014;**1**:63-72

[60] Lopez-Legarrea P, Fuller NR, Zulet MA, Martinez JA, Caterson ID. The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state. Asia Pacific Journal of Clinical Nutrition. 2014;**23**(3):360-368

[61] Singh RK et al. Influence of diet on the gut microbiome and implications for human health. Journal of Translational Medicine. 2017;**15**:73

[62] DeFilippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut. 2015:gutjnl-2015. Gut. 2016;**65**:1812-1821

[63] Hentges DJ, Maier BR, Burton GC, Flynn MA, Tsutakawa RK. Effect of a high-beef diet on the fecal bacterial flora of humans. Cancer Research. 1977;**37**(2):568-571

[64] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;**505**(7484):559-563

[65] Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. The American Journal of Clinical Nutrition. 2011;**93**(5):1062-1072

[66] Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, et al. A decrease of the butyrate-producing species Roseburia hominis and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. Gut. 2014;**63**(8):1275-1283

[67] Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, C. C., Madia F, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metabolism. 2014;**19**(3):407-417

[68] Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. Journal of the American Medical Association. 2004;**284**(3):311-318

[69] Fava F, Gitau R, Griffin BA, Gibson GR, Tuohy KM, Lovegrove JA. The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome 'at-risk' population. International Journal of Obesity. 2013;**37**(2):216-223

[70] Lecomte V, Kaakoush NO, Maloney CA, Raipuria M, H. K, Mitchell HM, et al. Changes in gut microbiota in rats fed a high fat diet correlate with obesity-associated metabolic parameters. PLoS One. 2015;**10**(5):e0126931

[71] Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metabolism. 2015;**22**(4):658-668

[72] Parvin S. Nutritional analysis of date fruits (*Phoenix dactylifera* L.) in perspective of Bangladesh. American Journal of Life Sciences. 2015;**3**(4):274

[73] Eid N, Enani S, Walton G, Corona G, Costabile A, Gibson G, et al. The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. Journal of Nutrition Science. 2014;**3**:e46

[74] Francavilla R, Calasso M, Calace L, Siragusa S, N. M., Vernocchi P, et al. Effect of lactose on gut microbiota and metabolome of infants with cow's milk allergy. Pediatric Allergy and Immunology. 2012;**23**(5):420-427

[75] Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014; **514**(7521):181-186

[76] de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Advances in Biochemical Engineering/Biotechnology. 2008;**111**:1-66

[77] Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics – A review. The Journal of Food Science and Technology. 2015;**52**(12):7577-7587

[78] Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2015;**64**(1):93-100

[79] Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, et al. Dietary intervention impact on gut microbial gene richness. Nature. 2013;**500**(7464):585-588

[80] Costabile A, Klinder A, Fava F, Napolitano A, Fogliano V, Leonard C, Gibson GR, Tuohy KM. Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: A double-blind, placebo-controlled, crossover study. British Journal of Nutrition. 2008;**99**(1):110-120

[81] Carvalho-Wells AL, Helmolz K, Nodet C, Molzer C, Leonard C, McKevith B, et al. Determination of the in vivo prebiotic potential of a maizebased whole grain breakfast cereal: A human feeding study. British Journal of Nutrition. 2010;**104**(9):1353-1356.

[82] Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(44):15718-15723

[83] Bäckhed F, Manchester JK, Semenkovich CF, et al. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(3):979-984

[84] Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;**490**(7418):55-60

[85] Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;**444**(7122):1027-1031

[86] Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;**5**(2):e9085

[87] Serino M, Luche E, Gres S, et al. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut. 2012;**61**(4):543-553

[88] Shin NR, Lee JC, Lee HY, et al. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut. 2014;**63**(5):727-735

[89] Forslund K et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;**528**(7581):262-266

[90] Duan F, Curtis KL, March JC. Secretion of insulinotropic proteins by commensal bacteria: Rewiring the gut to treat diabetes. Applied and Environmental Microbiology. 2008;**74**(23):7437-7438

[91] Paszti-Gere E, Szeker K, Csibrik-Nemeth E, Csizinszky R, Marosi A, Palocz O, Farkas O, Galfi P. Metabolites of *Lactobacillus plantarum* 2142 prevent oxidative stressinduced overexpression of proinflammatory cytokines in IPEC-J2 cell line. Inflammation. 2012;**35**(4):1487-1499

[92] Matsuzaki T, Yamazaki R, Hashimoto S, Yokokura T. Antidiabetic effect of an oral administration of *Lactobacillus casei* in a non-insulin dependent diabetes mellitus (NIDDM) model using KK-Ay mice. Endocrine Journal. 1997;**44**(3):357-365

[93] Matsuzaki T, Takagi A, Ikemura H, Matsuguchi T, Yokokura T. Intestinal Microflora: Probiotics and Autoimmunity. Journal of Nutrition. 2007;**137**(3 Suppl 2):798S-802S

[94] Tabuchi M, Ozaki M, Tamura A, et al. Antidiabetic effect of Lactobacillus GG in streptozotocin-induced diabetic rats. Bioscience, Biotechnology, and Biochemistry. 2003;**67**(6):1421-1424

[95] Yadav H, Jain S. Antidiabetic effect of probiotic dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei* in high fructose fed rats. Nutrition. 2007;**23**(1):62-68

[96] Yadav H, Jain S. Oral administration of dahi containing probiotic *Lactobacillus acidophilus* and *Lactobacillus casei* delayed the progression of streptozotocin-induced diabetes in rats. Dairy Research. 2008;**75**(2):1-7

[97] Al-Salami H, Butt G, Tucker I, Skrbic R, Golocorbin-Kon S, Mikov M. Probiotic pretreatment reduces gliclazide permeation (ex vivo) in healthy rats but increases it in diabetic rats to the level seen in untreated healthy rats. Archives of Drug Information 2008;**1**(1):35-41

[98] Ma X, Hua J. Probiotics improve high fat diet-induced hepatic steatosis and insulin resistance by increasing hepatic NKT cells. Journal of Hepatology. 2008;**49**(5):821-830

[99] Andersson U, Bränning C, Ahrné S, et al. Probiotics lower plasma glucose in the high-fat fed C57BL/6 J mouse. Beneficial Microbes. 2010;**1**:189-196

[100] Lu YC, Yin LT, Chang WT, Huang JS. Effect of *Lactobacillus reuteri* GMNL-263 treatment on renal fibrosis in diabetic rats. Journal of Bioscience and Bioengineering. 2010;**110**(6):709-715

[101] Manirarora JN, Parnell SA, Hu YH, Kosiewich MM, Alard P. NOD dendritic cells stimulated with lactobacilli preferentially produce IL-10 versus IL-12 and decrease diabetes incidence. Clinical and Developmental Immunology. 2011;**2011**:1-12

[102] Chen JJ, Wang R, Li XF, Wang RL. *Bifidobacterium longum* supplementation improved high-fat-fed-induced metabolic syndrome and promoted intestinal Reg I gene expression. Experimental Biology and Medicine. 2011;**236**:823-831

[103] Amar J, Chabo C, Waget A, et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: Molecular mechanisms and probiotic treatment. EMBO Molecular Medicine. 2011;**3**:559-572

[104] Ejtahed HS, Mohtadi-Nia J, H., Rad A, et al. Effect of probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* on lipid profile in individuals with type 2 mellitus. Journal of Dairy Science. 2011;**94**:3288-3294

[105] Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition. 2012;**28**:539-543

[106] Moroti C, Souza Magri L, de Rezende Costa M, Cavallini DC, Sivieri K. Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with type 2 diabetes mellitus. Lipids in Health and Disease. 2012;**11**(1):29

[107] Shao F, Yang CG, Liu X, Yang DG. Application of microbiological and immunological enteral nutrition in patients with gastrointestinal cancer complicated with diabetes mellitus. Chinese Journal of Gastrointestinal Surgery. 2012;**15**:476-479

[108] Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counseling during pregnancy on colostrum adiponectin concentration: A prospective, randomized, placebo-controlled study. Early Human Development. 2012;**88**:339-344

[109] Andreasen AS, Larsen N, Skovsgaard T, et al. Effects of *Lactobacillus acidophilus* NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. British Journal of Nutrition. 2010;**104**:1831-1838

[110] Gibson GR, Roberfroid M. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. Journal of Nutrition. 1995;**125**(6):1401-1412

[111] Roberfroid M. Prebiotics: The concept revisited. American Society of Nutrition. 2007; **137**(3 Suppl 2):830S-837S

[112] Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutrition Research Reviews. 2004;**17**(2):259-275

[113] Przemyslaw J, Tomasik PT. Probiotics and Prebiotics. Cereal Chemistry. 2003;**80**(2): 113-117

[114] Pourghassem GB, Dehghan P, Aliasgharzadeh A, Asghari Jafar-abadi M. Effects of high performance inulin supplementation on glycemic control and antioxidant status in women with type 2 diabetes. Journal of Diabetes & Metabolism. 2013;**37**(2):140-148

[115] Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter bacteroidetes and firmicutes in lean and obese JCR:LA-cp rats. British Journal of Nutrition. 2012;**107**(4):601-613

[116] Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM, Possemiers S. van Holle A, Francois P, de Vos WM, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes. 2011;**60**(11):2775-2786

[117] Ahren B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. Hormone and Metabolic Research. 2004;**36**(11-12):867-876

[118] Kim M, Shin HK. The water-soluble extract of chicory influences serum and liver lipid concentrations, cecal short-chain fatty acid concentrations and fecal lipid excretion in rats. Journal of Nutrition. 1998;**128**(10):1731-1736

[119] Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal, environment in hypercholesterolemic men. Nutrition Research. 2000;**20**(2):191-201

[120] Brighenti F, Casiraghi MC, Canzi E, Ferrari A. Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers. European Journal of Clinical Nutrition. 1999;**53**(9):726-733

[121] Dikeman CL, Murphy MR, Fahey GC Jr. Dietary fibers affect viscosity of solutions and simulated human gastric and small intestinal digesta. Journal of Nutrition. 2006; **136**(4):913-919

[122] Hald S, Schioldan AG, Moore ME, Dige A, Lærke HN, Agnholt J, Bach Knudsen KE, Hermansen K, Marco ML, Gregersen DJ. Effects of arabinoxylan and resistant starch on intestinal microbiota and short-chain fatty acids in subjects with metabolic syndrome: A randomised crossover study. PLoS One. 2016;**11**:e0159223

[123] Kim YA, Keogh JB, Clifton PM. Polyphenols and glycemic control. Nutrients. 2016;**8**: pii: E17. DOI: 10.3390/nu8010017

[124] Queipo-Ortuno MI, Boto-Ordonez M, Murri M, Gomez-Zumaquero JM, Clemente-Postigo M, Estruch R, Cardona Diaz F, Andres-Lacueva C, Tinahones F. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. American Journal of Clinical Nutrition. 2012;**95**(6):1323-1334

[125] Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: A systematic review and meta-analysis of randomized trials. American Journal of Clinical Nutrition. 2012;**95**(3):740-751

[126] Almoosawi S, Tsang C, Ostertag LM, Fyfe L, Al-Dujaili EA. Differential effect of polyphenol-rich dark chocolate on biomarkers of glucose metabolism and cardiovascular risk factors in healthy, overweight and obese subjects: A randomized clinical trial. Food & Function. 2012;**3**(10):1035-1043

[127] Davison K, Coates AM, Buckley JD, Howe PR. Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects. International Journal of Obesity. 2008;**32**(8):1289-1296

[128] Rostami A, Khalili M, Haghighat N, Eghtesadi S, Shidfar F, Heidari I, Ebrahimpour-Koujan S, Eghtesadi M. High-cocoa polyphenol-rich chocolate improves blood pressure in patients with diabetes and hypertension. ARYA Atherosclerosis. 2015;**11**(1):21-29

[129] Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003;**26**(12):3215-3218

[130] Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, Hahn A. Effects of a cinnamon extract on plasma glucose, hba, and serum lipids in diabetes mellitus type 2. European Journal of Clinical Investigation. 2006;**36**(5):340-344

[131] Blevins SM, Leyva MJ, Brown J, Wright J, Scofield RH, Aston CE. Effect of cinnamon on glucose and lipid levels in non insulin-dependent type 2 diabetes. Diabetes Care. 2007; **30**(9):2236-2237

[132] Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. Journal of Nutrition. 2006;**136**(4):977-980

[133] Tang M, Larson-Meyer DE, Liebman M. Effect of cinnamon and turmeric on urinary oxalate excretion, plasma lipids, and plasma glucose in healthy subjects. American Journal of Clinical Nutrition. 2008;**87**(5):1262-1267

[134] Altschuler JA, Casella SJ, MacKenzie TA, Curtis KM. The effect of cinnamon on A1C among adolescents with type 1 diabetes. Diabetes Care. 2007;**30**(4):813-816

[135] Akilen R, Tsiami A, Devendra D, Robinson N. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic type 2 diabetic patients in the UK: A randomized, placebo-controlled, double-blind clinical trial. Diabetes Medicine. 2010; **27**(10):1159-1167

[136] Perez-Jimenez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of polyphenols: An application of the phenol-explorer database. European Journal of Clinical Nutrition. 2010;**64**(Suppl 3):S112-S120

[137] Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. Journal of Nutrition. 2012;**142**(7):1304-1313

[138] Cardona F, Andres-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuno MI. Benefits of polyphenols on gut microbiota and implications in human health. Journal of Nutritional Biochemistry. 2013;**24**(8):1415-1422

[139] Estruch R. Anti-inflammatory effects of the mediterranean diet: The experience of the PREDIMED study. Proceedings of the Nutrition Society. 2010;**69**(3):333-340

[140] Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, et al. Prevention of diabetes with mediterranean diets: A subgroup analysis of a randomized trial. Annals of Internal Medicine. 2014;**160**(1):1-10

[141] Shiomi Y et al. GCMS-based metabolomic study in mice with colitis induced by dextran sulfate sodium. Inflammatory Bowel Disease. 2011;**17**:2261-2274

[142] De Bock M, Derraik JG, Brennan CM, Biggs JB, Morgan PE, Hodgkinson SC, Hofman PL, Cutfield WS. Olive (olea europaea l.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: A randomized, placebo-controlled, crossover trial. PLoS One. 2013;e57622

[143] Wainstein J, Ganz T, Boaz M, Bar Dayan Y, Dolev E, Kerem Z, Madar Z. Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats. Journal of Medicinal Food. 2012;605-610

[144] Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, Hoeks J, van der Krieken S, Ryu D, Kersten S, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metabolism. 2011;612-622

IntechOpen

IntechOpen

IntechOpen