Abstract

In worldwide there is an alarming prevalence of obesity, diabetes mellitus, cardiovascular disease among others metabolic syndromes. These diseases have consequences on quality and expectancy of life of population. Significant efforts are devoted to the development of effective strategies for to prevent the development of specific diseases and conceptually achieve the human metabolic homeostasis. Growing evidence suggests that diet is the environmental central drivers that can affect the genetic information altering the metabolic function and consequently defining the health or disease state of an individual. Indeed, it has only been in recent years that gut microbiota has been associated with development of metabolic dysfunction, where their structure and composition can affect the host metabolism through multiple pathways. Recently, is well established that altering the dietary habits may influence the gut microbiota leading an imbalanced, a phenomenon known as dysbiosis. When there is the disruption of gut homeostasis is expected that certain microorganisms are linked to the pathogenesis being associated with multiple diseases. For this reason, extensive efforts have been carried out to overcome these obstacles and particular interest is involving in the pivotal role of diet on human health. In this context, the currently review aims to provide an overview and shed some light on fundamental characteristics of how diet act at the gut microbiota level in modulating some disorders including irritable bowel syndrome, obesity, type 2 diabetes mellitus, celiac disease among others disorders and consequently to draw up alternative strategies to use the diet as a therapeutic target.

INTRODUCTION

Currently there is intensive research to understand the effects of interactions between gut bacteria and their hosts and mainly how this relationship is affected by host diet: Naturally, this is a result of significant advances in science in order to contribute to health maintenance or can even prevent the development of specific diseases: In this regard, how can this relationship occur? Given the considerable mass of the 10 to 100 trillion microorganisms that inhabit the gastrointestinal tract (GI) make it a metabolically active “organ” that aids physiologically in the digestion of fibers, in the production of vitamins, minerals, and is responsible for the proper functioning of the Immune system: It is now evident that the composition of the gut microbiota is associated with the function of the intestinal barrier, energetic metabolism, nutritional status, genetic, diet and age [1].

The initial identification of bacteria such as Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria were fundamental to know the colonization of the GI: Not only the proportions between phyla, but also the microbial diversity is relevant in the pathophysiology of diseases: It should have an important role in the identification of bacterial species in different experimental models and thus, might contribute to certain of increase the knowledge about the metabolic effects of the microbiota [2,3]. Moreover, it is unclear, but it is believed that some disorders are related to the onset and aggravation of diseases, such as obesity, type 2 diabetes mellitus (DM 2), food allergy, celiac disease and inflammatory bowel disease, given the product of bacterial metabolism to component present in the diet, since the nutrient and its variations through temporal and spatial scales affect the gut microbiota [4]. Thus, the individualized dietary strategies were reformulated, respecting the genetic and social characteristics of the individual in the prevention and control of diseases.

DIET AS THERAPY

Nutrients are essential for human survival since the origin of life, highlighting breast milk as one of the richest and essential food for growth. Over time, the diet is introduced with a large number of variable mixture of nutrients and other components where the bioavailability, bioactivity and bioefficacy are important in dietary prescription. The dietary prescription should be individualized considering the gender, age, physical activity and genotypic aspects: It is important to note that there has been an increasing of knowledge about micro and macronutrients as important dietary signals that can influence the cellular functions at gene and protein expression level.

In this context, the nutritional research has shed some light about how nutrients act at the molecular level where the mechanisms of interaction between the genome and the nutrition research is called nutrigenomics [5]. The processes by which occurs the interaction between human genome and nutrients are still obscure. However, the nutrigenomics is considered a potential approach for discovery of genes that are important as dietary targets, elucidating nutrient signaling that might be linked to the state of health or reducing the risk of diseases [5-7].

Besides that, human health is closely linked to the compounds produced by the microorganisms of the gut microbiota, through the nutrients present in the diet. Conceptually, the gut microbiota and foods are the two most important environmental factors and consequently playing a pivotal role in epigenetic patterns [8].

In the last decade, the relationship between the gastrointestinal tract and the microbiome has been studied, providing evidence of an environment conducive to the nutrient and water absorbing process of the diet, as well as for microbial multiplication, being differentiated when the density and diversity [2]. Therefore, a diversity of the microbiome is influenced by different factors throughout the life cycles, specifically by the diet, fact observed in numerous population studies that demonstrate that the diversity of the microbial community has co-evolved with humans [2,9].

Recently, was demonstrated that gut microbial colonization is responsible to regulates global histone acetylation and methylation in tissues outside the gut in a diet-dependent manner [10]. The authors emphasize that this study was one of the first to show that gut bacteria could actively drive epigenetic pattern, rather than simply being associated with it.

More intriguing is that epigenetic changes associated with imbalance of diet and gut microbiota can be inherited and affect the health of future generations. An imbalance in the food or even in the gut microbiota may lead to late negative effects. It is known that genetic variants result in different nutritional responses. The bioactive molecules of alimentary origin or even of microorganism, can be divided into different groups when its functional aspect. The effects may be expressed in molecules within cells, in the intercellular matrix or even in organs or physiological systems. The ability of these molecules to turn on/off the gene is due to direct interaction of receptors with DNA (deoxyribonucleic acid), RNA (ribonucleic acid), chromatin, or kinases [8].

However, there is still a challenge to understand the interaction between genotype, microbiota and nutrition. Under these conditions, studies using well-established test have demonstrated the close relationship in the evaluation of the role of diet and its nutrients in the prevention and reduction of diseases and consequently maintain the dynamic balance of the organism [1,2,4].

Microbiota and gut dysbacteriosis

The densest microbial communities are those found in the gut, with estimates of 10 to 100 trillion microbes [1,11]. A recent study pointed out that there are 1057 species at gut microbiota, distributed in 92 species of Eukarya, 8 Archaea and 957 Bacteria [12]. In this context, the most richness and abundance species of the gut microbiota belong to the phyla Actinobacteria, Bacteroidetes Firmicutes and Proteobacteria in the other hand the rare diversity of the gut microbiota including Verrucomicrobia, Lentisphaerae, Synergistetes, Planctomycetes, Tenericutes and Deinococcus-Thermus [12].

There can be no doubt that the composition and structure of microbial communities can varies across host lifestyle, influenced by diet, different anatomical sites and it is very sensitive to host’s genome and their physiological condition [13]. Increasingly, studies on the understanding of the complex interactions between microbial and their hosts have been researched; these interactions can be conceptualized as symbiotic. In support of this concept, the micro organisms live in harmonious coexistence with the host. However, it is noted that the same microorganism may assume different roles depending on the abundance and quality of the nutrients in the diet. Understanding this proposition and the factors that determine the type of microbe-host symbiosis is useful in the prevention and effective treatment of diseases [14].

In fact, there are several benefits provided by the gut microbial to host. These benefits are characterized to participate in the physiology of the digestion of fiber-based diets, the production of vitamins and responsible for the proper functioning of the immune system. However, the influence of the microbial gut on regulating the host’s appetite is still poorly understood [15].

Besides the biochemical functions, the gut microbiota contributes significantly to the increase of the fecal volume, being one of the determinants for intestinal health, associated with a high fiber diet, consequently module the microbial composition of the gut lumen, participating in the process of dilution and elimination of toxins through the fecal volume, driving by increases of fermentative bacteria and by the presence of fibers that maintain the water [5].

Although, studies using well-established test have demonstrated that microorganisms present in the considered “healthy human” have different patterns when compared at higher-level with cohorts of patients with different pathologies, the close relationship between beneficial or harmful microorganisms have not clearly been defined on human host. Under these conditions, the dysbiosis is defined as a disturbance in the microbiome structure and abundance [16-18]. Nevertheless, when the homeostasis is disturbed it has been hypothesized that this process may lead specific diseases. It has long been believed that these disturbances are associated with
the variety of metabolites detectable in host circulation which are produced by gut microbiota [4,11].

For example, Bacteria such as *Lactobacillus*, *Bacteroides*, *Roseburia*, *Bifidobacterium*, *Fecalibacterium*, *Enterobacteria*, *Clostridial*, *Firmicutes* and *Coprococcus* participate in the synthesis of short chain fatty acids (SCFA) such as butyrate, propionate and acetate, providing energy to host epithelial cells. In this regard, the SCFA have been implicated in both disease promoting and therapeutic effects, implicated in human obesity, insulin resistance and DM 2, and colorectal cancer [19].

Members of the gut microbiota such as *Bacteroides*, *Bifidobacterium* and *Enterococcus* are able to synthesize vitamin K as well as most water soluble B vitamins such as biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin and thiamine. It is noteworthy that dietary vitamins are absorbed in the proximal tract of the small intestine, and the absorption of the microbial produced vitamins occurs in the colon [20] FIGURA. Thus, in the large intestine bacterial phytases degrade the phytic acid present in the grains, releasing minerals such as calcium, magnesium and phosphate, making them available to host cells [21]. Interesting, mucins are degraded by bacteria enzymes that currently assist bacteria to meet their energy needs and aid in the normal rotation of the mucus barrier that lines the intestine [22].

Since then, there is a strong interaction between the host immune system and the gut microbiota, with both producing compounds that influence each other. Some bacteria such as the butyrate-producer *Faecalibacterium prausnitzii* may produce anti-inflammatory compounds. Secondary components including bile acids are synthesis by *Lactobacillus*, *Bifidobacterium* and *Bacteroideses* that participate in the transport of lipids. Numerous lipids with biological activity are produced by bacteria, including lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria that can cause tissue inflammation. In addition, many enteropathogenic bacteria (strains of *E. coli*) can produce toxins or cause diabetes under the right conditions, but under “normal circumstances” other nonpathogenic commensal bacteria with similar metabolic activities overtake and eventually eliminate themselves bacteria like *Bifidobacterium* may also help to prevent pathogenic infection through the production of acetate [23,24].

**Gut microbiota and Food Allergy**

The food allergy (FA) has been increasing notably in the last 30 years [25], and it is viewed as a pathological condition [26], that worries public health officials [27]. Considering any condition, effect or reaction that is harmful to health the FA derives from a specific immune response from exposure to a particular type of food and lead to the development of gastrointestinal and target organ manifestations as well as regions of lesser impact [28].

There are numerous assumptions about the etiology of FA, these assumptions are linked to the significant increase in the number of cases, especially the genetic predisposition (TH2 cell); deficiency of filaggrin protein, essential for the maintenance of cutaneous integrity [26], and the diet factor [25]. In particular, studies suggest pathogenetic role for gut dysbacteriosis as other factor that must be considered in the in FA development [29]. Although there is evidence suggesting that dysbacteriosis are linked to allergy signs until now no specific bacterial taxa have been consistently associated with food allergy.

As reported above, the dietary patterns play an important role in modulating the composition of the gut microbiota, for this reason the gut microbiota associated with development of dietary patterns offers ample opportunities for intervention against food allergy [30,31]. It has previously been reported that dietary habits consisting mainly of vegetables and fruit in high levels was associated with less risk of FA development (diet and food allergy development during infancy).

In this context, there is no assertive treatment for FA. It is
suggested to avoid ingestion of the food allergen, since there is no cure, a fact that implies food elimination plans and emergency intervention, when necessary in order to reduce the probability of death [26,27,32].

Some studies mention one alternative form to minimize the exacerbated effects due to allergic processes, characterized by the complete withdrawal of the food allergen and its replacement in a gradual manner, in order to cause the immune system of the allergic individual to adjust slowly, to the point of diminishing the reaction [26]. This explains the determinant and significant role of the diet, already debated, in order to prevent the development of FA. One of the most relevant factors in the food context is breastfeeding, expressively addressed theme, moment of sensibilization to food allergens [25]. Another therapeutic and preventive factor of great relevance is the modulation of the microbiota through prebiotics and probiotics, with the objective of ensure intestinal reestablishment and homeostasis and consequently the development of immunological tolerance [33,34].

Indeed, when viewed as a whole, the diet habits associated with gut microbiota until is a complex relationship responsible for in maintaining the health of the host. The consequences of unbalance of this relationship, manly the nutrient deprivation suggests that it may also be an important factor in the pathogenesis of a variety of diseases

**Gut microbiota during nutrient deprivation**

In the last decades, there has been an increase in the supply of food variety, but with reduced nutritional quality. The human organism has undergone changes, in some cases requires more nutrients to deal with the unbalances generated by situations such as environment pollution, physical and emotional stress, major consume of food with antinutritional and industrialized factors [35]. Conceptually, the food restriction or the food deprivation involves an interaction between environmental and physiological signals related to diet change being able to cause homeostatic imbalance [36].

In fact, the nutritional status and the microbiota are intimately associated. It is now evident that the gut microbiota can vary between obese and lean individuals and also of accord occur with change of weight [37,38]. The short-term dietary interventions in healthy humans lead to significant and rapid changes in the composition of the gut microbiota. Increased incidence shows that the short-term restrictive diets, as carbohydrate-free diets associated with the consumption of fruit fibers and vegetables, have been shown to have a more paring effect on human microbiota [39].

Naturally, since the gut microbiota has become a source of speculation as an etiological factor in the pathogenesis of the disease, the fluctuations in diet can have significant effects for gut microbiota and the host. Furthermore, in cases of severe nutrients starvation or hyporexia, there is a need to alter the alimentary route. In more restrictive cases Total Parenteral Nutrition (TPN) may be the route of choice. In a prospective study of 30 patients with resting gut on TPN, n = 25 (83%) achieved baseline remission, but relapse was common. Despite conflicting evidence, TPN may improve symptoms, at least in the short term. It is observed that the intestinal pause can favor the microbiota in a therapeutic way in the Inflammatory Bowel Diseases, since fasting has been shown to have an effect on the gut microbiota, at least in mice [40].

Another important food route is exclusive enteral nutrition (EEN), especially the elemental formulas. The semi-elemental diets have been extensively studied for induction and maintenance of the remission phase, allowing greater flexibility of the diets in the inflammatory diseases of the intestine, aiding in the healing of the mucosa. However, the mechanisms of action are not well characterized, so there seems to be no great differences in the efficacy of EEN and the composition of the formula. In a meta-analysis the similar efficacy of formulas was studied when using formulas with varying degrees of protein hydrolysis. Formulas with a very low fat content and a concentration of middle-chain triglycerides may be somewhat more effective, but this needs to be confirmed in future studies. The modulation of the gut microbiota was proposed, although current data are scarce [40].

In another study, patients treated with EEN, when compared to a cohort of healthy patients on a regular oral diet, observed that the diversity of bacteria present was similar between the two groups. However, patients with inflammatory diseases using a more restrictive enteral diet than the oral route had a significant decrease in bacterial diversity that was maintained for several months after completion of therapy. In the healthy control, the intestinal bacterial composition remained stable. In this way the nutritional therapy highlights the importance of characterizing the interactions between the diet, the gut microbiota, and the mucosal immune system [40].

The dietary composition is essential to maximize the therapeutic efficacy of a particular disease. The technological advances that now allow a more comprehensive characterization of microbial communities, along with studies showing the impact of diet on the gut microbiota, provide a strong justification for further investigation [40].

**Role of diet in some diseases**

A very interesting hypothesis was showed that the diet patterns had guided the evolution of *Homo sapiens*. This hypothesis suggested that the gut microbiota between different primates are clustered more closely with other primates than nonprimates. These comparisons directly demonstrated that diet was the most important determinant in the human microbiota [41]. Consistent with these results, the high bacterial gene richness is associated with human health that have elevated consumption of vegetables, fruits and higher-fiber diets [42].

For this reason, at the moment, there can be no doubt that the interplay of gut microbiota could be a useful biomarker of short or long-term consumption of healthy or unhealthy diets. In support of this concept, over 25 diseases or syndromes have been linked to a diet with an altered gut microbiome where these diseases range from like inflammatory bowel diseases (IBD), obesity, type 2 diabetes mellitus, celiac disease as well as several other metabolic disorders [2,43].

Thus, scientific interest has been directed toward understanding the contributions of diet and gut microbiota in...
metabolic disease. In this context, dietary patterns interfere in the composition of the gut microbiota and have relevance in metabolic modulation and regulation of body adiposity [44].

The mechanisms involved in the microbiota relationship and metabolic diseases are explained by the suppression of Fasting Induced Adipose Factor (FIAF), inhibition of the activated 5’-monophosphate-adenosine protein kinase (AMP-Q) pathway, stimulation of the free fatty acid receptor receptors) and lipopolysaccharide (LPS) translocation. It contribute to deposition of fatty acids, increase the body adiposity, stimulate inflammatory cytokines and induce insulin resistance, deteriorating the cardiometabolic profile [3].

In support of this concept, it is recommended the association of probiotic and prebiotic functional foods (galactooligosacharides, xyl-o-oligosacharides, fructo-oligosacharides, inulin, phospho-oligosacharides, isomalto-oligosacharides, lactulose, pectin) that after fermentation promote changes in composition and / or activity of gut microbiota [45], as demonstrated the results of the present study indicate the benefits of fiber on the decrease of fasting glycemia, prandial and glycosylated hemoglobin in type 1 and DM 2 [46].

In the liver, adipose tissue and hypothalamus [47] formulated the hypothesis that bacterial lipopolysaccharides (LPS) derived from gram-negative bacteria residing in the gut microbiota act as a triggering factor, interconnecting the inflammation with a hyperlipidic diet and induction of type 2 diabetes mellitus and obesity. The authors suggests that this type of diet resulted in a significant modulation of the population of dominant bacteria of the gut microbiota. The reduction in the number of Bifidobacteria, from the group Eubacterium rectal-Clostridium coccoides and Bacteroides, favoring an increase in the ratio of gram-negative to gram-positive. This modulation of the gut microbiota was associated with a significant increase in fat mass, body weight gain and LPS, liver triglyceride accumulation, insulin resistance and diabetes mellitus [48].

Therefore, the use of probiotic symbiosis and prebiotics in food may be a preventive and therapeutic measure, as it favors the healthy composition and greater functionality of the gut microbiota, decreases circulating LPS, consequently, endotoxemia and chronic subclinical inflammation. Thus, it can be stated that dietary patterns interfere not only with the composition of the microbiota, but also with the pathophysiological mechanisms of chronic metabolic diseases, and that prebiotics and probiotics have an effect on the cardiometabolic risk profile [3].

**DISCUSSION & CONCLUSION**

It is now clear that food nutrients and bioactive compounds from the gut microbiota host’s play critical roles to health maintenance. There can be no doubt that diet can alter the gut microbiota due to effects on several factors and consequently to contribute for pathogenesis. A very interesting hypothesis consist in manipulating the gut microbiota, either by pre and probiotics or fecal microbial transplantation, seems an idea rational for the prevention and treatment of disease. More intriguing is the possibility of understanding of the human microbiome and their relationship to some variations in dietary preferences. Probably the biggest challenge is show how we can use the dietary interventions to open the possibility to promising therapeutic and diagnostic applications.

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**REFERENCES**