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Review Article

State of the Art: Intestinal Microbiota and Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (DM2) has unquestionable epidemiological importance and a well-established association with increased cardiovascular risk, morbidity and mortality, in such a way that the expansion of its prevalence is considered a public health issue. The involvement of the intestinal microbiota, which alterations appear to predispose to systemic inflammation, obesity and insulin resistance, could contribute to the pathogenesis of T2DM.

Aims: To analyze the association between the intestinal microbiota and DM2, determining its participation in the development of the disease and the therapeutic possibilities related to the recent findings.

Methods: A literature review of the main scientific articles related to DM2 and intestinal microbiota in the PubMed, Scielo and Google Academic databases was carried out.

Results: The intestinal microbiota has multiple functions that affect the functioning of the host organism. These include response to pathogens, influence on glucose metabolism, and metabolism of essential substances such as bile acids and polysaccharides. Thus, dysbiosis, that is imbalance between the components of the microbiome, seems to be directly related to the onset of pathologies, such as DM2.

Conclusion: Although the discussions on this topic are still recent and often discordant, the importance of the intestinal microbiota for the onset of DM2, as well as other pathologies related to systemic inflammation is clear. Further research, especially evaluating human beings, is needed to create concepts that can help in the prevention and treatment of the disease.

Keywords: *Diabetes Mellitus; Type 2; Microbiota; Gastrointestinal Microbiome*

Introduction

Diabetes Mellitus (DM), a metabolic disorder that culminates in persistent hyperglycemia, is considered a global public health problem. According to the International Diabetes Federation [1], it is estimated that 425 million of people around the world are carriers of the disease, approximately 8.8% of individuals between 20 and 79 years of age. The estimated values for 2045, considering the maintenance of the current trend, are even more alarming: up to 629 million of adults in this age group will be compromised.

The statistics of 2017 give Brazil the fourth place in absolute numbers of diabetic patients (12.5 million), being the sixth country with the largest financial expense destined to the treatment of the disease and management of its complications - about 24 billion dollars Annual [1]. The prevalence of DM in the Brazilian population accompanies the worldwide propensity, with a noticeable increase. While a multicentric study [2] conducted between 1986 and 1988 detected that 7.6% of the population was affected, two more recent studies conducted in Ribeirão Preto [3] and São Carlos [4], showed values of 12.1% and 13.5%, respectively.

The frank rise in the number of people affected by diabetes has devastating consequences. It is estimated that the pathology is responsible for up to 10.7% of all deaths of individuals between 20 and 79 years-higher than the sum of deaths from HIV/AIDS, tuberculosis and Malaria [1]. In Brazil, 2011 data revealed a mortality rate of 30.1 per 100 thousand [5] inhabitants. Even more important is the morbid potential of the disease: besides the classic complications (nephropathy, retinopathy, neuropathy and coronary dysfunctions, cerebrovascular and peripheral arterial), DM has been associated with other diseases, such as those related to Gastrointestinal tract, psychic and cognitive activity and musculoskeletal apparatus, as well as several [6] neoplasms.

Age Range	North region	Northeast Region	Southeast Region	South Region	Midwest Region	Total
0 to 29 years	0,5	0,6	0,5	0,5	0,6	0,5
30 to 39 years	2,6	3,8	3	2,4	3,4	3,1
40 to 49 years	11,8	13,3	10,3	8,5	10	10,8
50 to 59 years	46,1	49,1	35,4	33,1	38	39,1
60 years and over	245,6	292,7	190,9	209,3	192,6	223,8
Total	21,8	36,6	28,6	30,6	22,6	30,1

Table 1: *Mortality rate due to diabetes (every 100,000 inhabitants), by Brazilian geographic macro-region, according to age group, in the year 2011.*

Source: DATASUS/MS5.

Type 2 diabetes mellitus (DM2) is the most common, accounting for 90 to 95% of the cases. In these patients, a previous state of decrease in the body's response to insulin (the so-called insulin resistance) generates a compensatory increase in the production of the hormone, which, in a chronic way, culminates in progressive loss of the secretory function and, thus, in sustained hyperglycemia [5,6]. Characteristically, DM2 most frequently affects adults after the third decade of life, although the prevalence of children and adolescents is undergoing elevation.

Although the etiology of the disease is not completely explained, many risk factors are well established, highlighting obesity or overweight, sedentarism, family history and advanced age. Metabolic syndrome, low nutritional value diet, smoking, pre-diabetes or glucose intolerance and intrauterine exposure to hyperglycemia (maternal gestational diabetes) are also considered predisposing conditions for the emergence of DM2 [5,6].

Due to the epidemiological importance of DM2 and the great morbidity and mortality associated with such pathology, several studies have been conducted with the objective of eliciting possible contributors to the genesis of the disease. Among the agents suggested, the composition of the intestinal microbiota is recently highlighted as one of the multiple variants that could interfere with the pathogenesis of DM2.

The intestinal microbiota consists of a set of microorganisms - Archaea, Eukarya, viruses and mainly anaerobic bacteria - that establish a symbiotic relationship with the human being [7]. These components have an active role in multiple organic functions, including the aid to the synthesis of vitamins, the digestive process and the [8] immune response.

In general, it is admitted that, among the almost 5,000 species of bacteria of the colonic flora, more than 90% are grouped into two psychrophiles: *Firmicutes* (Gram-positive) and *Bacteroidetes* (Gram-negative) [9]. Although discrete variations of these microorganisms are expected among humans, recent studies have demonstrated that certain alterations in the composition of the intestinal microbiota would be directly related to the development of pathologies such as cardiovascular diseases, obesity, insulin resistance, neurological disorders, type 1 diabetes mellitus and inflammatory bowel disease.

Thus, the enteric microbiome seems to have a relevant role not only in the genesis of DM2, but also as a possible therapeutic target in the treatment of the disease.

Objective of the Study

The primary objective of the present study was to analyze the association between intestinal microbiota and DM2. The secondary objectives consisted in determining the involvement of intestinal microbiota in the development of DM2, to support changes in the composition of the flora related to this pathology and to verify the possibility of using microbiota modulation as therapeutic tool.

Methods

To accomplish this work, a systematic review was carried out from scientific articles listed through databases such as PubMed, Scientific Electronic Library Online (Scielo) and Google scholar. The keywords "microbiota" and "diabetes mellitus, type 2" and the corresponding in Portuguese "type 2 diabetes mellitus" were used for the search. Of the 361 articles located, 327 were discarded due to the date of production, disagreement with the theme or absence of relevant data. In this way, 34 scientific researches were used, published in the period between 1992 and 2018.

We also used guidelines and Atlas recommended by the largest scientific authorities in the themes, including the Brazilian Diabetes Society (SBD) and the International Diabetes Federation (International Diabetes Federation - IDF).

Results and Discussion

The frank increase in the number of cases of type 2 diabetes mellitus, as well as the worrying association between this pathology and other health problems, such as cardiovascular, renal and neurological diseases, have generated enormous interest in the discoveries of possible modifying factors of the disease. Recently, the composition of intestinal microbiota has been suggested as one of the possible contributors to the genesis of DM2, and its modulation is an important focus of study in the Endocrinological area.

The Intestinal Microbiota

The gastrointestinal tract (GIT) of an adult has approximately 300 m^2 of exposed surface, consisting of several organs that have as primary function the absorption of nutrients from the diet, in order to generate energy substrate for the body. This system is continually subjected to pyocyanin aggressions, necessitating defense mechanisms that include mucus production, stomach pH, protective immune cells and abundant microbial colonization [10].

The microorganisms colonizers of the GIT are collectively called intestinal microbiota and establish a relationship of commensalism with the human being, the large intestine being the place of greatest occupation [8]. The gastrointestinal tract, sterile at birth, is cumulatively populated from breastfeeding. The composition of the microbiota in childhood, predominantly formed by *Bifidobacteria* and *Enterobacteria*, slowly changes to the most complex pattern observed in adults [9].

Although the constituents of the intestinal microbiota have not been fully elucidated, it is believed that it is composed of viruses, fungi, Archaea and, mainly, bacteria's [11]. Studies using phylogenetic microarrangements based on the sequence that codifies the RNA of the lower ribosome subunit (SSU rRNA), showed a predominance of the bacteria belonging to the Phyto *Firmicutes* and *Actinobacteria* (Gram-positives) and *Bacteroidetes* (Gram-Negative) [10].

Thus, although aerobic (such as *Pseudomonas* spp.) and facultative anaerobes (e.g. *E. coli* and *Proteus* spp.) are found in intestinal colonization, about 96 to 99% of microorganisms are strict anaerobic, including *Clostridium* genera, *Bifidobacterium, Fusobacterium* and *Bacteroides* [8].

However, the composition of the intestinal microbiota suffers large internal and external interferences, varying according to factors such as age, diet, lifestyle, body mass index, use of antibiotics, gender, pathologies and hygiene [8,11]. It has been demonstrated, for example, that the amount of *Bacteroides* and *Bifidobacteria* is reduced in older individuals, as well as the amylolytic capacity and production of short-chain fatty acids. On the other hand, there is an increase in facultative anaerobic, *Fusobacterium*, *Clostridium, Eubacteria* and proteolytic activity in this age range [12].

Recently, a study conducted by UNIFESP [13] evaluated the intestinal flora of low-income children living in the region without basic sanitation, in order to analyze the influence of environmental exposure in the microbiome constitution. It was revealed that 61% of the individuals had bacterial overgrowth in the small intestine, with increased *Salmonella* and reduction of *Eubacteria* and *Firmicutes*. This group also obtained lower mean height and decrease in serum hemoglobin values.

The increase in weight is also related to modifications of the microbiota. Researches have shown an increase in the population of *Firmicutes* concomitant to the reduction of *Bacteroidetes* in the intestinal flora of obese individuals. The hypocaloric diet institution seems to help normalize this pattern: apparently, the type of restriction (of carbohydrates or lipids) does not matter, being the change in the amount of microorganisms correlated to the percentage of weight loss reached [14].

In addition to the important function of immune response to food pathogens that reach the gastrointestinal tract, microflora has essential participation in the digestion of diet components. Many of the metabolites derived from their participation in this process seem to have bioactivity, being found in the systemic circulation, with possible activity in the neuro-humoral communication established between the intestine and organs such as liver and brain [15].

Among the substances metabolized by the microbiota are endogenous products such as bile salts, macromolecules of the mucosa (mucin, for example), dietary residues and even xenobiotics. Dietary substrates include amino acids, carbohydrates and some lipids, such as poly-unsaturated fatty acids, and phytochemicals.

Short-chain fatty acids (SCFA) are derived from complex carbohydrates, whose use by the organism is dependent on the bacteria fermentation [8]. Generally speaking, the most commonly found are acetate, propionate and butyrate. In addition to constituting an important source of energy for colonic epithelial cells, the SCFA have the ability to bind to G-protein-coupled receptors, triggering processes of production of YY peptide (which has satiogenic effect) and GLP-1 (Glucagon Like Peptide-1), which stimulates insulin secretion.

Some of the G-protein-coupled receptors are also found in immune cells, such as neutrophils, highlighting the GPR43. Thus, the SCFA seem to be related to the activation of chemokines and cytokines, modulating the systemic immune response, especially the unspecific [15].

The aromatic amino acids, such as phenylalanine and tyrosine, whose main metabolization seems to be performed by the bacteria of the intestinal flora, likewise have an important systemic effect. In addition to the immune articulation function, its metabolites are apparently linked to cerebral neurotransmission. Recent studies comparing mice with and without intestinal colonization have shown that germ-free animals have reduced levels of plasma and local serotonin. Platelet function and gastrointestinal motility were decreased, as well as other organic activities [16].

Similarly, bile acids are metabolized by the intestinal microflora, with an indispensable role in the host's physiology. The formation of primary bile acids occurs in the liver, resulting mainly in colate and chenodeoxycholate. These substances, after conjugation, are secreted in the intestine, with a facilitating action in the absorption of lipids. Although most (about 95%) of the primary bile acids is absorbed in the ileum and between the hepatic circulation, the remainder suffers action of the microorganisms, with hydropyrrolation that generates the secondary bile acids (lithocholic and Deoxycholic) [15].

While primary bile acids bind to the FXR receptors (Farnesoid X receptor), the secondary ones are coupled to the TGR5 (G protein-coupled receptor), with protective effects, including resistance to hepatic steatosis and decreased weight gain. There also appears to be stimulus to the secretion of GLP-1 and therefore, Antidiabetogenic activity [8].

Countless other products of metabolization performed by colonic microorganisms have effects on organic homeostasis. It has been shown that choline, for example, can be formed by certain bacteria, which express the cutC gene. At increased levels, this substance is related to non-alcoholic fatty liver disease, to increased cardiovascular risk and even to cancer of colon [15].

Microbiota and DM2

Although the intestinal microbiota is recognized as a structure of great value for the functioning of the digestive process, the questions about the extent of its influence in the systemic activities are recent. One of the first major studies associating these microorganisms with metabolic reactions was performed in 2004. By submitting mice previously free from bacterial populations to colonization with germs taken from other animals bred with normal intestinal flora, Backhed [17] showed an increase of almost 60% in the percentages of body fat stock and Insulin resistance.

Subsequently, many other researches were carried out with the same objective. In general, the authors seem to agree that a process of dysbiosis, that is, imbalance between the components of the microbiome, would be related to increased risk of DM2. The data, however, is conflicting. A study in mice showed increased *Lactobacillus* spp., reduction of *Bacteroidales* and *Lachnospiraceae* and appearance of the genera *Tricoated* and SMB53 in obese and diabetic animals [18].

On the other hand, many of the sources could atone that, among other alterations, the microbiota of patients with DM2 and obesity has a primordial alteration in the two main commensal psychrophiles: While Firmicutes would be elevated in these individuals, the Bacteroidetes would be diminished by [19,20].

Unfortunately, the two main studies carried out on this topic, with metagenomic researches conducted in China and the Swedish [22], were not able to confirm the importance of the alteration in the *Bacteroidetes/Firmicutes* ratio. Both showed reduction in the butyrate-producing bacteria, notably *Roseburia* and *Faecalibacterium prausnitzii*. These analyses, however, have been criticized, in view of the difficult access to information of individuals, such as medications used, comorbidities and acute infectious pathologies.

In Denmark, Le Chatelier [23] determined an increase in bacteria belonging to the phylum *Proteobacteria*, including *Escherichia coli*. More recently, Larsen [24], comparing adults with and without DM2, found a significant decrease in the proportions of the phylum *Firmicutes* and the *Clostridia* class in the affected individuals, contradicting several of the previous researches. A positive correlation was also established between the *Bacteroidetes/Firmicutes* ratio and the plasma glucose concentration.

In 2016, Egshatyan [25] defined the genus *Blautia* as the most found in DM2 patients. In addition, it was described that patients with DM2 had higher amounts of this microorganism than individuals with pre-diabetes, whose quantities of *Blautia*, in turn, were higher than those of patients with normal tolerance to glucose.

Despite the divergences found regarding the composition of the microbiota in individuals with and without DM2, many of the sources seem to agree with the main means by which it is modified, establishing dysbiosis. As already mentioned, the components of the flora are influenced by many factors, including age, physical exercise, genetics, comorbidities and use of certain medications, especially antibiotics. It is accepted, however, that the diet is the main precipitant factor of the alterations specifically related to the DM [9,25,27].

Changes in food content seem to result in rapid changes in the composition and functions of the microflora. Thus, the intestinal microbiota would be codependent of the diet and, largely, modulated by long-term consumption. It is postulated that a diet rich in fat would alter this environment, culminating in increased intestinal permeability and susceptibility to microbial antigens [7,9].

Feeding with high lipid intake is related to increased insulin resistance and the occurrence of endotoxemia. This type of feeding increases beta-oxidation in the liver and adipose tissue, with production of reactive oxygen species that seem to reduce the production of mucus in the intestinal epithelium. With the weakening of the mucosal protection barrier, the bacterial translocation is facilitated, a process that is also favored by the elevation of Malondialdehyde, a marker of oxidative stress resulting from the breakdown of lipids that damages the cells epithelial intestinalis [9].

In addition, it is believed that the fat-rich diet modulates the components of the microbiota, resulting in an increase in the levels of lipopolysaccharide (LPS's) due to bacterial translocation and the uptake of these particles coupled to the chylomicrons secreted by Enterocytes. LPS's are constituent molecules of the outer layer of Gram-negative bacteria, whose role in the induction of endotoxemia, stimulating the secretion of pro-inflammatory cytokines, is well known [7].

Thus, the diet with high lipid intake would be responsible for the modification in the components of the microbiota and by the increase of intestinal bacterial translocation, culminating in a systemic inflammatory process. This cascade is associated with changes in glucose metabolism and energy consumption, both of which are proven to be influenced by intestinal microflora.

The butyrate-producing bacteria, reduced in the aforementioned metagenomic studies, are mostly of the phylum *Firmicutes* and Gram-positive. They compete with Gram-negative bacteria, maintaining the equilibrium of the intestinal microbiota and preventing the reproduction of pathogenic germs. Although the genus Blautia is also part of this phylum, it is not considered the producer of Butyrate. It is believed, however, that these microorganisms are potential activators of the cytokines TNF alfa (tumor necrosis factor alpha), with powers regulating the amazing [25] immune cascade.

Thus, although many others are considered, there are three main mechanisms that relate dysbiosis to glucose metabolism: the elevation of LPS in the systemic circulation; The production of short-chain fatty acids; and metabolization of bile acids.

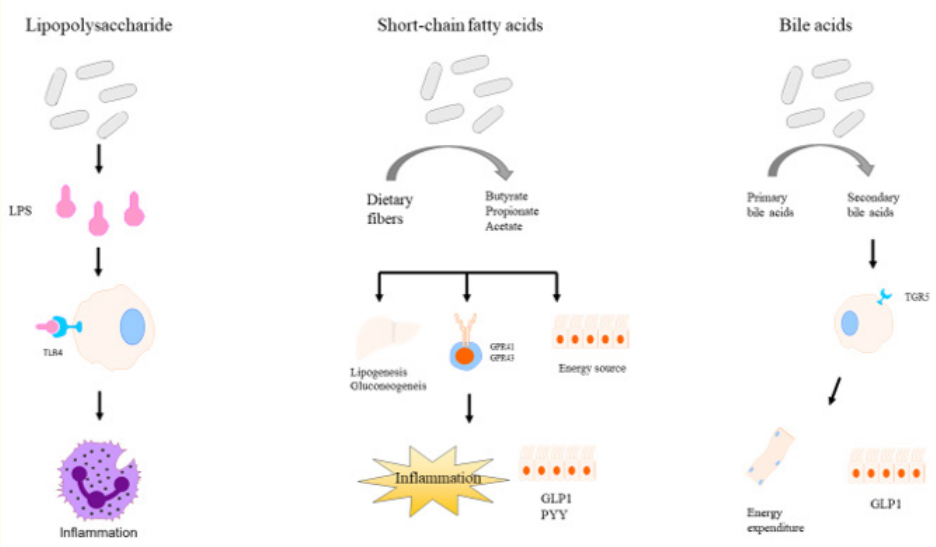

Figure 1: *Microbiota and the host metabolism.*

Adapted from Allin KH. Mechanisms in endocrinology: Gut microbiota in patients with type 2 diabetes mellitus [7].

The increase in circulating LPS is related to the greater activation of the host immune system through Toll-like receptors, especially the TLR4/CD14 complex, culminating in pro-inflammatory signaling [7]. This activation raises the amount of nitric oxide-induced synthase (iNOS), and the nitric oxide produced reacts with cysteine residues, forming nitrosothiol. This substance prevents the transduction of insulin signal through phosphorylation of the substrate of insulin receptor 1 (IRS-1) in serine and therefore generates resistance to the action of the hormone in liver, muscle and fat cells. Similarly, other insulin signaling pathways are proven to be affected by the inflammatory process, including that of NF-κB [9].

On the other hand, the microbiota produces short-chain fatty acids from the complex polysaccharides of the diet. The SCFA, mainly butyrate, bind to G-protein-coupled receptors, such as GPR41 and GPR43, inducing the secretion of GLP-1 (*Glucagon-like peptide-1*, an incretin) and PYY (peptide YY, with anorexigenic effect) by the L cells of the colon, resulting in improved insulin secretion. The SCFA also seem to suppress inflammation by connecting to GPR43 receptors in leukocytes, in addition to increasing hepatic gluconeogenesis and glucose utilization by enterocytes [7].

The transformation of primary bile acids into secondary by intestinal bacteria is also related to glycemic metabolism. These substances bind to the TGR5 receptors, activating the secretion of GLP-1 and, therefore, a signaling pathway that protects against obesity and resistance to insulin [7,8].

Thus, it is clear that intestinal microbiota can interfere in different ways with glucose metabolism and the use of insulin. While chronic systemic inflammation, of low intensity, determines resistance to hormonal action, other metabolites resulting from bacterial activity may determine improvement in the use of glucose and insulin profile.

Therapeutic possibility

In view of the functions and influence of the intestinal microbiota on the carbohydrate metabolism, it is great interest in the use of strategies for the modulation of the same, with possible improvement of the glycemic profile of diabetic patients or with high risk for the development of the pathology.

Probiotics are a group of living microorganisms that, if administered optimally, can cause benefits to the health of the host. The prebiotics, on the other hand, are mostly non-digestible oligosaccharides fermented by the intestinal flora, with the function of stimulating the growth and activity of bacteria commensals [9,26]. In conjunction with antibiotic drugs, these substances could play an important role in microbiota modulation.

Studies using prebiotics, especially fructans, suggest that the modulation of intestinal microbiota with these agents could decrease food intake and gain of fat mass and body weight. The plasma levels of PYY after feeding were elevated, while the values of ghrelin, an orexigenic substance produced by stomach cells, were reduced [27]. Moreover, the use of prebiotics for two weeks, with 16 grams per day, increased the rates of GLP-1, PYY and gastric inhibitor peptide (GIP), with improvement of the glycemic metabolization standard [28]. It is assumed that, by favoring the maintenance of the commensal microorganisms, especially *Bifidobacterium* spp., the prebiotics hinder dysbiosis and thus the inflammatory and metabolic alterations discussed [29].

Studies in mice treated with prebiotics have shown that the increase in GLP-1 production is related to the benefit in insulin response and glycemic, satiogenic effect and decreased fat mass. Moreover, the high secretion of GLP-2 (peptide similar to Glucagon-2, Co-secreted with GLP-1 by L cells) is associated with the fall in the LPS and in the circulating pro-inflammatory cytokines, reducing the systemic inflammatory response [30].

Commonly composed of *Bifidobacteria* and *Lactobacilli,* probiotics exert their beneficial effects when competing with pathogenic bacteria, increasing the integrity of the mucosal barrier and the responsiveness immune [9,26]. With the use of *Lactobacillus gasseri* in obese patients, Kadooka [31] verified a reduction in the percentage of visceral fat, body weight and abdominal circumference.

The administration of probiotics was related to several beneficial effects: reduction of the activity of the protein kinase C delta (PKC-δ), which promotes dispersion of the adherent joints, increasing the intestinal permeability; Quantitative elevation of Paneth cells, responsible for the secretion of antimicrobial substances, resulting in improvement of the barrier against pathogens; Reduction of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and inhibitor of plasminogen activator (PAI-1) in the central adipose tissue; Increased activity of antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase and catalase and decreased glycemia, improved glucose tolerance and reduced insulin resistance [9].

The incretin mimetic drugs, such as exenatide (GLP-1 receptor agonist), liraglutide (GLP-1 analogue) and lixisenatide (GLP-1 receptor agonist), are related to the stimulation of insulin secretion, reduction in glucagon production and decreased Gastric emptying, resulting in a decrease in food intake and favoring satiety. Unfortunately, however, these medications commonly present, after a certain time of use, a decrease in the pharmacological response, which seems to be related to a certain resistance to GLP-1 [32]. Recently, Grasset [33] determined that intestinal microbiota is the key for the sensitivity to GLP-1 to remain, which can contribute to the development of new drugs and therapeutic alternatives for DM2. In addition to the importance of the neuro-intestinal axis, alteration in the production of nitric oxide by enteric neurons and possible alteration of the immune system was demonstrated.

Cani [35], when using broad-spectrum antibiotics in mice, demonstrated changes in the microbiota that resulted in a decrease in endotoxemia and in the cecal content of LPS. These alterations correlated with the reduction in systemic inflammation, oxidative stress, weight gain and glucose intolerance.

Although the modulation of intestinal microbiota seems promising regarding the prevention and treatment of DM2, many other variables should be analyzed. As this theme is considered recent, a large part of the studies that refer to these interventions were based on animals or have small population sampling. Thus, it becomes necessary a greater contingent of research and clinical experiences before the indication of antibiotics, probiotics or prebiotics for this purpose.

Conclusion

This work aimed to gather the main and most recent contributions of the scientific environment to the proposed theme. Thus, we analyzed the information that associated the intestinal microbiota with DM2, both those who considered the microorganisms as factors involved in the pathogenesis of the disease, as well as those that proposed the bacterial modulation as a possible therapeutic maneuver. In the midst of such coverage of opinions and divergence of results, there is at least one consonant factor: the importance of intestinal microflora for the maintenance of homeostasis is true and still little known. Considering the enormous contingent population affected by DM2, it is clear the need for new scientific studies, especially in humans, that can make palpable and practical the association between intestinal dysbiosis and the emergence of resistance insulin.

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