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Review Article

# Gut Microbiota and Health: A Review

**Begoña Cerdá Martínez-Pujalte[1], Pilar Zafrilla[1] and Javier Marhuenda Hernández[1]***

*[1]Faculty of Health Sciences, Catholic University of San Antonio, Avenida de los Jerónimos s/n, Murcia, Spain*

***Corresponding Author**: Javier Marhuenda Hernández, Faculty of Health Sciences, Catholic University of San Antonio, Avenida de los Jerónimos s/n, Murcia, Spain.

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## Abstract

The intestinal microbiota has been studied and analyzed in recent years by the scientific community. Until few years ago, scientific literature focused on gastrointestinal pathology and prolonged antibiotic therapies. However, microbiota performs important functions in the organism, including certain metabolic processes and immunity. Regarding metabolism, intestinal microbiota participates in the synthesis of vitamins, and the production of short chain fatty acids or bile acids metabolism. Regarding immunity, the microbiota influences both in the development of immune protection and against pathogenic microorganisms. Nowadays, the best composition of the microbiota so that all functions could be carried out successfully has not been entirely defined yet. The balance or homeostasis between commensal and pathogenic populations heavily influences the maintenance of health. When this balance is broken, it is logical to think that health declines, rising to the appearance of different pathologies. The most studied pathologies include inflammatory bowel disease and some metabolic pathologies (diabetes, metabolic syndrome and obesity). However, there are many diseases in which an alteration has been found either at the composition of the microbiota or functionality. There are numerous investigations conducted in all parts of the world descripting what the composition of the microbiota should be for the maintenance and improvement of health, besides the way that microbiota affects health or influence the development of different diseases. This review aims to analyze the relationship between microbiota and health through scientific literature review.

***Keywords:*** *Microbiota; Diet; Health; Symbiosis*

## Introduction

The term Microbiota was established to design microbial communities colonizing a particular ecological niche. The intestinal microbiota is formed by the microorganisms (viruses, bacteria and fungi) living in the intestine, which are in symbiosis with the organism. The term microbiota has replaced the term flora, since it does not consider non-bacterial organisms (viruses and fungi), normal occupants of the intestine.

In the year 400 BC, Hippocrates said, "death is in the bowels" and "poor digestion is the root of all evil", recognizing the role of the intestine in human health. Recently, most of the research on the impact of intestinal bacteria has been focused on the gastrointestinal pathogens, including the way in which cause the disease. However, studies analyzing the effects of the commensal organisms in the intestine and its relationship with health and disease have been increased recently [1]. The structure and composition of the intestinal microflora reflects a natural selection in microorganisms and host organisms, promoting mutual cooperation and functional stability of this complex ecosystem. Moreover, although dominated by bacteria, they are also defined by Archaea and eukaryotes [2].

In human organisms, there are approximately 100 bacteria per cell. That fact allowed some authors to define the human organism as a symbiont super-organism of eukaryotic cells and prokaryotes [3]. The majority of bacteria are in the gastrointestinal system, where their

number and diversity increases from the stomach to the colon, forming the intestinal microbiota. The intestinal microbiota is a complex ecosystem that home between 300 and 500 bacterial species.

The first efforts to characterize gut microbiota were limited to microorganisms that could be grown *in vitro*, which reduced the number of verifiable bacteria. Recent advances in sequencing and computational biology technologies allow the use of metagenomics for the characterization of microbial communities. This has led to a large number of investigations of the Microbiome and metagenomics in the intestine. These advances have allowed studies to large-scale, such as metagenomics of the tract (MetaHIT) human Intestinal project, and the Project of the Human Microbiome (HMP) [4].

The microorganisms that form the intestinal microbiota produce various signaling molecules of hormonal nature that are released into the bloodstream and distal sites [5].

The composition of the intestinal microbiota begins to shape up from birth and continues during lactation. Traditionally, it has been considered that babies in the womb are sterile, and can therefore be immediately colonized by microbiota. There is evidence of the presence of bacteria in the amniotic fluid in the womb even in healthy infants, but taking into account both the number and the diversity of the microbes, the content is low. The first stool of the baby, meconium, are virus-free and they have a very low diversity of bacteria. Babies, from the moment of birth, are exposed to great diversity of microbes from different environments, and are quickly colonized by microbes that are first, whether from germs on the skin of the vagina or from his mother, according to the type of distribution. Vaginally-born babies present communities similar to those found in the vaginal microbiota of their mothers. Conversely, those born by caesarean section are features of the microbiota of the skin with domain of *Staphylococcus* and *Propionibacterium* spp. [6]. It seems that, during the first year of life, the way of birth also influences immune functions through the development of the intestinal microbiota. Thus, babies born by caesarean section have counts fewer bacterial cells and a greater number of antibody-secreting cells in fecal samples [7]. Babies who are born vaginally presented a more diverse microbiota, dominated by species of *Lactobacillus*, *Prevotella*, or *Sneathia*, differing from babies who are born by caesarean section, which is dominated by *Staphylococcus, Corynebacterium* and *Propionibacterium* [6].

In the childhood, microbiota is adopting progressively the composition of adulthood [8], of which 90% of the phylotypes belongs to the *Firmicutes* edges (60 - 80%), and *Bacteroidetes* (15 - 30%) [9,10], while the other edges are *Proteobacteria* and *Actinobacteria, Fusobacteria, Verrucomicrobia* [11].

During the first weeks of life, there is a reduction in the activity of the TLRs (Toll-Like Receptors), allowing the formation of a necessary and stable bacterial community in the intestine. As baby grows, with the introduction of solid food, the diversity of the microbiota increases, and the community is converging to that found in the adult. At the same time, the immune system learns to differentiate between bacteria, commensal and pathogenic bacteria. In adulthood, the composition of the microbiota is relatively stable, although it varies among different individuals, being mostly dominated by *Bacteroidetes* and *Firmicutes* [7].

As for his involvement in the metabolism, the enteric microflora metabolized substrates or non-digestible dietary waste, endogenous mucus and detritus cells. The diversity of genes in the microbial community (Microbiome) provides a variety of enzymes and biochemical pathways other than own resources of the host [12]. Special interest is the degradation of non-fermentable fiber, such as resistant starch, fatty acids of short chain (AGCC), mainly by bacteria of the phylum *Bacteroidetes*. These AGCC - acetic, propionic and butyric acid- have anti-inflammatory and immune signaling properties, becoming a source of energy for epithelial cells [13]. Also, known that enteric bacteria can produce nutrients and vitamins, such as folic acid and vitamin K, metabolize bile acids, and metabolize some drugs (such as sulfasalazine) within the intestinal lumen. However, the full metabolic potential of the Microbiome was not fully recognized until now. The potential contributions of the microbiota to the metabolic state of the host, in relation to health and disease, are at present still field of study. The application of genomics, metabolomics and Transcriptomics can reveal, in detail, the metabolic potential of a given organism [14].

The intestinal microbiota shows a fundamental role in the development of immunity. The intestinal mucosa also provides protection in the host defense against the constant presence of food antigens and microorganisms in the intestinal lumen. The protective effect of the microbiota includes "barrier effect", which is characterized due to the dealing with bacteria [7]. Own microbiota also prevents the overgrowth of opportunistic bacteria that are present in the intestine but presenting a restricted proliferation. The balance between the resident bacterial species gives stability to the whole of the microbial population. The barrier effect is due to the capacity that has certain bacteria antimicrobial substances (bacteriocins) that inhibit the growth of other bacteria, besides the competition between bacteria by the resources of the system [12].

It is widely demonstrated that microbiota is directly related to the immune system, both in terms of the development of lymphoid tissues associated with the intestine (GALTs), as to the polarization of the specific immune response in the prevention of the colonization of the bowel by pathogens. The intestinal immune responses that are induced by microorganism regulate the composition of the microbiota. It is therefore necessary to maintain the intestinal homeostasis, the interaction between the immune system of the host and the microbiota. When the relationship between the host and the microbiota is interrupted, the intestinal microbiota may contribute to the development of diseases [15]. If the bacteria interaction is not correct, the homeostasis between environmental antigenic burden and the response of the individual may fail. That fact can influence the development of pathologies of immune nature, which include autoimmunity, inflammatory bowel disease and atopy [16].

The intestinal microbiota provides an important source of stimulation of the immune system [17]. The development of the microbiota of the newborn is involved in the activation of both acquired as innate immune response. Continuous microbial stimulation is essential for the proper development of the intestinal immune system. In the immune system of the newborn tends to dominate T-helper 2 (Th2) phenotype, during postnatal maturation, there is a progressive inhibition of Th2 and an increase in the affinity for the Th1. When maintaining the predominance of Th2 phenotype is more likely to develop allergic disease. So, the change in lymphocyte subpopulation is carried out, is required the participation of the intestinal microbiota [18,19].

**Factors Affecting the Intestinal Microbiota**

The intestinal microbiota is influenced by various factors such as the genetics of the guest or the age [38], pregnancy [39] and also by some environmental factors such as diet [40], birth way, stress, and the intake of antibiotics [24]. In recent years, a new factor which modifies the intestinal microbiota has emerged: physical exercise.

While there are several factors that influence microbiota, seems to be that the microbiota has remained relatively constant during our life. While it is true that in old age, species diversity appears to be lower [41]. When studying the gut microbiota to levels below the cutting edge, a greater variation of the intestinal microbiota between individuals is observed. While now known that a number of benefits (protection against pathogens, modulation of the immune system etc.) give the intestinal microbiota of healthy individuals, it is not clear what the ideal formation of a "healthy microbiota", although it begins to know that the presence of certain species as *Faecalibacterium prausnitzii, Roseburia intestinalis* and *Bacteroides uniformis* are determinant to the formation of the "healthy microbiota" [42].

The modification of the microbiota as a tool to treat or prevent diseases is complicated due to both its complexity and variability intra and interpersonal. To date, it is unknown if there are other factors that influence the composition of the intestinal microbiota. Scientific investigations are designed to try to find what are the predominant factors that modify the microbiota, and the interrelations between the composition of the microbiota, its pool of genes (Microbiome), functions that express and physiological phenotypes or disease of the host [43].

**New Methodologies for the Analysis of the Microbiota**

The composition of the microbiota has been traditionally studied using methods of cultivation. These methods of cultivation are quite limited since only 10 to 50% of the intestinal microbiota can be cultured, so the vision of the whole of the intestinal microbiota that pro-

vides these methods is not appropriate [42]. In recent years, the understanding of the Microbiome, has increased significantly, due to the development of technologies that identify and quickly quantify the various agencies that make up the Human Microbiome, most of which are not arable with routine microbiological techniques. Currently there are sequencers for DNA of high performance that can quickly and cost-effectively sequence specific regions in the ribosoma16S or 18S genes, thus enabling identify bodies and their relative abundance of quickly and cheaply.

Among the new methods of mass DNA sequencing, there is one, "short-gun", sequences of DNA sequencing directly, allowing that other micro-organisms other than bacteria to be identified. This method can directly analyze the bacterial region which encodes a protein of acquired DNA and analyze the level of gender, with results based on sequencing depth and complexity of communities.

Given that the number of bodies contained in the samples is very high, has been necessary to the advancement of the bioinformatics simultaneously, so that they can come to understand the results and interpret the data obtained in the sequencing of DNA. In 2008, it launches the Human Microbiome Project, which aims to identify and characterize microorganisms that are associated with the healthy and diseased humans.

**Microbiota and Health**

The relationship between microbiota and health is becoming more evident.

A study in humans has been shown a strong interaction between diet, intestinal microbiota and health [20]. The intestinal microbiota is essential for the development of the immune system [21]. The two-way interaction of microbiota with the host immune system begins at birth, from which the intestinal microbiota modulates the development of the immune system and the immune system directly influences the composition of the microbiota [22,23].

Immune microbiota-system communication is mediated by many metabolic pathways in which a large number of molecules are involved. These signaling processes, besides the chemical interactions occuring between microorganisms and the host, lead to the activation of various organs such as bowel, liver, muscle and brain, forming various metabolic host-microorganism axes, which physiologically connects these organs [24].

The balance between the immune system and resident microbiota is essential for the maintenance of health, since the breakdown of this balance can trigger many diseases not only related to the gastrointestinal system, such as colitis, Crohn's disease, colon and gastric cancers [25-27]. However, the intestinal microbiota also affects other diseases such as obesity and metabolic syndrome [28], diabetes type I and type II [29,30] cancer of the prostate [27], allergy and atopic disease and autism [1].

The presence of certain strains of bacteria from the genera *Lactobacillus* and *Bifidobacterium* provides nutritional benefits, inhibition of pathogens and immunomodulation. The presence of these microorganisms in our intestinal microbiota increases the absorption of minerals and vitamins, improves lactose intolerance, has antidiabetic effects, reduces cholesterol levels, increases resistance to infections of the gastrointestinal tract, reduces the incidence of cancer of the colon [31,32] and exerts anti-inflammatory effects to local and systemic, improving the development of a protective and controlled immune system [33]. Besides the function exercised by the microbiota on development of the immune system, the microbiota has such metabolic capacity which has been referred to as the "forgotten organ" [2], since their metabolism is comparable to the liver [34]. Communities of bacteria that make up the microbiota present a great variety of metabolizing enzymes and biochemical routes different from those of the host [35,36]. In addition, the microbiota is also capable of influencing the production of hepatic triglycerides, systemic lipid metabolism, and carbohydrate metabolism and of low grade systemic inflammation associated with obesity, the resistance to insulin and metabolic syndrome [37]. In terms of proteins, some studies indicate that excessive fermentation of proteins in the colon by the microbiota could play a detrimental role in colon cancer and inflammatory bowel disease [11].

**Intestinal Microbiota and the Immune System**

Human organisms contains ten times more bacteria, fungi and other microorganisms to human cells, thus enabling us to provide for the existence of an interrelation between the physiology of the human host and these microorganisms, being stablished along thousands of years of evolution [44].

As mentioned above, there are approximately 100 bacteria by every cell in the human organism, so it can consider the human as a symbiont super-organism of eukaryotes and prokaryotes [3]. In the body the microorganisms are found mainly in the skin, mucous membranes (oral, nasal and genital) and in the digestive tract. All of them, the majority of bacteria in our body are in the gastrointestinal system. This population is which is called intestinal microbiota.

The human digestive tract is constantly in contact with a great antigenic burden in the form of commensal bacteria and food antigens. Therefore, as Maranduba., *et al*. the immune system must be able to discriminate against pathogens, which require an immune response, the normal microbiota or antigens from food, where it will not be necessary any immune response [44]. Interestingly, in the gastrointestinal tract of the host, the microbiota may have different effects at immunity level. Recent studies have suggested that commensal microbiota influences the intestinal immune response of the host. In this sense, Carilli., *et al*. highlighted that certain components of the intestinal microbiota are capable of inducing responses mediated by immunoglobulin A (IgA) and the development of Effector T, Th1 cells / Th17 and regulatory T (Treg) cells [45,46].

**Immunophysiology of the bowel**

The intestinal mucosa has, from the point of view of immune, unique characteristics, since it is permanent exposed to a large number of antigens of a very diverse nature. It is able to recognize the pathogenic substances harmless antigens (from food and commensal bacteria), generating an immune response appropriate for each type of substance.

Associated lymphoid tissues bowel (GALT) constitute the largest mass of lymphoid tissues of the body. The GALTs are immune structures in which Antigen can be collected and presented by the cells antigen-presenting and therefore, these structures have an important role in the functions of the cell leading to inflammation or tolerance. Therefore, the GALT are also important elements of the immunological capacity of the host. The intestinal immune response is regulated in different physiological compartments: lymphoid follicles in Peyer's patches and isolated, and distributed in the mucosa, epithelium and intestinal secretory sites [47]. From an anatomical point of view the GALT develops into two distinct compartments: GALT organized and diffuse GALT. The first is responsible for the intestinal immune response and is formed by the isolated lymphoid follicles, Peyer's patches and mesenteric lymph nodes. The second is the Effector of the immune response and is made up of scattered populations of lymphocytes in the epithelial lattice (intraepithelial lymphocytes, IEL) or in the intestinal lamina propria (lamina propria lymphocytes, LPL) [48].

The lamina propria is equipped with cells belonging to the lineage of cell B. Immunoglobulin A (IgA) is the most abundant in the intestinal mucosa, acting as a first defense against the entry of pathogens. In contrast to IgA in serum, secretory IgA in the intestine is present in dimeric forms or polymers. The secretory IgA is resistant to proteolysis intramural and does not activate the complement or inflammatory responses, which makes it ideal for the protection of [47] mucosal surfaces.

Secretory IgA antibodies in the gut are part of the immune system of the common mucosa, including respiratory and lachrymal, salivary and mammary glands. As a result, immune response initiated in the GALT can affect immune responses in other mucosal surfaces. Intraepithelial lymphocytes, T cells with the receptor gamma and delta, are normally other least explored mechanisms of mucosal immunity. These cells interact with skin cells and protect the mucosa killing infected cells and attract other immune cells to fight infection.

All components of the immune system are directly or indirectly regulated by the microbiota. For example, the microbiota and its metabolic by-products influence on dendritic cells and macrophages either directly or through the intervention of epithelial cells. This cellular activity can be regulated by epigenetic mechanisms. Similarly, regulatory T cells can be induced by metabolic products of the microbiota.

The intestinal microbiota may induce the maturation of B cells as well as changing its immunoglobulin isotype. A preference for IgE instead of IgA can lead to the activation of basophils and mast cells, which in turn is a modified microbiota. The dissonance between the intestinal microbiota and the immune system stimulates the development of the immune system of the intestinal mucosa, which is one of the mechanisms to prevent exogenous pathogenic intrusion [5].

It is known that the resident microbiota regulates the development of specific subsets of lymphocytes in the gut. T-cell auxiliary 17 ($T_H17$) are a specific lineage of cells CD4 + $T_H$ which are essential for the defense of the host and which play an important role in the development of autoimmune disease by the production of pro-inflammatory cytokines interleukin-17A (IL-17A), IL-17F and IL-22 (15). T cellsH17 preferentially accumulates in the gut; indicating that the development of T-cellsH17 may be regulated by intrinsic mechanisms of the intestine. In fact, Ivanov., *et al.* reported species of the genus *Clostridia* as promoters of the development of these cells in mice [15,50].

**Microbiota and resistance to pathogens**

Long been known that one of the functions of the microbiota is to prevent colonization of the bowel by pathogenic microorganisms. The intestinal microbiota has different mechanisms to avoid / resist colonization by the pathogen. Some of these mechanisms are direct and others are indirect.

The resident microorganisms directly inhibit colonization and/or proliferation of inbound enteric pathogens. The commensal organisms are more competitive than the pathogens for nutrients that they share, such as the carbohydrates, amino acids and organic acids. In addition, as indicated by Kamada and colleagues, commensal bacterial strains such as *Bacteroides thetaiotaomicron* catabolized mucin to produce fucose, which inhibits the expression of virulence factor by *Escherichia coli* pathogenic [15]. The enteric pathogens have developed strategies to overcome the competition of the commensal bacteria. According to Kamada and colleagues, some pathogens can directly kill competing guests through secretion system type VI (T6SS). The pathogens inducing inflammation, increase the renewal of skin cells, which will be providing nutrients that selectively promote the growth of pathogens. In addition, pathogens can locate epithelium associated niches that are devoid of commensal bacteria and so use close to epithelium nutrients that escape direct competition with resident microorganisms. Among the indirect mechanisms of competition between bacteria commensals and pathogens are the following: bacteria Diners catabolized polysaccharides to generate fatty acid of short chain (AGCC), such as acetate, which improves the function of intestinal epithelial cell barrier; In addition, the commensal microbiota promotes the production of mucus and the release of antimicrobial peptides such as the regeneration of protein 3γ derived from epithelial cells islet (REGIIIγ) to bound the colonization of pathogens and the proliferation. Immune cells innate, such as intestinal resident macrophages, neutrophils and some innate Group 3 (ILC3s) lymphoid cells, like the cells T helper 1 (Th1), TH17 cells and B-cells and IgA-producing plasma cells, are also activated by the microbiota to limit the colonization of pathogens [15].

**Microbiota and Disease**

Recently, it was found that qualitative changes in microbiota are involved in the pathogenesis of obesity. Law has postulated that a change in the composition of the microbiota to a population dominated by bacteria that are the most avid cooker hoods of absorbable nutrients, which would be then available for assimilation by the host, could play an important role in obesity [51].

The characterization of intestinal microbiota and its connections with the described host, have provided an initial image of what could be a good state of health from the microbial perspective. The study of diseases, however, has been traditionally dealt with from the point of view "a Microbe - a disease". Viruses, bacteria, and eukaryotes have been studied in conditions in which is believed to cause the disease. However, such, as the perspective "a gene - enzyme" it was not adequate to explain the complex phenotypes, is now beginning to consider the fact that humans are colonized with eukaryotes, bacteria, and viruses, and that some diseases could be the result of a dysbiosis, rather than being due to the presence of a single organism as cause of disease [7]. Understanding dysbiosis, both structural and functional

changes in the intestinal microbiota, lead to alterations in homeostasis of the host favoring the susceptibility to various diseases [52]. Examples of pathologies associated with microbial dysbiosis include autoimmune and allergic diseases, obesity, inflammatory disease of the bowel (IBD), and diabetes [7].

**Microbiota and inflammatory bowel disease**

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and disease Crohn (EC). It is defined as different diseases that share the common characteristic produce a chronic inflammation of the gastrointestinal tract, what occurs is an immune attack in the gastrointestinal tract [53]. The UC affects the colon, while the EC can affect any segment of the digestive tract. Inflammation of the intestinal mucosa causes ulceration, edema, bleeding, and fluid and electrolyte imbalance. The clinical manifestations of IBD depend on the involved area, although often patients present with bloody diarrhea and rectal tenesmus.

The treatment of IBD can be both pharmacological and surgical, usually, a combination of both [53].

Caricilli and collaborators reported that diversity and the composition of the microbiota, play a key role in the maintenance of intestinal homeostasis and partially explain the link between changes in intestinal microbiota and disorders related to the bowel [45]. Intestinal mononuclear phagocytes human show hiposensibilidad to the stimulation of microbial in steady-state conditions. However, in patients with IBD, intestinal mononuclear phagocytes respond strongly to microbial products and resident bacteria, which results in the production of large amounts of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-23 (IL-23). Therefore, abnormal activation of resident intestinal mononuclear phagocytes by commensal bacteria could facilitate the development or persistence of intestinal inflammation in IBD [15].

**Microorganisms in IBD**

Recent metagenomic studies have analyzed microbial compositions in IBD, suggesting that not only reduces the amount of commensal bacteria but also alter the quality and composition of the microbiota, reducing the enrichment of *Proteobacteria* and *Actinobacteria* and *Firmicutes* and *Bacteroidetes* [54]. These results agree with those obtained by Zhang., *et al.* [55]. Also, noted that there is an abnormal colonization of the ileac mucosa in IBD patients in comparison with healthy controls by *E. coli* invader (AIEC) and reduced ileac mucosal concentrations of *Faecalibacterium prausnitzii*, subsets of *Clostridium* IV. I comito and collaborators, have been recently identified a molecular subset of *Bacteroides fragilis*, called enterotoxigenic *B. fragilis* in abnormal concentrations in patients with active IBD [56].

**Microbiota and Diabetes mellitus**

Diabetes mellitus (DM) is a multifactorial disease, which involves genetic and environmental factors. The DM is characterized by a partial or absolute deficit of insulin, resulting in hyperglycemia [57].

Different studies have shown the relationship between the intestinal microbiota and the development of metabolic diseases, such as obesity and diabetes. It has been observed that these cases present changes in the proportions of *Bacteroidetes, Firmicutes* and *Proteobacteria* [58]. Diet is essential for the regulation of the intestinal microbiota. An excess of nutrients, as saturated and polyunsaturated fatty acids, or shortage of oligosaccharides and phytochemicals can modify the bacterial metabolic activity. High fat diets alter the intestinal microbiota, giving rise to increased intestinal permeability and susceptibility to antigens microbial, which correlates ultimately with the onset of resistance to insulin [57,58].

The scientific evidence suggests that a greater inflammatory stress is related to the molecular mechanisms that lead to insulin resistance and that the intestinal microbiota interacts with environmental factors and genetic factors likely to contribute to the development of diabetes [58]. This metabolic inflammation is characterized by excessive moderate in the production of cytokine, including interleukin (IL)- 6, IL-1, or tumor necrosis factor alpha (TNF-α), that damages cell insulin signals and contributes to the resistance to insulin and diabetes. Recently, two studies have shown that intestinal microbiota could contribute to the development of T2DM. Both studies showed that the microbiota of patients with DM2 were characterized by a reduction in the number of *Clostridial* bacteria (*Roseburia* and

*Faecalibacterium prausnitzii*), that produce Butyrate [58]. In this sense, another study found changes microbiota in patients with diabetes or insulin resistance compared with subjects with no alterations in the metabolism of carbohydrates [59].

The intestinal microbiota may play an important role in the pathogenesis of the DM2 to influence body weight, metabolism of bile acids, in the pro-inflammatory activity and insulin resistance, and in the modulation of intestinal hormones [60]. The exact mechanisms by which the microbiota affects the development of T2DM is today still do not know.

The immune system of the intestine has a key role in the development of autoimmune diabetes (DM1), and the factors that control the intestinal immune system are also regulators of Autoimmunity of the beta cells. According to Vaarala, the intestinal microbiota modulates the function of the intestinal immune system due to its effect on the innate immune system, intestinal epithelial cells and dendritic cells, and the immune system adaptive, in particular, intestinal T cells. Based on animal studies, changes in intestinal microbiota alter the development of autoimmune diabetes. This has been demonstrated with antibiotics that induce changes in the intestinal microbiota. Additionally, the microorganisms that colonize the intestine can modify the incidence of autoimmune diabetes in animal models. Although few studies have been conducted in humans, recent studies suggest that the abundance of *Bacteroides* and lack of fecal microbiota in butyrate-producing bacteria are associated with the beta cell Autoimmunity and type 1 diabetes. It is possible that the altered intestinal microbiota is associated with immunologic aberrations in DM1. Changes in intestinal microbiota could lead to alterations in the immune system of the intestine, as increased intestinal permeability, inflammation of the intestine, and impaired tolerance to food antigens, all these changes are observed in type 1 diabetes. The poor condition of the intestinal microbiota could explain why children who develop type 1 diabetes are prone to enterovirus infections, and do not develop tolerance to antigens of cow's milk. This suggests that the presence of an altered intestinal microbiota may lead to an increased risk of DM1 [61].

**Microbiota and Physical Exercise**

Physical exercise when performed in the doses recommended by who manages to improve physical condition and improving the quality of life. The exercise aims to be a useful tool in the prevention of diseases and the improvement of the prognosis of these. Diseases in which the exercise promotes a beneficial effect are numerous, we can highlight the cancer of the prostate and the ovary [62,63], cardiovascular diseases, diabetes [64,65] and stress-related disorders as anxiety and depression [66].

The mechanisms by which exercise has a beneficial effect on health are numerous: effects on the hypothalamic-pituitary - adrenal axis, the promotion of a State anti-inflammatory and increase of neuroplasticity [66]. One factor that could be modified by physical exercise and through which the welfare of health could be promoted is the intestinal microbiota. Although several years Backhed and collaborators suggested that there could be a muscle spindle microbiota [67], there are very few studies in the literature that have dealt with the modification of the intestinal microbiota by exercise. In a recent study, Choi and colleagues have shown changes in the composition of the microbiota in mice that did exercise to sedentary mice. Mice that did exercise had more wealth of the order *Lactobacillales*, presenting up to 24 times more bacteria *Enterococcus faecium* sedentary mice, and a very marked decrease (- 361 times) of the C11_K211 bacteria of the phylum Tenericutes [68]. These results coincide with those of Queipo-Ortuño and collaborators, which show that in rats undergoing exercise occurs an increase in the *Lactobacillus* group and *Blautia coccoides-Eubacterium rectale* [69]. In a study conducted with strains of rats (Wistar = normal, obese Zucker = SH = hypertensive) described an increase in bacterial diversity in exercised rats and more specifically an increase in genera *Lactobacillus* in obese rats subjected to physical exercise [70]. Interestingly, high significant inverse correlation between the concentrations of lactate in blood and the families of the genera *Clostridiaceae* and *Bacteroidaeae* and *forage*, was found while the genus *Oscillospira* was positively correlated with the levels of lactate [70]. However, the sample size in each experimental group in this study (n = 3) threatens the reliability of these results, therefore needed more studies confirming it. On the other hand, amazing data were not found when you compare to the microbiota of mice on a diet high in fat (with and without exercise) and on a normal diet (with and without exercise). Exercise not only offset microbiota changes induced by high-fat diet, if not causing major changes in the edges Firmicutes and Bacteroidetes Tenericutes in the same direction and order of magnitude, than those caused by diet rich in fats [71].

When the exercise was applied to healthy and diabetic mice were observed changes in *Bacteroides/Prevotella* spp., *Methanobrevibacter* spp., *Clostridium* in both groups, while an increase in the level of *Bifidobacterium* spp. was only observed in non-diabetic mice exercised, thus indicating the presence of diabetes repealed this effect [72]. These data may indicate that exercise-induced changes are influenced by the metabolic State of the people, and this factor should be taken into account in future studies. From a different approach, Hsu and collaborators reported that mice lacking microbiota, the monolithic mice with *Bacteroides fragilis* and normal mice had different exercise performance in vigorous exercise. The observed effect seemed to be mediated by the impact of the resident microbiota in the antioxidant status [73]. In the one human study carried out by Clarke et to the so far, where you compare the microbiota of athletes (rugby player) front healthy controls, it has been observed that the Group of athletes had a greater diversity of microbial species, 22 blades, 68 families and 113 genera, in contrast with 11 edges, 33 families and 65 genera of the control group. However, this study has an important limitation; it should have controlled the diet of both groups to have been able to determine what the effect of exercise on the diversity of the intestinal microbiota. Effect that cannot be determined, taking into account the considerable impact of diet on intestinal microbiota [74].

Although muscle-microbiota has proposed a shaft, the mechanism of communication of these two "bodies" is unknown [75] Studies in animals lacking intestinal microbiota ("germ-free"), suggest that the introduction of the intestinal microbiota decreases muscle activity. When animals were compared with conventional microbiota lacking animal microbiota was observed, that the latter, showed increased AMPK and CPT-1 activity in skeletal muscle and therefore a increase oxidation of fatty acids [67]. In addition, locomotive animals "germ-free" activity was greater than that of their controls with microbiota, although the cause of this increased activity of the locomotive is unknown, it could indicate a relationship between microbiota metabolic activity and behaviors that may contribute to the observed differences in adiposity among animals without microbiota and conventional [67]. Another factor that could unite metabolically muscle and the microbiota are metabolites produced by the microbiota from bile acids. These metabolites could reach the muscle to increase their energy expenditure through the activation of thyroid hormone, or protect the muscle of the deposition of fat by triggering nuclear receptor of farnesoide X [75]. The activation of the NF-κB factor in muscle through the Toll-like receptors (TLRs) would be another route by which muscle and microbiota could be in communication. Muscle presents receptor TLR4 and TLR5 which could be activated by lipopolysaccharide (LPS) or by flagellin, respectively, of bacteria present in the intestine [75].

Currently the causes that can cause these changes are unknown. One hypothesis is that exercise causes changes in the profile of bile acids (which are more or less antimicrobial effect) can exert a selective pressure on the microbial groups. In addition, the exercise could also result in an increase in the production of fatty acids of short-chain that would modify the pH, and therefore, would favor or interfere the growth of certain bacterial groups and ultimately, the alteration of the intestinal immune system. The increase in the production of IgA and Cytokines in the duodenum, such as IL-6 and TNF-α, as well as the decrease in the number of B and CD4 + T cells due to physical exercise [76], could cause secondary alterations in the interaction bacteria-huesped inducing selective pressure in certain groups of bacteria [68]. Another factor that could be causing changes in the composition of the microbiota due to exercise could be weight loss, which sometimes can be associated with physical exercise, since the diversity and composition of the microbiota in obese individuals differs from the microbiota of individuals non-obese [77].

**Microbiota and Metabolism of Drugs**

In recent years, the microbiota has starred in a leading role in the metabolism of drugs, to such an extent that the presence of one kind or another of microbiota can determine the degree of effectiveness of a drug [78]. The intestinal microbiota may change the metabolism of a drug in different ways, 1) by enzymes of the microbiota that degrade or activate the drug or 2) indirectly by inducing other enzymes involved in the mechanisms of detoxification of the drug or 3) through the production of microbial metabolites which are in competition with the drug by the enzymes that metabolize it [79]. In this way, the intestinal microbiota turns out to be a source of inter-individual variations in phenotypic metabolism, since the intestinal microbiota varies from a few individuals to others implying considerable differences in the metabolism of a drug [79]. Such is the influence that has the microbiota in the metabolism of drugs that researchers suggested that the study of the activity of the intestinal microbiota has to take part in the development of drugs and personalized health

treatments since also the intestinal microbiota could be deliberately manipulated to improve effectiveness and reduce possible reactions adverse drug [80].

**Metabolizing microbiota activity**

The intestinal microbiota is able to carry out a wide variety of biotransformations in drugs such as reactions of reduction, hydrolysis, decarboxylation, dehidroxilacion, dealkylation, dehalogenation, chemical, demethylation, fission of rings, acetylation, deacetilacion and deconjugacion of glucuronides and sulfates. Some examples of drugs metabolized by the microbiota are nitrazepam, clonazepam, misonidazole, omeprazole, sulfinpyrazone, sulindac, digoxin and zonisamide (reduction reaction), levodopa (dehidroxilacion), 5-aminosalicylic acid (acetylation), fenacetin (deacetilacion), indomethacin (deconjugacion) [79,81] etc. These biotransformations are directly linked to the type of intestinal microbiota so vary from one individual to another. The enzyme β-glucuronidase could release the glucuronide conjugate, rising to the aglycone or initial drug that could be absorbed by the intestinal enterocytes increasing the systemic bioavailability of the drug [82].

**Induction/repression of enzymes involved in the metabolism of drugs in other organs**

The intestine and liver (main body metabolizador of drugs and Xenobiotics) are connected through the so-called enterohepatic circulation. Nutrients and other metabolites are transported to the liver settling therefore a large number of molecules that circulate between the intestine and the liver. Björkholm and collaborators showed that colonization with microbiota of animals with absence of microbiota "germ-free" produced changes in the expression of 112 genes in the liver, the vast majority related to the metabolism of xenobiotics and endobiotics [83]. This could indicate that the metabolites produced by the microbiota are able to vary the expression of certain proteins or enzymes in the liver by altering the metabolism of drugs and other Xenobiotics [83].

A third mechanism by which the intestinal microbiota may affect the metabolism of a drug's direct competition of the metabolites of bacterial enzymes that metabolize drugs. Individuals who present a microbiota which produces high concentration of the bacterial metabolite p-cresol possibly submit fewer metabolites conjugated with sulphate that individuals who present a microbiota with low production of p-cresol [80,84].

On the other hand the continued drug treatment can also cause deleterious or beneficial changes in intestinal microbiota. So far there are very few studies in the literature that related changes in intestinal microbiota after administration of a drug with the exception of studies in which antibiotics are used and some studies which have identified changes that chemotherapy has on the microbiota [85,86]. However, there are numerous studies that indicate that compounds in the diet such as fibre, fat or polyphenols, whose chemical structure is similar to some drugs, have the ability to modulate the intestinal microbiota [87]. So, the diet could be a tool that would allow us to be able to modulate the profile of microbiota in order to be able to improve the effectiveness of a drug or reduce its toxicity [81].

## Conclusions

The intestinal microbiota is being considered as the "new body". Different studies corroborate the microbiota has important functions, both metabolic and immune. A composition between micro-organisms that make up the intestinal microbiota is essential for the maintenance of health.

When breaking the balance between microorganisms commensals and pathogens, dysbiosis, disease development is more likely. The direct involvement of the microbiota in the development and evolution of the immune system, suggests that it is essential to keep the balance between both types of microorganisms that health is not put at risk.

There are many diseases that have been linked to an alteration of the intestinal microbiota, some of intestinal origin and others whose relationship with the microbiota is harder to explain. Inflammatory bowel disease has been one of the most studied as to how it affects microbiota to the development of the disease. It was noted that not only the amount of commensal bacteria is reduced in IBD but that will also alter the quality and composition of the microbiota, with reduction of *Firmicutes* and *Bacteroidetes* and enrichment of *Proteobacteria*

and *Actinobacteria*. The implications of the microbiota with metabolic diseases are also being studied. In the DM1 as the DM2, both found that the microbiota is altered, that has to be studied in greater depth is what is the mechanism by which the microbiota is involved in the development of these pathologies.

It is widely demonstrated that exercise has a health promoting effect. However, that this beneficial effect can be linked in part to a modulation of intestinal microbiota has been investigated shortly. Most of the studies indicate that exercise modifies the intestinal microbiota, however is not all clear neither the population nor the way in which. The observed changes in the intestinal flora are caused by mechanisms that are quite unknown today.

The microbiota can determine the degree of effectiveness of a drug, since you can alter the metabolism of the same, through own enzymes that degrade or activate the drug or indirectly via the induction of other enzymes involved in the mechanisms of detoxification of the drug or the production of microbial metabolites that compete with the drug by the enzymes that metabolize it. The intestinal microbiota could be manipulated to improve effectiveness and reduce possible adverse reactions from the drugs.

Further research given the important role of microbiota in the organism, are necessary to get to know both the mechanism whereby the microbiota is involved in the development of different diseases such as what should be the optimal composition of the same to maintain the State of health. When these aspects are known, perhaps the treatment of some diseases may be more effective.

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