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Does microbiota influence the risk of childhood obesity?
¿Influye la microbiota en el riesgo de obesidad infantil?

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ABSTRACT

Childhood obesity is associated to incremented risk of developing diseases such as diabetes, cardiovascular diseases, or cancer, later in life. Several factors affect infant weight gain such as genetics, maternal lifestyle, and other environmental factors. Perinatal period is considered to be the most important one to when defining metabolic programming of the future adult. Several previous researches have discussed the role that gut microbiota might play on obesity risk and its development between 3-5 years old. Again, perinatal period is crucial to define quantity and diversity of a healthy intestinal microbiota. Maternal diet/BMI, delivery mode, antibiotic exposure and breastfeeding are some of the processes that will determine a favorable gut microbiota. Functions of gut microbiota, mostly by producing short-chain fatty acids as metabolites, include regulation of metabolism and immune system of the host, which may be compromised in case of dysbiosis. This review pretends to evaluate the state of the art concerning infant obesity and the role of gut microbiota. Despite the large amount of scientific publications, there is still much work to do regarding the clarification of mechanisms and the possible therapy for childhood obesity.

Keywords: Obesity; Gastrointestinal Microbiome; Pediatric Obesity; Breast Feeding; Dysbiosis.

RESUMEN

La obesidad infantil se asocia con el incremento del riesgo de desarrollar futuras enfermedades como la diabetes, las enfermedades cardiovasculares o el cáncer. Varios factores afectan la ganancia de peso infantil, como la genética, el estilo de vida materno y otros factores ambientales. El período perinatal es considerado como el más importante a la hora de definir la programación metabólica del futuro adulto. Varias investigaciones previas han discutido el rol que podría tener la microbiota intestinal en el riesgo de obesidad y su desarrollo entre los 3 y 5 años. Una vez más, el período perinatal es crucial para definir la cantidad y la diversidad de una microbiota intestinal saludable. La dieta materna, el tipo de parto, la exposición a los antibióticos y la lactancia materna son algunos de los procesos que determinarán una microbiota intestinal favorable. Las funciones de la microbiota intestinal, principalmente mediante la producción de ácidos grasos de cadena corta como metabolitos, incluyen la regulación del metabolismo y el sistema inmunológico del huésped, que pueden estar comprometidos en caso de disbiosis. Esta revisión pretende evaluar el estado del arte en relación con la obesidad infantil y el papel de la microbiota intestinal. A pesar de la gran cantidad de publicaciones científicas, todavía hace falta aclarar los mecanismos y la posible terapia para la obesidad infantil.

Palabras clave: Obesidad; Microbioma Gastrointestinal; Obesidad Pediátrica; Lactancia Materna; Disbiosis.

INTRODUCTION

World Health Organization (WHO) has stated the following facts about obesity[1]:

- Obesity is defined as an abnormal or excessive fat accumulation that may impair health and results from an energy imbalance between calories consumed and calories expended;
- Overweight and obesity are linked to more deaths worldwide than underweight;
- Globally there are more people who are obese than underweight – this occurs in every region except parts of sub-Saharan Africa and Asia;
- In 2014, more than 1.9 billion adults, 18 years and older, were overweight and of these over 600 million were obese;
- In 2014, 41 million children under the age of 5 were overweight or obese.

Obesity is considered an epidemic disease escalating in all population groups in developed and developing countries. The prevalence of overweight and obesity combined has risen by 27.5% for adults and 47.1% for children between 1980 and 2013[2]. Some explanations for the epidemiological obesity where proposed including increases in energy intake, changes in the composition of diet, reduced physical activity, and changes in the gut microbiome[2]. Excessive weight gain in infancy is associated with persistence of high weight status and later obesity, resulting in an incremented risk to develop diseases such as diabetes, cardiovascular diseases, musculoskeletal disorders, cancer and mortality[1,3]. Obese children can also present breath difficulties, increased risk of fractures, hypertension, insulin resistance and psychological disorders[1]. Infant obesity and severe obesity has increased over the recent decades and despite this increase appears to slow down, the prevalence of child obesity is still too high worldwide[4].

Woo Baidal et al. concluded in their systematic review from prospective studies with scientific evidence, that the main factors affecting childhood obesity are higher maternal pre-pregnancy body mass index (BMI), prenatal tobacco exposure, maternal excess gestational weight gain, high infant birth weight, and accelerated infant weight gain. They also found that the critical period is from conception through 2nd years old[5].

With different degrees of evidence, there are some important issues that appear to determine the risk of obesity in childhood: genetics[6-8] and epigenetics[3,9]; in uterus environment and maternal health[4,10]; growth acceleration in the 1st six months[10,11]; metabolic programming of endocrine response[11-14]; breastfeeding and infant formulas[15-24]; introduction of solid food[25]; and intestinal microbiota[12]. Intestinal microbiota is defined early in life and recent studies suggested its relation to later obesity risk and other diseases. The intestinal microbiota influences energy balance producing short-chain fatty acids (SCFA) from polysaccharides digestion. Different bacteria have

diverse modes of influencing absorption and storage of energy and several factors define colonization in infants[12].

To prevent childhood obesity, it is imperative to work on these factors, particularly those who can be affected by maternal or caregiver behavior: maternal BMI, breastfeeding human milk (breast vs bottle), formula composition, feeding practices for introduction of solids, early nutritional education with impact on metabolism routes, taste preferences and food choices in the future[26]. The intestinal microbiota is a new insight that has emerged in recent investigations as a modulating factor of obesity. Knowing its possible role as a risk factor in childhood obesity is the main goal of this review.

MECHANISMS OF ACTION OF THE INTESTINAL MICROBIOTA

The impact of microbiota metabolism in human body has been discovered as more studies have been published linking intestinal microbiota and some developed pathologies, in germ-free mice and in humans. Alterations in microbiota populations are related to the development of inflammatory and metabolic diseases like inflammatory bowel disease, obesity, type 2 diabetes, atherosclerosis, allergy, and cancer[27,28].

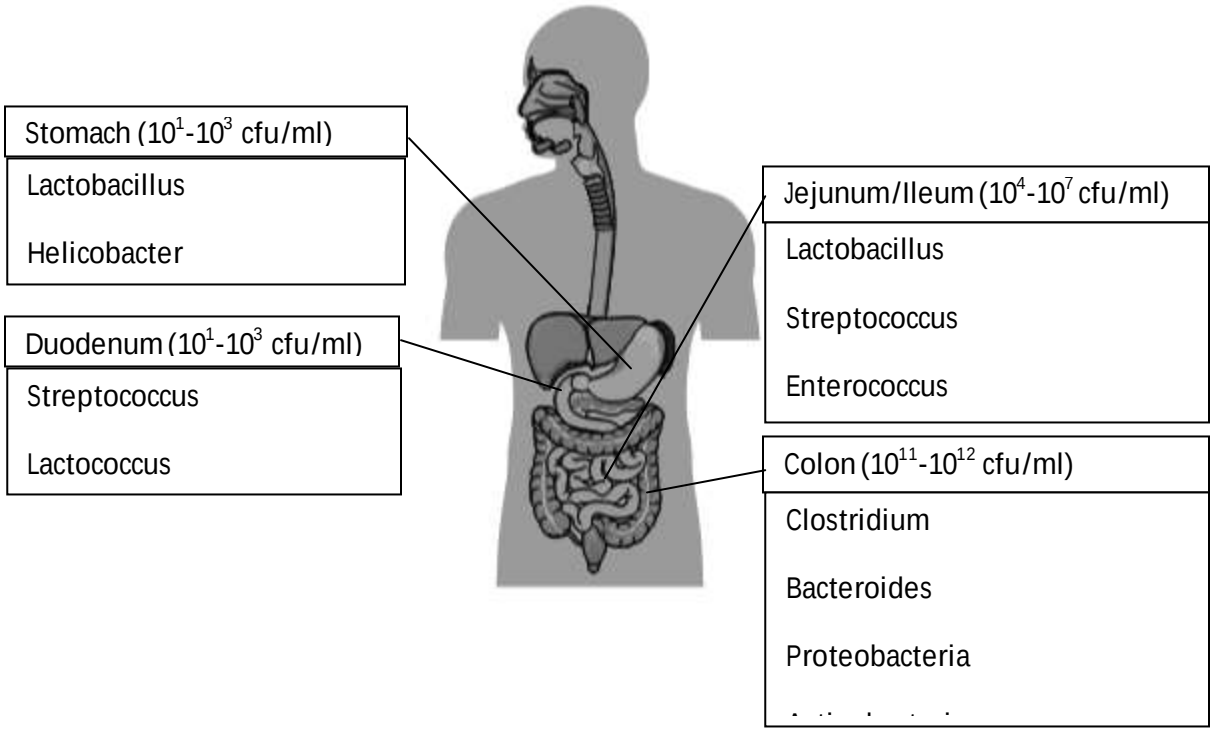
Gut microbiota ferment complex polysaccharides and residual proteins that cannot be digested by human enzymes to SCFA, branched-chain fatty acids, gases, and other metabolites. Acetate (C2), propionate (C3) and butyrate (C4) are the main products with impact in health. These compounds are energy source for colonic epithelium (butyrate) and peripheral tissues (acetate, propionate). The composition of microbiota and the diet carbohydrates determine the amount and proportion of SCFA produced[29]. SCFA play a direct role on epithelial gut cells providing energy and promoting cell proliferation and differentiation. SCFA deficiency originates an energy deficit state that activates autophagy with impact in the integrity of intestinal barrier[27]. SCFA receptors named G-protein coupled receptors (GPCR) are also present in peripheral tissues (white adipose tissue, skeletal muscle, and liver), acting as signaling molecules with impact in metabolism regulation (fatty acid oxidation, increasing leptin) and immune functions (reduction of pro-inflammatory cytokines and macrophage activation)[30,31].

Besides the production of SCFA, gut microbiota mediates other metabolism functions: bile acid conjugation to secondary bile acids acting as signaling molecules to regulate metabolism and immune cells[32]; vitamin (complex B and K), amino acids and lipid synthesis, digestion or absorption[27,33,34]; pathogens barrier[27]; immune function by gut associated lymphoid tissue (GALT) that represents about 70% of the total immune system[35]; neuroendocrine regulation by the gut-brain axis, where dysbalanced axis is associated to gastrointestinal diseases (chronic gut inflammations, pain, and metabolic disorders) as well as mood, behavior, stress disorders and satiety mechanism[36,37].

The intestinal microbiota is composed by numerous microorganisms mostly from Bacteria kingdom. About 90% belong to the phyla Firmicutes and Bacteroidetes and the most abundant genera are Bacteroides, Faecalibacterium and Bifidobacterium which proportions vary between individuals. At species level, there is a great variety which can originate a unique profile for each host[38].

Environmental variations influence intestinal microbiota composition such as pH, oxygen and nutrient availability. The bacterial concentration is higher in the lower portion of the gastrointestinal tract dominating the anaerobes (Figure 1).

Figure 1. Gut microbiota composition (Adapted from Gotteland[39] and Verdu et al.[40]).



The composition of gut microbiota is defined at birth and evolves until about 3 years old, then it remains constant during lifetime and a few factors can temporarily change it such as antibiotics and diet[39,41]. A human study found that in twins, the similarity of microbiota is within the same family members and not only in monozygotic twins. This fact indicates that environmental exposure has more impact than genotype in microbiota development[42]. Diet rich on non-digestible carbohydrates provide substrate to fermentation by gut bacteria. Limited amounts of fat and proteins are necessary to maintain a healthy gut metabolism. High fat and protein diets significantly reduced SCFA and alter intestinal bacteria composition[43,44]. The supplementation with prebiotics promote the growth of specific gut microbiota species and the use of probiotics has benefits in host health, but the impact on large-term gut microbiota remains to be proven[45].

OBESITY AND GUT MICROBIOTA

Backhed et al.[46] inoculated germ-free mice with normal gut microbial cells from conventionally raised mice, which resulted in a 60% increase in body fat and insulin resistance, even with a 27% reduction in food intake. They also found that bacterial colonization increased the storage of triglycerides in the adipocytes of the inoculated mice[46]. Ridaura et al.[47] also performed a study in which germ-free mice were colonized by fecal microbiota of twins discordant for obesity or by cultured collection of lean or obese animals. Fecal cultured or uncultured feces of obese animals originate significantly higher increase in body mass and adiposity than those of lean animals, whereas transplanted microbiota of lean animals was correlated to higher quantity of SCFA (butyrate and propionate). When the animals were cohoused (obese and lean) the obese animals stopped their body weight gain modifying also their microbiota profile like lean animals (increasing Bacteroides). The study was also conducted under 2 types of diet (low saturated fat and high saturated fat). The bacterial colonization and phenotype change only occur in low saturated fat diet revealing a diet-dependent mechanism between diet and microbiota[47].

Recently, increasingly studies embody the evidence of intestinal microbiota intervention in obesity. Intestinal dysbiosis implies an alteration in quality and quantity of intestinal commensal bacteria which means altered fermentation products (mainly SCFA), and occurs in obese people. In obesity, gut microbiota is known to be altered by a decreased ratio of Bacteroidetes to Firmicutes, with increased capacity to harvest energy from diet[48,49]. It is also known that long-term diet habits influence composition of gut microbiota. Intestinal bacteria react to daily dietary fat and carbohydrates and change its metabolic pattern but the extent, mechanisms and consequences of a dietary shift are still unknown[29].

The main mechanisms influenced by SCFA regulation in peripheral tissues are well developed in several studies[29-31]: energy harvesting[50,51], substrate metabolism[52], energy expenditure[53,54], anorectic hormone production and appetite regulation[55-58]. These mechanisms may counterbalance the extra energy source that SCFA intestinal production represent in obesity as well as the establishment of the low-grade inflammatory state characteristic of obese persons[27]. All these effects were observed in vitro or in animals, lacking evidence in humans, and so, those properties should be seen with caution.

FACTORS AFFECTING INTESTINAL COLONIZATION IN CHILDREN

The intestinal microbiota colonization occurs at birth, or before in uterus according to some authors, and it is the perinatal period the most important one to define gut microbiota in later ages.

Early life environment factors involved are[59]: a) host genetics that controls gut microbiota diversity but, animal studies revealed that changes in diet population may alter gut microbiota despite host genetics[60,61]; b) in uterus colonization were recent studies revealed a uterine microbiota in healthy pregnant women[62,63]; c) maternal lifestyle includind diet during pregnacy[64], overweight or excessive weight gain[65], and stress[66,67] modulating gut microbiota, immune system and milk composition[68]; d) birth delivery mode determine maternal transfer of vaginal, colonic and skin microbiota, colonizing the neonate specially with Lactobacillus and Prevotella[69-71]; e) breastfeeding versus formula with a major impact on early microbiota composition and function, when compared to introduction of solid food or even the birth mode[70] and were milk bacteria (specially bifidobacteria) act as probiotics to children's gut[72-75]; f) solid food which increases diversity and promotes the growth of Bacteroides and Clostridium butyrate producers and may be a major determinant for gut microbiota development[76,77]; g) antibiotics exposure that rapidly alters gut microbiota with short-term and long-term influences[78,79]; h) hygene level that also determines the microbial exposure and may influence the early development and diversity of gut microbiota[80-82]; i) prebiotics and probiotics administration to pregnant women and neonates have shown a modulation effect of child microbiota[83-87]. At 3 to 5 years old the gut microbiota composition is similar to adults and remains more or less stable. Changes may occur because of bacterial infections, surgeries, diet[40,62], lifestyle[88], and geographical area[89].

Continued research regarding the factors that can influence the development of human gut microbiota will enlighten the mechanism to achieve and promote children's health.

IMPACT OF GUT MICROBIOTA ON DEVELOPMENT OF CHILD OBESITY

Research in animal models have linked gut microbiota to obesity and is contributing to elucidate its mechanisms of interaction. However, there are not many studies in infants and several demand attention to their confounding factors undermining some results.

In Table 1 are summarized the studies in infant obesity related to gut microbiota.

Table 1. Studies on infant obesity and gut microbiome.

Type of study	N. of individuals	Ages (years)	Results (in obese individuals compared to lean)	Ref.
Case-study	20	4-5	- ↑ Enterobacteriaceae - ↓ Desulfovibrio and Akkermansia - ↔ Lactobacillus, Bifidobacterium and Bacteroides fragilis	90
Case-study	53	6-16	- ↑Firmicutes: Bacteroidetes ratio - ↑ Lactobacillus spp.	91
Case-study	84	N.a.	- ↑ B. fragilis and Lactobacillus - ↓ Bifidobacterium	92
Case-study	15	8-14	- No differences in gut microbiota composition - ↑ SCFA butyrate and propionate	93
Prospective study	30	Followed until 10	- ↓ mother's colostrum adiponectin - ↓ Bifidobacterium at 3 months	94
Prospective study	138	Followed until 3	- ↑ B. fragilis and ↓ Staphylococcus between 3 weeks and 1 year	95
Prospective study	909	Followed until 3	- ↑ B. fragilis	96
Prospective study	246	Followed until 2	- ↓ Bacteroides spp. - ↑ Staphylococcus spp.	97
Follow-up interventional study (perinatal $1x10^{10}$ cfu of L. rhamnosus GG, ATCC 53103 against placebo)	113	Followed until 10	- Correlation found between perinatal gut microbiota modulation and early obesity until 48 months	98
randomized controlled trial (symbiotic against placebo for 8 weeks)	70	6-18	- significant decrease of tumor necrosis-α and interleukin-6, and significant increase in adiponectin; - No differences in C-reactive protein	99
Randomized controlled trial (prebiotic against placebo)	38	7-12	- normalized weight gain, reduced whole body and trunk body fat, modified primary fecal bile acids, and selectively altered gut microbiota	100
Open-labelled self-controlled nutritional intervention for 30 days	38	3-16	- both obese groups share the same dysbiosis - gut microbiota modulation within 30 days of non-digestible carbohydrates diet - significant decrease of inflammatory markers	101

↑: increase; ↓: decrease; ↔: maintenance; N.a.: non-available.

Observational studies reveal differences between gut microbiota of obese and lean children. Karlsson et al.[90] studied 20 overweight or obese children and 20 normal range children with ages between 4-5 years old. After analyzing their intestinal microbiota they found significant differences in abundance but only a tendency in their diversity. The abundance of Enterobacteriaceae was significantly higher in the obese or overweight children, whereas a significantly lower of Desulfovibrio and Akkermansia muciniphila-like bacteria. No significant differences were found in content of Lactobacillus, Bifidobacterium or the B. fragilis group[90]. In another study comparing children between 6 and 16 years old the authors found elevated Firmicutes-to-Bacteroidetes ratio in obese children compared with lean ones. Additionally, low relative proportions of B. vulgatus and high levels of Lactobacillus spp. were observed in the obese children[91]. Gut microbiota of 30 obese, 24 overweight and 30 lean children were verified, and the authors found a positive correlation between BMI and high levels of B. fragilis group and Lactobacillus spp. while a negative correlation was found for Bifidobacterium spp.[92]. Obese (n=15) and normal weight (n=15) children aged between 8 and 14 years old were studied for their gut microbiota showing no significant quantitative differences in gut microbiota. However, higher concentrations of butyrate and propionate were found in obese versus normal weight children. Lower concentrations of intermediate metabolites detected in obese children, may suggest higher metabolic activity by obese gut microbiota leading to future dysbiosis[93].

In a prospective study, Luoto et al.[94] correlated the post-natal diet (maternal colostrum adiponectin concentration) and gut microbiota (at the age of 3 months) to subsequently normal weight (n=15) versus overweight (n=15) 10 years old children. Sex, gestational age, BMI at birth, mode of delivery, probiotic intervention, and duration of breast-feeding were similar in both groups. Colostrum adiponectin concentrations were significantly higher in mothers whose children were normal weight as well as the Bifidobacterium levels[94]. In a similar study design, 138 infants were studied for their gut microbiota at 3, 26 and 52 weeks of age and related to their BMI at 1 and 3 years old. A low Staphylococcus and a high B. fragilis concentration, was associated with a higher BMI during the first three years of life[95]. The same correlation was found between B. fragilis group and a higher BMI when fecal samples of 909 one-month-old infants were analyzed and BMI were evaluated between 1 and 10 years old[96].

An interesting prospective study tried to stablish a timeline between early gut microbiota patterns and infant growth. Collection of fecal samples were made at postpartum day 4 (mother sample) and their infants at 4, 10, 30, and 120 days old, totalizing 246 children after the study of inclusion process was concluded. Possible study confounders such as antibiotics use (after day 4 of life), sex, having received milk substitutes, maternal smoking, and parity were analysed and

removed. The aim of this work was the detection of specific gut microbiota groups that were significantly associated with infant growth trajectory. The samples showed 16 gut ecosystem developing patterns that were detected over time and some results were: detection of Bacteroides spp. at day 30 was significantly associated with reducing growth in males when compared to non-detection; detection of Staphylococcus spp. at day 4 was associated with expected growth in females and males; Escherichia coli detection from day 4 through to 30 was associated with expected growth in males. These results may be an insight to stablish a correlation between changes in gut microbiota development and consequent risk of obesity. This work also developed a novel approach to provide a potential time-dependent exposure window by observational data otherwise only occurred by experimental data[97].

Nadal et al.[102] and Santacruz et al.[103] found gut microbiota changes in obese adolescents when they altered their lifestyle, mainly diet and exercise, suggesting interactions between diet, gut microbiota and host metabolism and immunity in obesity.

To better stablish a timeline between early gut microbiota and its impact in developing obesity later in life, more experimental studies need to be done. Very few can be found since ethical issues limit their elaboration. Luoto et al.[98] performed an interventional study where 159 pregnant women were randomized and double-blinded to receive probiotics ($1x10^{10}$ CFU of L. rhamnosus GG, ATCC 53103) or placebo 4 weeks before delivery and extended until 6 months after. 113 children were enrolled in the study and their anthropometric measures were taken at 3, 6, 12 and 24 months and at 4, 7 and 10 years. The results showed that the perinatal probiotic intervention appeared to moderate the initial phase of excessive weight gain (until 24-48 months), especially among children who later became overweight, but not the second phase of excessive weight gain (after 4 years old). Early gut microbiota modulation appears to influence only infant growth in the first years of life[98].

A symbiotic (Protexin® 2.0×10^8 CFU/day of L. casei, L. rhamnosus, Streptococcus thermophilus, B. breve, L. acidophilus, B. longum, L. delbrueckii subsp. bulgaricus, and fructo-oligosaccharides, vitamin E, vitamin A, and vitamin C) was tested against placebo in a group of obese children of 6-18 years old in a 8 week randomized controlled trial in order to study its impact in obesity inflammatory markers. The symbiotic group had significant decrease in values of tumor necrosis-α and interleukin-6, with significant increase in adiponectin. No differences were found in C-reactive protein. The results were depending on weight reduction. Considering the duration of the intervention, symbiotic supplementation may positively influence inflammation markers[99].

In a randomized controlled trial[18], obese children aged between 7 and 12 years were randomly included to receive a prebiotic oligofructose-enriched inulin (n=20) or a placebo for 16 weeks. No

significant differences were found in BMI of prebiotic group while BMI significantly increased in the placebo group. Percent of total body fat was significantly lowered with prebiotic compared with placebo showing differences in body distribution. Lean mass had a significant increase in both groups. It was also observed a decrease tendency in inflammatory markers in prebiotic group. In respect to gut microbiota modulation it was observed an increase of Bifidobacterium spp. in the prebiotic group. The prebiotic administration normalized weight gain, reduced whole body and trunk body fat, modified primary fecal bile acids (microbiota metabolites), and selectively altered gut microbiota[100].

Zhang et al.[101] performed a nutritional intervention in 38 hospitalized children (3-16 years old) suffering from genetic obesity (n=17) or common obesity (n=21). After a diet rich in fermentable non-digestible carbohydrates (whole grains, vegetable, fruits, nuts, traditional Chinese medicinal food plants and prebiotics) for 30 days a significant weight loss and changes of the gut microbiota were observed together with a reduction of metabolic deterioration and inflammation markers (C-reactive protein, serum amyloid A protein, α-acid glycoprotein and white blood cell count). The levels of adiponectin increased and leptin decreased. Lipopolysaccharide binding protein, a marker for bacterial antigen load in the blood also decreased. The study revealed that both groups of obese children shared the same pattern of dysbiosis and in both it was observed gut microbiota modulation after the intervention. The authors also performed an *in vivo* essay by faecal transplantation to germ-free wild-type C57BL/6J mice. Those who received pre-intervention samples developed higher fat mass and presented high inflammatory markers and those who received post-intervention samples remained with the normal weight. The significant change on clinical parameters suggests overall structural changes at individual microbiome level. They also proved that long-term gut microbiota modulation by diet can be done[101].

DISCUSSION

Results from literature are often inconsistent as many confounders exist, namely the fact that different microbe identification techniques are used and the intra-individual and genotype differences that naturally occur. Besides in vivo animal essays, human clinical trial results are controversial and scarce in infant population.

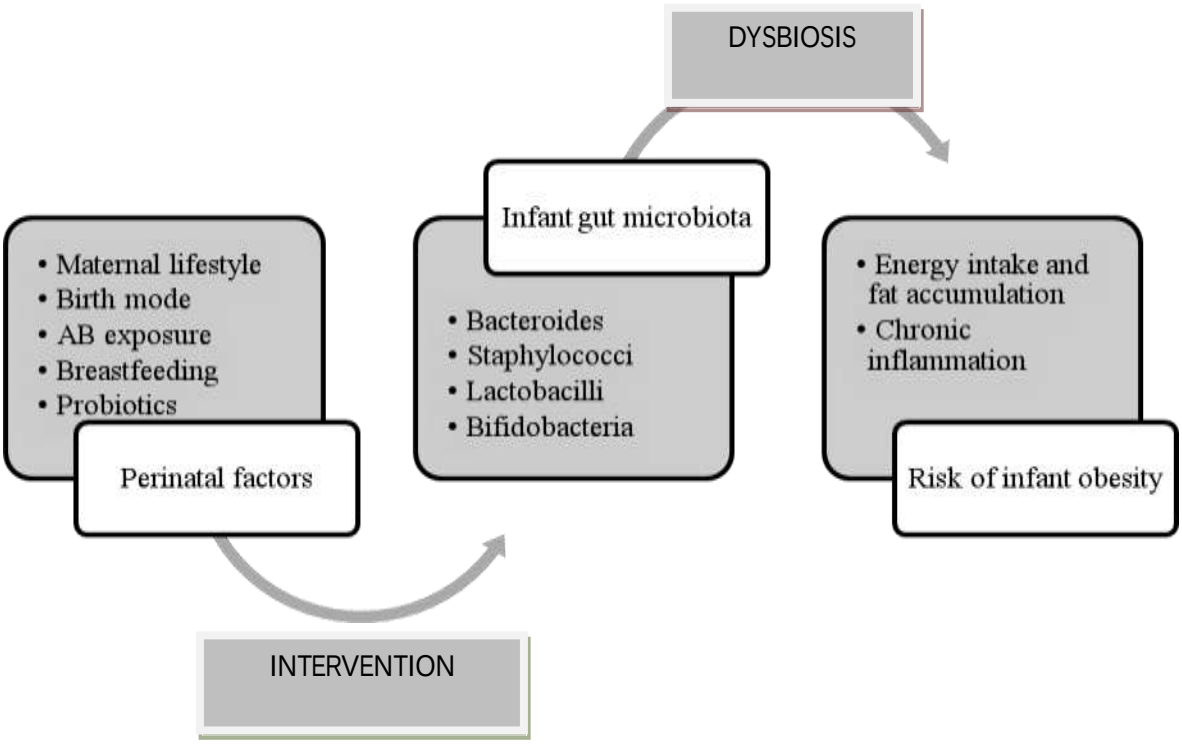
Until know it is not clear enough the correlation between gut microbiota and obesity but some statements can be summarized: gut microbiota is developed in early life and several factors contribute to its composition; gut microbiota from obese individuals differ from healthy ones, it is also apparent that Bacteroides spp. seem to play and important role in regulating childhood microbiota as well as lactobacilli, bifidobacteria, staphylococci, and a low Bacteroides/Firmicutes ratio, which can influence the development of overweight later in life.

Scientists are increasingly agreeing that dysbiosis can be one of the causes of obesity and that diet and prebiotic/probiotic interventions can qualitatively change gut microbiota during a period of time that is yet unknown. It is also well accepted that shifts in microbiota may result in healthier clinical parameters for obese individuals. Nevertheless, despite the intense research seen in the recent years, there is still much work to do either in animal models to elucidate the molecular mechanisms in which the gut microbiota controls weight gain, in identifying specific microbe species for shaping body composition or in laboratory analysis to standardize microbe identification and even in well-design human (infant) studies aiming to clarify the 'healthy gut microbiota' and which measures are effective to modulate a healthy gut microbiota development. Several recent reviews conclude the positive role of gut microbiota modulation in adult obesity treatment[104-106]. However, there are no sufficient data to state that child dysbiosis increase the risk of obesity later in life besides a few studies reported some discordant changes in gut microbiota of obese children. A timeline establishment between early gut microbiota and obesity was attempted by Richard A. et al.[97] but the study was very limited in time.

Even if more studies are still needing to clearly claim that gut microbiota modulation will play an important role in the treatment of obesity, earlier interventional trials in obese children open promising doors in that direction.

It is already known that pregnancy and perinatal factors (maternal health and lifestyle, birth mode, breastfeeding) are fundamental to the development of infant gut microbiota. Infant dysbiosis may be transmitted and responsible for obesity programming. Primary prevention strategies may include modeling maternal and infants gut microbiota and break the obesity cycle. The use of prebiotics, probiotics and changes on maternal lifestyle may be successful interventions to avoid children dysbiosis and consequent obesity (Figure 2).

Figure 2. Gut microbiota development and risk of infant obesity.



CONCLUSIONS

Despite the large amount of scientific publications, there is still much work to do regarding the clarification of mechanisms and the possible therapy for childhood obesity.

COMPETING INTERESTS

Authors state that there are no conflicts of interest in preparing the manuscript.

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