

New therapeutic approaches based on modulation of the intestinal microbiota to correct dysbiosis in patients with type 2 diabetes

Nouvelles approches thérapeutiques basées sur la modulation du microbiote intestinal pour corriger la dysbiose chez les patients atteints de diabète de type 2

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ABSTRACT

Type 2 diabetes is a chronic disease characterized by insulin resistance and reduced insulin production in pancreatic cells. Conventional treatment of type 2 diabetes relies on hypoglycemic drugs, physical activity and a balanced low-carbohydrate diet, but with technological advances in metagenomics and metabolomics researchers have developed new therapeutic approaches aimed to modulate the gut microbiota to correct the dysbiosis confirmed in people with type 2 diabetes. This literature review provides an update on therapies aimed to modulate the gut microbiota to correct dysbiosis in type 2 diabetics and summarizes the latest advances in this field.

Keywords: type 2 diabetes, gut microbiota, dysbiosis, Mediterranean diet, probiotic and prebiotics supplementation.

RÉSUMÉ

Le diabète de type 2 est une maladie chronique caractérisée par une résistance à l'insuline et une diminution de sa production dans les cellules pancréatiques. Le traitement classique du diabète de type 2 repose sur les médicaments hypoglycémisants, l'activité physique et sur une alimentation équilibrée pauvre en glucides, mais avec le progrès technologique en matière de la métagénomique et la métabolomique les chercheurs développent des nouvelles approches thérapeutiques qui visent la modulation du microbiote intestinal pour corriger la dysbiose confirmée chez les personnes atteintes du diabète de type 2. Cet article de littérature met le point sur les thérapies qui visent la modulation du microbiote intestinal pour corriger la dysbiose chez les diabétiques de type 2 et résume les dernières avancées dans ce domaine.

Mots clés : diabète de type 2, microbiote intestinal, dysbiose, régime Méditerranéen, supplémentation en probiotiques et prébiotiques

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease that accounts for more than 90% of diabetes cases worldwide; it is characterized by insulin resistance in target organs, or insufficient insulin production by pancreatic beta cells (1). In addition to genetic predisposition, obesity, poor eating habits and physical inactivity are the main risk factors for the development of T2DM (2). Type 2 diabetes is a disease that exposes people to microvascular and macrovascular complications that threaten the vital prognosis of people with this condition (3); the main macrovascular complication is cardiovascular disease,

which increases the risk of death by three to four times compared to people without cardiovascular disease (4).

The intestinal microbiota formerly known as the intestinal flora, is a highly complex ecosystem made up of microorganisms (bacteria, viruses, archaea and fungi) that are ten times more numerous than the human cells in our body. The intestinal microbiota comprises 10¹⁴ bacteria (5-6). These bacteria are divided into four major phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria, with Firmicutes (60% to 75%) and Bacteroidetes (30% to 40%) the most dominant groups (6-7).

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The microbiota is distributed throughout the digestive tract, from the mouth to the colon, with a colonic bacterial population that is qualitatively and quantitatively more diverse than oral, gastric and intestinal bacteria (6). Although there is a similarity of microbiota at phyla level, at species level; the microbiota is specific to each individual, and if we compare the microbiota of 10 different people, we find only one common species (6). Studies have shown that the mode of delivery is a determining factor in the intestinal microbiota of the newborn, as is the type of breastfeeding (8), heredity, ethnic origin and environmental, dietary and medicinal factors can modulate the composition of the intestinal microbiota (9). The microorganisms that make up the intestinal microbiota have the capacity to degrade and ferment food substrates (proteins, carbohydrates, lipids), in fact they generate metabolites that are beneficial to the host, mainly short-chain fatty acids. They also metabolize bile acids, steroid hormones and eliminate toxins, as well as synthesizing vitamins (B9, K) and neurotransmitters (10-11). The intestinal microbiota acts as a defensive barrier against ingested pathogens, maintaining the balance between pro- and anti-inflammatory actions. It also stimulates the development and maturation of the immune system and the renewal of epithelial cells (11-12).

In order to explore the relationship between diabetes and the gut microbiota, several studies have analyzed the composition of the gut microbiota in diabetics and have compared the composition of the gut microbiota in healthy people and diabetics. These studies have shown that there is a correlation between type 2 diabetes and gut dysbiosis, with a greater likelihood of developing putrefactive dysbiosis than of developing fermentative dysbiosis (13). Dysbiosis in patients with T2DM is characterized at the species level by a decrease in butyrate-producing bacteria and an increase in the lactobacillus genus (13-14-15). There are studies that have confirmed that the genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia* and *Roseburia* were negatively associated with T2DM, while the genera of *Ruminococcus*, *Fusobacterium*, and *Blautia* were positively associated with T2DM (16). A comparison of the composition of the intestinal microbiota between diabetics and healthy subjects showed that the proportions of the phylum Firmicutes and the class Clostridiales are reduced in diabetics compared with non-diabetics, and the Bacteroidetes/Firmicutes ratio correlates positively with plasma glucose concentration (17). The beneficial potential of protective bacteria against type 2 diabetes is linked to molecular mechanisms that prevent inflammation by inhibiting the synthesis of pro-inflammatory cytokines and chemokines, as well as protecting against intestinal permeability by increasing the expression of tight junction-related genes, thus preserving against endotoxemia, and improving glucose metabolism by increasing the expression of glucose transporters and improving insulin sensitivity in target cells and glucose intolerance (16).

With scientific development over the years, therapeutic strategies for type 2 diabetes have undergone a major

evolution, and the intestinal microbiota is becoming a relevant therapeutic target for treating diabetes. Indeed, several human and animal trials have studied the impact of diet, dietary fiber, probiotic and prebiotic supplementation and fecal transplantation on diabetes control. The aim of this article is to review the various therapies that target the gut microbiota in type 2 diabetics and their effect on the control of type 2 diabetes.

DIET

Mediterranean diet

The countries of the Mediterranean basin are at the origin of the Mediterranean diet (MD) (18); the cultural heritages, values and traditions, sustainability, biodiversity as well as health and well-being are all constituent elements of the DM concept (19). According to cultural and regional differences, three Mediterranean culinary regions can be distinguished: Southern Europe, Eastern Mediterranean and North Africa (19). However, all regions have common bases, since their diets are characterized by abundant consumption of fruit and vegetables and whole grains, as well as milk and fermented dairy products (yoghurt, cheese), high to moderate consumption of fish and shellfish, and moderate to low consumption of lean meats (rabbit, lamb, goat, poultry). Olive oil is also the main fat in Mediterranean cuisine (18-19-20). Aromatic herbs and condiments are also present in Mediterranean cuisine, and wine is the mainstay of the southern European diet (19). To understand the relationship between the Mediterranean diet and intestinal microbiota; several studies have shown that this diet has the power to shape bacterial composition and diversity with specific characteristics of the gut microbiota; in fact, people with a high adherence to the Mediterranean diet have higher levels of *Clostridium* group XIVa and *Faecalibacterium* *Prausnitzii* and a high abundance of Bacteroidetes, *Prevotella* and *Prevotellaceae*, and a low presence of Firmicutes and *Lachnospiraceae* (18). Other results have reported that the firmicutes /Bacteroidetes ratio is lower in these subjects (18-21). MD adhesion reduces the growth of pathobionts such as Proteobacteria and Firmicutes, and supports the growth of Bacteroidetes, Lactobacilli, Bifidobacteria and Roseburia (21).

MEDBIOME is a single-arm study for a period of 12 weeks in which participants received dietary guidelines based on the MD. At the end of the intervention, they observed a negative correlation between microbial richness and HOMA IR and fasting glycaemia, and a negative correlation between microbial diversity and HBA1C. In fact, the *Prevotella*/Bacteroides ratio was increased, and there was an improvement in glycated hemoglobin and the HOMA-IR index, consolidating the data on the treatment of type 2 diabetes by modulation of the gut microbiota (22). In another randomised, controlled, crossover two-month dietary intervention on 44 adults with metabolic syndrome, participants were divided into two groups, one consuming a MD and the second consuming a regular diet plus nuts, a significant

change in 65 circulating metabolites was associated with the MD (especially lipids, acylcarnitines, amino acids, steroids, and tricarboxylic acid intermediates), and these changes were linked to a decrease in glucose and the HOMAR-IR insulin resistance index. In addition, analysis of gut microbiota composition in this study revealed a correlated network between several bacterial genera and circulating metabolites, suggesting an interaction between diet, circulating metabolites and gut microbiota (23). In a comparative study of the MD and the hypocaloric ketogenic diet in overweight or obese patients recently diagnosed with type 2 diabetes showed that the ketogenic diet had a better beneficial effect than the MD with regard to anthropometric parameters, however there were no significant differences in the improvement of biochemical parameters; both approaches had an impact on the intestinal microbiota, taxonomic analyses showed that in the ketogenic group there was an increase in beneficial taxa such as the Verrucomicrobiota phylum and the Christensenellaceae family, and a decrease in Firmicutes and actinobacteria, whereas in the Mediterranean diet group there was a modification limited to an increase in the Actinobacteria phylum and Firmicutes. Deledda and al concluded that the health status of people with type 2 diabetes in both groups improved (24).

A diet rich in dietary fibre

Dietary fibers are compounds with a common polysaccharide nature (25) from a chemical and structural point of view, there are several types of dietary fibre: resistant starch (monomer unit ≥ 10) found in cereal products and starches, parietal fibers (monomer unit ≥ 10) from fruits and vegetables and oligosides (number of monomer units between 3 and 9) contained in certain foods such as bananas, garlic onion, milk and wheat bran (26). As the classification of dietary fibers can be made according to the number of monomer units, it can also be made according to physico-chemical properties: solubility, viscosity and fermentation: soluble fibers like beta glucan, pectin, psyllium and gums are fibers that dissolve in water and form a viscous body, and insoluble fibers like cellulose and hemicellulose as their name indicates that cannot dissolve in water (27-28). Insoluble fibers are less fermentable in the colon, whereas soluble fibers such as pectins, mucilage and gums are more fermentable (29). It should be noted that the degree of fermentation of dietary fibers depends on several factors, such as degree of polymerization, particle size and solubility.

Several dietary fibers are considered to be prebiotics, which are defined by WHO as follows "non-viable dietary components that provide a health benefit to the host through modulation of the microbiota". For dietary fibers to be classified as prebiotics, they must meet five criteria (30):

- Resistant to digestive enzymes and acids,
- Used exclusively as a substrate for a selected group of beneficial micro-organisms,
- Promotes growth and increases the number of favorable bacteria, while reducing the number of pathogenic bacteria.

- Beneficial effect on host health.

- Viable after thermal, chemical or physical treatment.

The most popular prebiotics include fructo-oligosaccharides, inulin, galacto-oligosaccharides, lactulose dextrin, etc (31-32). Soluble fibers are fermentable by the intestinal flora, releasing metabolites with health benefits such as regulation of carbohydrate and lipid metabolism and improvement of the immune system (28). A high intake of dietary fiber changes the composition and abundance of bacteria endowed with enzymatic fermentation mechanisms, increasing the production of short-chain fatty acids, which can reduce hyperlipidemia, hyperglycemia and hyperinsulinism, while a reduced intake of dietary fiber can result in restricted microbial diversity (33). Dietary interventions rich in dietary fiber are linked to an increase in the fecal abundance of several bacteria such as *Lactobacillus* esp, *Bifidobacteria* esp, *Akkermansia* esp, *Fecalobacteria* esp, *Rosburia* esp, *Bacteroides* esp, and *Prevotella* esp, in addition to a reduction in F/B ratio (34). In type 2 diabetics, a high intake of dietary fiber, particularly soluble fiber, improves blood sugar levels and reduces hyperinsulinism (35). Other studies have shown that glycated haemoglobin, total short-chain fatty acids and the relative abundance of *Bifidobacterium* are significantly improved by dietary fiber, while it had no significant effect on fasting blood glucose, HOMA-IR, acetic acid, propionic acid and butyric acid (32, 36). In this respect, several studies have analyzed the relationship between the effect of a high-fiber diet on diabetic control and the modulation of intestinal microbiota.

In a randomized clinical trial in type 2 diabetic patients, they analyzed variations in intestinal flora, serum metabolism and emotional mood after a high-fiber diet, showing a protective effect on the intestinal ecosystem by enriching the intestinal microbiota with beneficial bacteria (*Bifidobacteria*; *Akkermansia*, *Lactobacilli*) and a reduction in pathogenic bacteria, with an improvement in glucose homeostasis (fasting glycemia and HBA1C), systemic inflammation and psychiatric comorbidities (37). A placebo-controlled crossover study was carried out to assess the prebiotic effect of inulin-type fructans on faecal microbiota and short-chain fatty acids in type 2 diabetic patients, with results revealing a moderate but non-significant increase in faecal levels of *Bifidobacteria*, total SCFA, acetic acid and propionic acid in type 2 diabetic patients, but had no effect on overall microbial diversity or fecal butyric acid, suggesting a moderate potential for inulin-type fructans to improve the gut microenvironment in type 2 diabetes (38).

A 12-week double-blind, randomized, placebo-controlled trial investigating a prebiotic fiber-enriched nutritional formula containing resistant starch and β -glucan from oats, on health-related quality of life and metabolic control in type 2 diabetics; the results showed an improvement in the primary assessment system of type 2 diabetes-related distress at week 12 of the intervention as well as a decrease in HBA1C and fasting blood glucose and a significant reduction in weight and improvement in blood pressure and diastolic blood pressure. With regard to the microbiome, the results showed no change

in alpha diversity between the start and end of the intervention in any of the groups, whereas a small but significant variance in beta diversity was observed in the active arm compared with the control arm (39).

Wang et al found highly relevant results concerning the effect of consuming a diet rich in dietary fiber in their study, which was carried out over a 6-year period among Hispanic Latinos in the United States. The results revealed that high dietary fiber consumption was associated with an intestinal microbiota and metabolites favoring type 2 diabetes (40).

PROBIOTIC SUPPLEMENTATION

The concept of probiotics began with Henri Tissier, a French scientist and pediatrician at the Institut Pasteur, who experimented with the normal and pathological intestinal flora of infants, discovering *bifidobacterium bifidum* in 1899 (the first probiotic found in human stools). Later, Elie Metchnikoff (Russian scientist, Nobel laureate and professor at the Institut Pasteur in Paris) speculated that lactic acid bacteria could offer health benefits leading to greater longevity. He proposed that "intestinal auto-intoxication" and the resulting aging could be inhibited by modifying the intestinal microflora and replacing proteolytic microorganisms such as *Clostridium* with useful microbes. The term "probiotic" was first introduced in 1965 by Lilly and Stillwell; in comparison with antibiotics, probiotics were defined as factors derived from microorganisms by stimulating the growth of other organisms. In 1989, Roy Fuller emphasized the need for probiotics to be viable and introduced the idea that they had a beneficial effect on the host. Probiotics have been defined by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" (41).

Among the microorganisms most commonly used as probiotics are : *Lactobacillus* and *Bifidobacterium* species, but *Saccharomyces cerevisiae* yeast and some *E. coli* and *Bacillus* species are also used as probiotics. For microorganisms to be considered probiotics, the following criteria must be met: the strains must be identified and tested, they must be resistant to the gastrointestinal tract and even be able to adhere to the intestinal mucosa.

Several preclinical trials have asserted that probiotic supplementation can lower blood sugar levels and improve various metabolic indices that affect blood sugar. For this reason, various studies have shown that fermented foods such as yoghurt have beneficial effects for type 2 diabetic patients (42,43). A prospective study carried out in 2018 on Korean adults showed that yogurt consumption was inversely linked to the risk of T2D (44). Another study of American women showed that higher consumption of dairy products such as yoghurt was associated with a lower risk of T2DM (45). In Brazil, a clinical trial involving a sample of 50 patients with T2DM demonstrated that daily consumption of 120 g of fermented milk containing *Bifidobacterium lactis* BB-12

and *Lactobacillus acidophilus* La-5 over a 6-week period improved serum levels of fructosamine, hemoglobin A1c (HbA1c) and IL-10 (46). Meanwhile, *Lactobacillus reuteri* strains ADR-1 and ADR-3 reduced serum HbA1c and cholesterol levels by regulating the abundance of *Bacteroidetes* and *Bifidobacterium* in 68 T2DM patients (47). In addition, another study showed that 70 T2DM patients who consumed fermented milk treated with *Lactobacillus casei* Shirota for 16 weeks experienced a reduction in the translocation of intestinal bacteria into the bloodstream, leading to an increase in the abundance of *Clostridium coccoides*, *Clostridium leptum* and *Lactobacillus* in faeces (48). Another study conducted in Brazil on 20 T2DM patients aged over 30 showed that the administration of probiotics such as *Bacillus clausii* for 90 days significantly reduced blood glucose levels, increased plasma high-density lipoprotein (HDL) levels and improved intestinal microbiota profiles in the patients included in this study (49). In 2023, Chen and colleagues conducted a two-phase randomized control trial in which the use of probiotic supplementation with metformin was studied for 3 months. Their results showed that Co-administration of probiotics and metformin significantly lowered HbA1c and homeostasis model assessment- β (HOMA- β) compared with metformin alone in patients with T2DM (50).

Ziegler et al in 2022 conducted a clinical trial on a sample of 20 overweight or obese patients with T2DM who were assessed before and after the intervention. Patients drank a *Bacillus clausii* spore-based probiotic daily for 3 months. Results showed a statistically significant difference in blood glucose levels, an increase in plasma HDL levels and improved gut microbiota profiles in patients included in this study. Levels of TC, TG, LDL, VLDL, non-HDL cholesterol and BMI remained unchanged (51). Another study conducted in 2022 by Toeijing et al demonstrated the efficacy of *L. paracasei* on glycemia in patients with T2DM. Compared with the control group, administration of *L. paracasei* normalized blood glucose, LDL and HDL levels (52). Today, various clinical trials have shown that certain microbial strains can be beneficial for the intestinal microbiota and the maintenance of good health (53,54). In this sense, several studies have suggested that the use of probiotics as alternatives in the management of metabolic diseases, can have a positive effect on the intestinal microbiota in a safe and effective way and subsequently provoke a positive response to diseases (55,56). In general, probiotics have been shown to have beneficial effects, and several processes have been outlined for the treatment of T2DM. Following probiotic ingestion, an improvement in T2DM manifestations is generally observed, such as improved intestinal integrity, lower LPS levels, reduced endoplasmic reticulum stress and improved peripheral insulin sensitivity (57,58). The work of Firouzi et al in 2016 and O'Connor and colleagues in 2017 showed that probiotics could modulate the gut microbiota, and this through metabolic cascade processes could improve lipid profiles (decrease LDL, normalize TC, increase HDL), reduce fasting glucose, hemoglobin A1c, fasting insulinemia and C-reactive protein (CRP) levels (59,60).

FECAL TRANSPLANTATION

Fecal microbiota transplantation (FMT), also known as intestinal bacteriotherapy, is the transfer of fecal matter from a healthy donor to a recipient suffering from dysbiosis, with the aim of restoring the balance of intestinal flora (61). Although fecal microbiota transplantation is perceived as a new therapy, it was used in India 3000 years ago to treat gastrointestinal disorders, and during World War II German soldiers treated dysentery with camel feces (62-63). In 1958 Eisman used faecal enemas to treat patients with pseudomembranous colitis (64,65). FMT can be administered by colonoscopy, enema or nasal probe in the upper digestive tract (66). Fecal microbiota transplantation is an argument for the role played by microbiota in various diseases (67). Numerous studies have demonstrated the beneficial effect of fecal microbiota transplantation on neurological and psychiatric disorders, gastrointestinal diseases (mainly *Clostridium difficile* infection) and cancer. FMT also improves immune response and metabolic disorders (68,69).

The use of fecal microbiota transplantation in animal and human models of type 2 diabetes reported a decrease in glycemic values, BMI, blood pressure, glycated hemoglobin, triglycerides and total cholesterol. This suggests that FMT may be an efficient alternative therapy for the management of type 2 diabetes or a complementary treatment to conventional treatment of type 2 diabetes (70). A trial on genetically diabetic mice showed that FMT treatment improved fasting blood glucose, serum insulin and oral glucose tolerance test (71). Researchers in another study used fecal bacteria from *Kasakhs* with normal glucose tolerance in *ob/ob* mice and observed a significant improvement in gut microbiota composition with an increase in the abundance of *Akkermansia muciniphila* as well as a reduction in fasting blood glucose levels and postprandial glycemia (72). X.HAN and al concluded that FMT from glucose-tolerant *Kasakhs* in diabetic mice would help improve glycolipid disorders by modifying the composition of the intestinal microbiota, which promotes the production of short-chain fatty acids, and also by activating the RGP43 and GLP-1 pathways (73). In a prospective, randomized, controlled study of three groups of type 2 diabetic patients who were treated with either FMT alone, metformin alone or FMT plus metformin, FMT improved insulin resistance in type 2 diabetics with and without metformin, as well as fasting and postprandial blood glucose and HbA1c four weeks after the intervention (74). In a study in mouse models over a six-week period, FMT was administered to mice that had previously been fed a high-fat diet combined with streptozotocin for six weeks, the results showed an increase in insulin sensitivity and a decrease in the inflammatory response, so FMT stopped beta-cell apoptosis (75). However, the results of a trial in patients with type 2 diabetes, which was divided into three arms: FMT from lean donors or probiotics or placebo, showed no improvement in insulin sensitivity or HbA1c in any of the three groups (76).

POSTBIOTICS

In 2021, the International Scientific Association for Probiotics and Prebiotics defined postbiotics as “a preparation of non-living microorganisms and/or their cellular components that confer a health benefit on the host” (77). However, a new, more precise definition has now been proposed, which only applies the term “postbiotics” to metabolites produced by a probiotic microorganism (78). Other scientists suggest classifying postbiotics into two categories: bacterial components and bacterial metabolites (79). Research suggests that metabolites derived from the microbiota may also contribute to beneficial physiological effects (80). Clinical trials have revealed that postbiotics can optimally improve obesity and diabetes. In fact, two in-depth meta-analyses have highlighted the potential of heat-inactivated *Lactobacillus* to effectively lower blood sugar levels, HOMA IR, body weight, triglycerides, total cholesterol, and LDL levels, while improving insulin sensitivity and high-density lipoprotein levels (81). Fang et al highlighted key points related to the metabolic and immune actions of butyrate, propionate, and acetate as postbiotics. These short-chain fatty acids (SCFAs) increase anorexigenic hormones such as glucagon-like peptide 1 (GLP-1) and plasma peptide (PYY) in diet-induced obese mice, these SCFAs increase energy expenditure, and the same results are observed in humans (79). Another study in male mice treated with sodium butyrate administered intragastrically showed that sodium butyrate could reduce diabetes-induced intestinal inflammation by regulating the gut microbiota (82). Nam et al obtained results suggesting that heat-inhibited *Lactiplantibacillus plantarum* LRCC5314 has protective properties against stress-related type 2 diabetes via modulation of the gut microbiota, suggesting its potential as an aid in the management of stress-related type 2 diabetes (83). The majority of studies conducted in dietary and non-dietary animal models of type 2 diabetes and insulin resistance, which received inactivated bacteria, reported a significant decrease in blood glucose and/or insulin levels, as well as an improvement in insulin resistance indices (84).

MICROBIOTA-DERIVED THERAPEUTICS

Obesity and associated metabolic disorders, such as type 2 diabetes and insulin resistance, are associated with low-grade inflammation (85), which may be caused by increased plasma concentrations of lipopolysaccharides (LPS), a condition known as metabolic endotoxemia (86). Obesity is also characterized by increased endocannabinoid system (eCB) tone (87, 88). The eCB system consists of endogenous bioactive lipids that activate specific G-coupled receptors, namely CB1 and CB2 receptors. Among these lipids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the best known (89). Deregulation of eCB concentrations can contribute to conditions such as obesity and type 2 diabetes. For this reason, several clinical studies have examined the effects of CB1 antagonists on weight loss and changes

in carbohydrate and lipid metabolism (90, 91). These effects are only partially explained by reduced food intake and calorie consumption (92, 93). Indeed, several scientific studies have confirmed that LPS produced by the gut microbiota plays a key role in the onset of adipose tissue inflammation (94, 95, 96) and also stimulates eCB synthesis (97). Furthermore, several studies (98, 99) have revealed the involvement of the eCB system in modulating glucose stabilization in humans and in animal models of obesity, as well as insulin sensitivity (100). The influence of the eCB system on glucose homeostasis and muscle metabolism therefore appears to be a potential mechanism explaining the metabolic changes associated with obesity and type 2 diabetes. Therefore, CB1 receptor blockade reduces plasma glucose and inflammation levels through a mechanism that depends on intestinal barrier function (reduction in intestinal permeability). A study conducted in 2013 on mice that were chronically treated with a cannabinoid receptor (CB) agonist (HU210) or a low dose of LPS before and during a high-fat (HF) diet for 6 weeks. After 3 weeks of treatment with the control diet (CT), half of the mice in each group were subjected to a high fat (HF) diet for an additional 3 weeks. The results of this study demonstrated that under baseline conditions (control diet), chronic treatment with CB receptor agonists (i.e., 6 weeks) caused glucose intolerance, stimulation of metabolic endotoxemia, and increased macrophage infiltration in muscles. In contrast, chronic LPS treatment increased body weight and fat mass, with a slightly moderate influence on other metabolic parameters. Subjecting mice to an HF diet after pretreatment with the CB agonist disrupted the glucose intolerance caused by the HF diet, muscle macrophage infiltration, and muscle lipid content, without affecting body weight or adipose tissue mass (101).

NEXT-GENERATION PROBIOTICS : AKKERMANSIA MUCINIPHILA

The definition of traditional probiotics also encompasses new-generation probiotics, which also meet the criteria for live biotherapeutic products as defined by the US Food and Drug Administration as: "biological products that include living organisms, including microbes, that are relevant to the prevention, treatment, or alleviation of human disease or conditions; and are not a form of vaccination" (102,103). Probiotics can have several effects on the health of the host, mainly changes in the intestinal microbiome, modulation of the immune system, and the production of bioactive substances. The pathways and modes of action of PNGs can vary depending on their strain (104,105).

Numerous studies have shown that Akkermansia muciniphila, Faecalibacterium prausnitzii, and Roseburia hominis promote the balance of the host's intestinal microbiome. As a result, next-generation probiotics are being proposed as a therapeutic approach for the treatment of obesity and type 2 diabetes (106).

Lactobacillus rhamnosus and Bifidobacterium lactis are among the new generation of probiotics that promote

Lactis are among the new generation of probiotics that promote the treatment of metabolic diseases. They improve insulin sensitivity and lipid metabolism and reduce body weight in obese individuals with type 2 diabetes (107).

B. Longum is an antidiabetic agent. In diabetic mice induced by a high-fat diet combined with streptozotocin, B. Longum improved insulin resistance and inflammation related to endotoxemia, lowered fasting blood sugar levels, and regulated intestinal microbiota imbalance, particularly through an increase in the abundance of Akkermansia (108).

Akkermansia helped prevent and improve numerous conditions such as obesity, diabetes, metabolic syndrome, and inflammation (109). Indeed, A muciniphila generated immunoglobulin G1 (IgG1) antibodies and antigen-specific T-cell responses in gnotobiotic mice, and the outer membrane of Akkermansia possesses a specific protein (Amuc_1100) that signals to the specific Toll-like receptor 2 (TLR2) (110).

A study of 21 people with type 2 diabetes who received a probiotic formulation containing five strains, including Akkermansia muciniphila and inulin, showed an improvement in postprandial blood sugar levels (111).

BACTERIOPHAGE THERAPY

Bacteriophage therapy, or phage therapy, is considered a promising therapeutic approach that targets specific pro-diabetic gut microbes, which could have a positive effect on mitigating metabolic disorders such as type 2 diabetes. This method relies on the use of bacteriophages, which are defined as viruses or natural enemies that specifically infect bacteria and are among the most abundant and diverse biological entities on earth (112,113). They have the ability to selectively eliminate harmful intestinal microbes without disrupting the overall balance of the microbiota (114). The work of Ye et al demonstrated that administering a phage cocktail significantly altered the gut microbiome, improving the dysbiosis observed in mice with diabetes induced by a high-fat diet and streptozotocin. This effect was achieved by altering the microbial composition as well as metabolic pathways and metabolites (115).

Although bacteriophage therapy offers a new strategy for treating pro-diabetic gut microbes, challenges remain, including the need for a personalized approach and the fight against potential bacterial resistance to phages. Further research is needed to fully exploit the therapeutic potential of bacteriophage therapy.

TRADITIONAL OR HERBAL MEDICINES

Phytotherapy is the oldest form of medicine, using medicinal plants or parts of plants to treat and relieve various ailments or to promote well-being and balance in the body (116). Today, several studies have shown that modulating the gut microbiota with plant extracts such as berberine and curcumin significantly improves glycemic markers. These two ingredients influence the composition

of the gut microbiota, which in turn influences glucose metabolism and overall metabolic health.

Berberine (BBR) is an isoquinoline alkaloid produced by certain plants and can be extracted from the roots and rhizomes of a variety of medicinal plants, such as *Berberis kansuensis* C.K. Schneid. (Berberidaceae), *Coptis chinensis* Franch. (Ranunculaceae), *Coscinium fenestratum* (Goetgh.) Colebr. (Menispermaceae), *Argemone mexicana* L. (Papaveraceae), and *Phellodendron amurense* Rupr. (Rutaceae) (117). Despite its low bioavailability, it is widely used to treat various diseases, particularly tumors, endocrine diseases, cardiovascular diseases, neurological diseases, and digestive diseases (118). According to the latest animal and clinical research, BBR promotes insulin secretion, increases insulin sensitivity, inhibits gluconeogenesis, reduces lipid accumulation, inhibits steatosis and fibrosis, has properties that reduce inflammatory responses and oxidative stress, modulates the immune system, and may interact with the gut microbiota (119,120).

A study was conducted to test the effects of BBR on mice with glucose and lipid metabolism disorders, compared to a normal control group and an untreated group with metabolic disorders. The results of this study demonstrated that BBR significantly improved blood glucose and lipid levels in the host, with fasting blood glucose levels decreasing by approximately 30% after 8 weeks in the berberine-treated group. In addition, in the berberine-treated group, oral glucose tolerance tests showed that blood glucose levels were consistently lower than those in the untreated group with impaired metabolism at all times, and that BBR also significantly reduced body weight, total plasma cholesterol, and triglyceride levels. The results also showed a significant change in the overall structure of the gut microbiota by BBR, which enriched many beneficial bacteria, such as *Akkermansia* ($p < 0.01$), *Eubacterium* ($p < 0.01$), and *Ruminococcus* ($p < 0.01$), which are associated with improved glucose metabolism (121). In another study, in a rat model of diabetes, intragastric administration of BBR at a dose of 200 mg/kg resulted in a decrease in blood glucose levels, improved glucose tolerance, and improved serum lipid parameters after 6 weeks. The relative abundance of *Bacteroides* increased in the berberine-treated group, while that of *Proteobacteria* and *Verrucomicrobia* decreased (122, 123). Similarly, another study conducted by Ming and colleagues over an 18-week period with newly diagnosed hyperglycemic patients randomly assigned to the following four groups: BBR *Bifidobacterium* (Bi), berberine and *Bifidobacterium* (BB), and placebo. The results showed a significant reduction in fasting blood glucose levels in the BBR and BB groups compared to the placebo group. At the same time, the BBR and BB groups also showed a significant decrease in postprandial plasma glucose levels at 2 hours. A reduction in HbA1c was observed in the BB group compared to the placebo group. Also, relative to the Bi and placebo groups, the BBR and BB groups showed greater changes in the gut microbiota compared to baseline (124).

Another study was conducted on Goto-Kakizaki rats,

which were divided into three groups and received saline (Mo), metformin (Me), or BBR over an eight-week observation period. According to the results obtained, compared with the Mo group, the Me and BBR groups showed significant differences in fasting blood glucose ($P < 0.01$) and glucagon-like peptide-1 (GLP-1) ($P < 0.05$). A significant reduction in weight and insulin resistance was observed in the BBR group compared to the Me group ($P < 0.01$). The Me and BBR groups showed a change in the structure of the gut microbiota compared to the Mo group. Correlation analysis confirmed that body weight was strongly positively correlated with *Clostridia_UCG-014* ($P < 0.01$) and negatively correlated with *Allobaculum* ($P < 0.01$). Body weight showed a positive correlation with *Desulfovibrionaceae* ($P < 0.01$) and a negative correlation with *Akkermansia* ($P < 0.01$). The results demonstrated that Me and BBR could significantly reduce *Bacteroidetes* ($P < 0.01$) and the *Bacteroidetes/Firmicutes* ratio ($P < 0.01$). In addition, *Muribaculaceae* ($P < 0.01$; $P < 0.05$) decreased significantly in the Me and Be groups, and *Allobaculum* ($P < 0.01$) increased significantly (125).

Curcumin, the active compound in turmeric, is a natural polyphenolic compound known for its many biological properties, particularly its antioxidant, anti-inflammatory, antimicrobial, antitumor, antidiabetic, and anti-obesity effects (126, 127).

The benefits of curcumin, especially its hypoglycemic properties, are associated with its ability to modify intestinal dysbiosis, a condition observed in patients with type 2 diabetes and metabolic syndrome. Preclinical and clinical studies have indicated that restoring the intestinal flora may contribute to glycemic homeostasis and the regulation of glucose and lipid metabolism (128).

A study conducted to evaluate the protective effects of curcumin on intestinal dysbiosis, intestinal barrier integrity, and bile acid homeostasis in aged mice fed a high-fat, high-sugar diet, compared with a group of mice fed a normal diet with or without curcumin supplementation (0.4% w/w) for 8 and 15 weeks. The results showed that curcumin supplementation prevented weight gain and metabolic disorders induced by a high-fat, high-sugar diet. In the intestine, mice treated with curcumin had a greater abundance of beneficial bacteria, such as *Lachnospiraceae*, *Akkermansia*, *Mucispirillum*, and *Verrucomicrobiota*, as well as a lower abundance of harmful bacterial genera such as *Desulfofacteria*, *Alistipes*, and *Muribaculaceae*, compared to the control group. This change in the gut microbiota was linked to a restoration of intestinal integrity, such as increased expression of the tight junction protein occludin and decreased levels of the pro-inflammatory marker interleukin-1 β in the ileum. In addition, curcumin altered the expression of liver genes involved in bile acid homeostasis, resulting in a positive effect on liver health (129).

According to the results of another study, curcumin significantly improved intestinal integrity, hyperglycemia, insulin resistance, and body weight, and also reversed the dysbiosis of the intestinal microbiota in diabetic rats caused by a high-fat diet (130).

CONCLUSION

Type 2 diabetes is associated with intestinal dysbiosis, studies carried out to shed light on the impact of modulating the intestinal microbiota in type 2 diabetics by the Mediterranean diet, the high-fiber diet, probiotic supplementation, prebiotics and fecal transplantation have shown a restoration of intestinal balance with better management of type 2 diabetes. Further studies are needed to understand the relationship between type 2 diabetes and the gut microbiota and its metabolites, and therapeutic approaches aimed at modulating the gut flora.

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