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Current Insight into the Role of Gut Microbiota in Mexican Childhood Obesity

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Abstract

Obesity is an epidemic multifactorial metabolic malady worldwide. This review insights the influence of gut microbiota in developing obesity in Mexican children. High prevalence of childhood obesity in Mexico draws the importance to look for a therapeutic target to control it. Gut microbial disturbances in obese children may have a role in their metabolism. Excessive Short chain fatty acids produced by obese gut microbiota, present an additional energy which causes an imbalance in energy regulation. Thus Manipulating gut microbiota via diverse diet, probiotics and prebiotics treatment can provide a novel approach to treat obesity and other metabolic disorders, including type 2 diabetes and Metabolic syndrome.

Keywords: Obesity; Firmicutes; Bacteroidetes; Short chain fatty acids; Mexican children

Introduction

Obesity is a multifactorial metabolic disease associated with a high risk to develop other chronic diseases and an alarming issue worldwide [1, 2]. Imbalance between excess caloric intake and too little physical activity are the major factors which contribute to obesity, in addition to genetic and environmental factors. WHO reported that the prevalence of obesity has doubled remarkably worldwide in the last three decades, more than 1.9 billion adults of 18 years and older, were overweight. Among them 600 million were obese [3]. Mexico was placed in eleventh among the most populated country in the world [4]. The rate of obesity in Mexico increased significantly during 2000-2006 period [5]. Mexican National health survey revealed that the population of obesity among school children and adolescents increased from 9.0% to 14.6% from the survey 1996 to 2012 which are higher than other Latin American countries such as 7.3% in Brazil and 3.4% in Colombia [6,7]. Obesity can affect physical, social and emotional well-being state of a child through clinical complications such as high cholesterol, high blood pressure, asthma, sleep disorders and Nonalcoholic fatty liver diseases. In a population-based study of 5 to 17 year-olds revealed that 70% of obese youth are more susceptible to cardiovascular disease [8]. Obesity is a process that usually starts in childhood or adolescence, which is a prominent risk factor to other chronic diseases, such as Type 2 Diabetes and coronary disorders [9].

In the recent years, "Gut Microbiota" emerged as a vital field of research interest due to its vast role in human health. Trillions of diverse microorganisms that reside inside the gastrointestinal tract are called as gut microbiota. They can regulate the human physiology directly or indirectly through its metabolites such as Short chain fatty acids (SCFAs), Neurotransmitters and vitamins. An imbalance in the diversity of gut may contribute to several metabolic disorders such as obesity, type 2 diabetes and metabolic syndrome. The aim of this review is to give an insight into the role of gut microbiota as a disposing factor to develop obesity in Mexican children.

Gut Microbiota

Gut harbors trillions of microorganisms which include bacteria, archaea, yeasts, protozoa, virus and phage. Gut microbiota dispersed in the GI tract as follows, stomach with 10^1–10^3 cfu/ml, and duodenum with 10^1–10^3 cfu/ml, ileum with 10^4–10^7cfu/ml and colon with 10^{11}–10^{12} cfu/ml [10]. Among them, bacteria are predominantly abundant in gut microbiota, while Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria are the most abundant phyla in Gut microbiota [11].

It was assumed that we are exposed to microorganisms at the time of birth and gradually start to be colonized developing a diverse gut microbiota. However, recently, several studies have shown the presence of diverse microbes in placenta, umbilical cord, amniotic fluid, and meconium [12,13]. The colonization of gut microbiota can be influenced by several factors such as mode of delivery, breast feeding, diet, antibiotics and life style [14]. The first colonizers are facultative anaerobes, such as *Escherichia coli* and *Streptococcus* spp., and obligate anaerobic species colonize as the oxygen levels are low in the gut. In general, the microbial diversity of a child at ~3 years of age stabilizes to adult-like

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microbiota as shown in a large study of three populations in different geographic locations [15].

Gut microbiota have tremendous potential to affect our physiology, both in health and in disease. They stimulate the maturation of immune system and assist the host by excluding pathogens. Many Studies have exposed the intestinal microbiota capability to manipulate host physiology to benefit both microbe and host [16]. The gut microbial communities and their metabolic activity are influenced by a several factors including the diet and health status of the host [17].

Since most of the gut microbes are not cultivable, culture independent techniques such as DGGE, RT-PCR and High throughput sequencing are the suitable tools to explore microbial diversity. DGGE is a effective but laborious and time taking technique. RT-PCR is effective but it is not appropriate for unexplored microorganisms. High throughput sequencing techniques on the other hand are currently lower cost and more effective to explore microbial diversity. 16S rDNA based sequencing of bacterial hypervariable regions or metagenomic sequencing is the immensely used methods in the field of microbiota. The 16S rDNA based technique helps to explore the diversity and metagenome is used to explore marker genes, metabolic route and enterotype patterns among different clinical conditions or experimental systems.

Role of Gut Microbiota

Gut microbiota conduct essential functions such as maintenance of gut, immune functions and digestion of nutrients by a symbiotic relationship with human host body [18]. Undigested carbohydrate fibers are fermented by gut microbiota and produces principal metabolites such as SCFA(acetic acid-65 %, propionic acid-25 % and butyric acid-15 %), vitamins, it degrades many dietary toxins and carcinogens, protects host from pathogens, maturation of immune system, Intestinal permeability, inflammation control and bile acid metabolism (Figure 1). Dysbiosis of gut microbiota, have been related with many diseases such as cancer, Rheumatoid arthritis including cardiovascular diseases, obesity, diabetes and metabolic syndrome. Role of gut microbiota also had been reported in cognitive disorders like Alzheimer and Parkinson's diseases liver or even brain diseases [19,20].

Gut microbial Metabolites

The gut microbiota can produce extremely diverse metabolites from anaerobic fermentation of exogenously undigested dietary fibers which reach the colon and endogenous compounds released from the microorganisms harbor in the host. These metabolites act as intermediators between the gut microbiota and the host to regulate many immunological functions and diseases control. SCFAs, TMAO (Trimethyl amine oxide), Polyphenols, Bile acids, Neurotransmitters such as serotonin, Dopamine, acetylcholine, Gamma amino butyric acid (GABA),B-vitamins, Polyamines are those well-known metabolites due to their impact on host physiology[21]. Among them, SCFAs play a vital role in host energy metabolism.

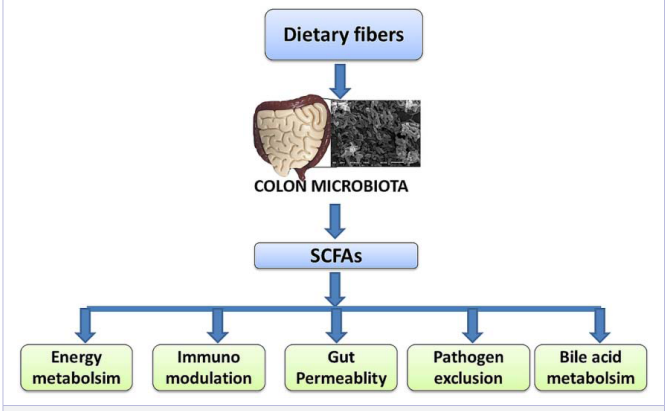

Figure 1: Role of Colon microbiota in human physiology.

Short Chain Fatty Acids (SCFA)

Soluble dietary fibers such as fructans, pectin, inulin and xylans and resistant starch can be actively saccharified by commensal microbiota in the distal colon of the host and produce biologically active SCFAs (acetate, propionate and butyrate). SCFAs are the main energy source (up to 70 %) for the intestinal epithelial cells [22]. Firmicutes and Bacteroidetes are the main contributors to produce SCFAs in gut microbiota. Among these bacteria, *Bacteroides*spp*., Faecalibacterium* spp*., Bifidobacterium* spp*., Clostridium* spp*., Eubacterium* spp*, Lactobacillus* spp. And *Ruminococcus* spp. has been reported as best producers [23].

Microbe-generated acetate has a number of physiological functions. Acetic acid, is a substrate for cholesterol synthesis [24], as well as a suppressor of appetite through a central hypothalamic mechanism [25].Propionic acid is a precursor for protein synthesis, gluconeogenesis, and liponeogenesis in the liver [26]. Acetate and propionate also induces adipogenicity through GPCR43 [27]. The colonic epithelium receives about 70 % of its energy from SCFAs, mainly from butyric acid [28]. Butyric acid is a Histone deacetylase inhibitor through which it regulates the gene expression and cell fate [29].

SCFAs are also involved in the improvement of cognition and behavior through the microbiota-gut-brain axis [30]. In neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases, there is a reported deficiency in glucose uptake, the main fuel source for astrocytes [31]. However, ketone bodies of SCFA origin such as β-hydroxy butyrate, acetoacetate, acetone and lactate can also function as substitute energy source in cognitive disorders. SCFAs moderate the inflammatory function by triggering the production of mediators like cytokines and Nitrogen Oxide (NO) by macrophages [32]. Among SCFA, butyrate inhibits de Histone Deacetylase (HDAC), and increases the availability of Histone acetyl Transferase (HAT) which increases histone acetylation. This inhibition has been reported that improves neuroprotection/regeneration in both in vitro and in vivo models of neurodegenerative diseases [33]. SCFAs may also influence innate immune cells in the brain and central nervous system.

Gut Microbiota and Host Metabolism

Gut microbiota provides an additional metabolic energy through undigested carbohydrate fibers. The Main metabolic products, SCFAs can be utilized for lipid or glucose *denovo* synthesis [34]. Alteration in the levels of SCFAs in obesity might be due to dysbiosis in the colon microbiota. So it is essential to explore the distal colon community members and SCFAs level to comprehend its role in development of obesity. This complex microbial system has the higher metabolic capacity and plays a vital role in regulating several processes in host intestine [18].

The basis that lead to the development of obesity, shows that in addition to the genetic component of the human genome; in many cases there is a clear influence of the human microbiome [35]. The microbiome is the full set of genes in the genomes of all microbes that live in the human body, and whose expression has influence on its systemic function [36]. Recent reports in mice model have shown that overweight and obesity are associated with a particular type of bacteria that inhabit the digestive tract; other studies in adult humans, have shown that variations in the relative abundance of two phyla Firmicutes and Bacteriodetes, are related to the condition of accumulation of body fat [37].

The short-chain fatty acids (SCFAs) have been used traditionally as a therapy for colitis and ulcerative colitis, due to their anti-inflammatory effect [38]. It is presumed that inhibition of the NFκB factor is involved in its mechanism of action; thus, these metabolites would be related with signal transduction pathways with influence in systemic inflammation state [39,40].

Gut Microbiota and Obesity

The gut microbiota involves in the fermentation of undigested polysaccharides to easily absorbable monosaccharides, and lipoprotein lipase activation on the villous epithelium, playing a role in nutrient acquisition and energy regulation by the host [41,42]. It has been suggested that gut microbiota contributes to obesity, by increasing energy harvesting from diet, and modulating through its metabolites, via hostlipid metabolic pathways and energy regulating homoeostasis [43]. To date, the reported main metabolic products of colon microbiota are acetic, propionic, and butyric acids. Alteration in the levels of SCFAs in obesity, might be associated to bacterial dysbiosis in the gut; making it essential to explore the diversity of bacterial communities and the SCFAs level to realize its role in the development of this disease (Figure 2).

It has been reported that difference in composition of gut microbiota with more abundant Firmicutes in obese than lean subjects which lead to the disruption in energy acquisition and regulation [44]. It has been demonstrated that overweight and obese adults from Netherlands have elevated fecal SCFA concentrations and Firmicutes abundance than their lean counterparts. It suggested that these obese individuals produce more colonic SCFA, indicating an increased microbial energy harvest [45]. Alteration in the levels of SCFAs in obesity might be due to dysbiosis in the colon microbiota.

In a study on obese Finnish children showed lower *Bifidobacterium* spp. and higher *Staphylococus aureus* abundances

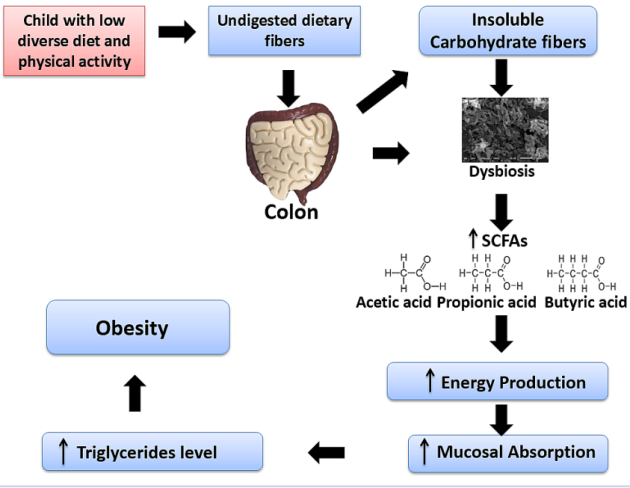

Figure 2: Influence of SCFAs in development of Obesity.

in obese children compared with normal weight children [46]. Another study on Obese children from Belgium revealed that obese children had a higher ratio of Firmicutes/Bacteroidetesas well as more abundant *Lactobacillus* spp. and *Staphylococcus* spp. which was positively correlated with inflammatory markers such as C-reactive protein and energy intake, respectively [47].

Only few literatures disclose the role of microbiota associated with obesity in Mexican children. In one important report, the fecal SCFA concentrations was lower in overweight and obese Mexican children with respect to normal children and was associated to an imbalance in the abundance of *Roseburia* spp., *Blautia* spp., *Coprococcus* spp., *Faecalibacterium* spp. and families like Lachnospiraceae which belongs to the phylum Firmicutes. The elevated triglycerides concentration in obese children might be the consequence of increased in mucosal absorption of SCFA [48]. This condition will enhance the development of metabolic disorder obesity along with lower physical activity. In has been also suggested a possible association of endothelial dysfunction with an alteration of gut microbiota in obese children [49]. Thus, it is considered that the gut microbiota plays an important role in weight regulation and may even be partly responsible for the development of obesity.

Conclusion

These collective evidences strongly propose that the gut microbiota play a significant role in regulating the energy balance and weight in children and may influence the development and progression of obesity in addition to lack of physical activity and other genetic factors. Manipulating gut microbiota through diverse diet, probiotics and prebiotics treatment can give a novel approach to treat obesity and other metabolic disorders, including type 2 diabetes and Metabolic syndrome.

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