Chapter 37

Obesity and Gut Microbiota: what do we know so far?

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ABSTRACT

Introduction: Obesity is a matter of global concern, which has been rising over the last decades. It is estimated that more than 600 million adults are obese. Treatments, such as changes in lifestyle, medications (Liraglutide) and bariatric surgery are well established in literature. The role of the gut microbiome in obesity involves many pathways, as in the glucose and leptin homeostasis, increasing in activity of enteroendocrine cells and maintenance of GLP-2. The impact of the microbiota in reduction of BMI, abdominal circumference and body fat. The main objective of this paper is to find the data known until this moment about the role of gut microbiota in obesity and the gaps in this relation.
Method: search in literature using the PRISMA method for articles about gut microbiome and obesity, trying to find the gaps in this relation.
Result: studies have shown associations between microbiota's species and obesity in diverse populations. It has been observed that probiotic's supplementation associated with diet had more impact on weight and body fat than diet only. Probiotics also impact in DM1 and DM2, metabolic syndrome and pregnancy.
Discussion: More systematized studies are necessary to understand which species and quantities lead to clinical results, in order to apply the practical use of these supplements.
Conclusion: Although more studies are necessary to elucidate the practical supplementation, the influence of gut microbiota in obesity is already clear.

Keywords: obesity, gut microbiota, review.

1 INTRODUCTION

Obesity

By definition, obesity is the result of complex interactions between genetics, cultural and socioeconomic influences (1). It can be defined as body mass index above 30 kg/m2. Body mass index (BMI) is the weight in kilograms divided by height in square meters. BMI is not used in children aged 2 to 18 years, as it is preferable to use percentile scale. Obesity can be classified according to BMI, and the normal indice between 18.5 and 24.9 kg/m², between 25.0 and 29.9 is considered overweight and from 30 kg/m² is considered obesity (1). Between 30.0 and 34.9 kg/m2 is grade I obesity, between 35.0 and 39.9 is grade II obesity and above 40 kg/m2 is grade III obesity.

Global data from 2015 showed that a total of 603.7 million adults and 107.7 million children were obese, and the proportionof obese people in the 1980s doubled in more than 70 countries (2). The proportion of adults with BMI greater than or equal to 25 kg/m² increased from 28.8% in 1980 to 36.9% in 2013 in men. In women, the increase went from 29.8% to 38% in the same period (3). The increase in the world's obesein the last 50 years has reached pandemic proportions (3). There was an accelerated increase in BMI in South Asia, the Caribbean and southern Latin America. Prevalence of BMI ⩾ 30 kg/m² ranging from 3.7% in Japan to 38.2% in the United States. Except in subsa AryanAfrica, there are more obese than underweight people in the world. The prevalence of obesity in children and adolescents increased from 0.7% to 5.6% in boys and from 0.9% to 7.8% for girls between 1975 and 2016. In an individual and continuous analysis of BMI in a population sampleof 51505 children with anthropometric data continuously evaluated during childhood, the highest weight gain was between 2 and 6 years, and 90% of children who were obese at 3 years of age were also overweight or obese in adolescence. The prevalence of overweight and obesity in the Brazilian population increased from 7.5% to 17% between 2002 and 2013 in adults between 20 and 39 years of age, and increased from 14.7% to 25.7% in adults between 40 and 59 years (4). These changes were not homogeneous: while the mayor change occurred in women with secondary school level, men of all educational levels had a similar increase in the prevalence of obesity. The prevalence of obesity in women in Brazil is negatively associated with the increase in educationlevels, while men had higher rates of obesity with higher educational levels, similar to the poorest countries. There are a set of complex interactions between biological (including genetic and epigenetic),behavioral and environmental factors (including chronic stress) involved in regulating energy balance and fat storage (4). These changes lead to hypertrophy and hyperplasia of adipocytes and inflammation, in addition to secretion of adipokines.

As for pathophysiology, the fundamental cause of obesity is a long-term energy balance between excess calories consumed and scarcity of calories expended (5). Certain brain regions play a key role in regulating body weight. With the mutation found in the ob gene (which encodes the hormone leptin) that causes severe obesity in ob/ob rats, it became apparent that the central neural circuits that control energy homeotase integrate signals from peripheral tissues, such as adipose tissue. The discovery of mutations in genes encoding leptin, leptin receptors, melanoretin receptor 4, pro-opiomelanocortina and others that can cause severe obesity in humans demonstrates the importance of biological factors in the pathogenesis of obesidade. However, only genetic causes cannot explain the epidemic dimension of obesity.

Products of intestinal microbiota metabolism can induce beneficial metabolic effects by improving mitochondrial activity, prevention of metabolic endotoxemia and activation of intestinal gluconeogenesis (6). Cultural and environmental factors, such as high energy density diet, increase in part size, physical inactivity and adoption of a sedentary lifestyle, as well asfeeding disorders, are considered important risk factors for the development of obesity (6). Several organs are affected by genes related to the predisposition to obesity (7). Mutations in genes of the central nervous system, the main regulator of energy gastand eating behavior, result in increased weight. In the digestive tract, mutations in the genes of taste receptors and enzymes in the mouth are co-related to higher BMI. Mutations in genes involved in lactose digestion, imbalance in the intestinal microbiota, and glucose and lipid metabolism also result in obesity. Genes involved in fat distribution and adipogenesis can result in obesity through a cascade of events affecting homeotase. The extent of thebody's regulatory physiological ecanisms depend on the environment (8). In an environment where physical effort is required for food safety and the amount of food is insufficient, body regulatory mechanisms work better and facilitate food productionto prevent mass loss. In an environment that has gradually changed to little physical activity and abundance of food in everyday life, physiological regulation seems to be insufficient to support positive energy balance and obeseage. In these situations, obesity seems to be a new "settling point". A 2012 study also showed that individuals with lower incomes and socio-educational level are disproportionately affected by obesity (8). Cheaper foods usually contain more sugar and fat and the way to get a higher calorie diet is to eat foods with more fat and sugar. In addition, these foods contribute to overeating.

Microbiota

The intestinal microbiota is the set of microorganisms (bacteria, fungi, viruses, protists) that colonize the gastrointestinal tract (9). It gradually forms from birth and is considered adult at 3 years of age and can be modulated by many environmental and genetic factors of the host. An unbalanced microbiota (dysbiosis) is observed in many diseases and is an important part of many others. The microbiota has a role to maintain the integrity of the intestinal barrier, provide nutrients such as vitamins and protect against pathogens (10).

Combined data from meta hit and human microbiome project showed that 93.5% of the human intestinal microbiota is formed by Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes (10). The modulation of this microbiota is also done by the immune system. Believes that defects in the tolerance of the human mucosa cause diseases such as inflammatory bowel disease (IBD) (11). Before culture methods for intestinal microbiota were available, many studies reported changes in fecal microbiota and intestinal mucosa in patients with IBD (12). In patients with Crohn's disease, a new disease-specific E. coli pathotype called adherent invasive E. coli (IAEC) has been described (12). The composition of the intestinal microbiota was also altered intype 1 diabetes mellitus in relation to humans without the disease (13). In children with DM1 there were more bacteria of the genera Clostridium, Bacteroides and Veillonella, while healthy children had more Lactobacillus, Bifidobacterium, Blautia coccoides / Eubacterium rectale.

Most of the microbiota is composed of 5 phylums - Bacteroidetes, Actinobacteria, Proteobacteria and Cerrucomicrobia - and there is great diversity in each of them (14). In the healthy intestine, Bacteroidetes and Firmicutes make up 90% of the microbiota, but the proportion of these two phylums is not the same in all individuals.

Atheosclerotic plaques contain bacterial DNA, and the bacterial taxon observed in these plates was also present in the intestine of these individuals, suggesting thepossibility of bacteria from different sites being the source of bacteria in the plates (14). During food digestion, the microbiota participates in two catabolic pathways, classified as sucroseand proteolytic (14). In the sucrose lore, the microbiota breaks down sugars and is rspongive by the production of most short chain fat acids (SCFA). The second catabolic pathway is represented by protein fermentation, which also induces the formation of SCFA, but forms along ammonia, amines, tiols, phenols and indóis. The microbiota also constitutes and regulates intestinal mucosa barriers, controls nutrients and metabolism. Metagenomic sequencing of the microbiota in feces revealed changes in the microbiota in patients with stable plaques (compared to stable plaques). Hypertension is the most prevalent modifiable risk factor for cardiovascular disease and recent studies have shown that germ-free rats had a higher blood pressure, implying a role of the microbiota in regulatingpressure, although the correlation in humans has not yet been demonstrated. A meta-analysis demonstrated a significant decrease in blood pressure in patients treated with probiotics. There is a growing literature that support the "intestinal hypothesis of cardiac insufience", which is that decreased postload in the heart and elevated systemic congestion lead to intestinal edema/ischemia, leading to an increase in bacterial translocation and increased circulation of endotoxins that contribute inflammation in pacientes with HF.

Obesity and Microbiota

The role of the microbiota in intestinal obesity is not yet fully understood, but many mechanisms have already been elucidated. In a study with DM2 patients using metformin, the microbiota analysis suggested mediation ofthe intestinal microbiota on the effects of metformin, both in therapeutic effects and adverse effects, although further validation of the data is still necessary (15). There is evidence that prebiotics, which stimulate the growth of probiotics, play an important role in obesity by different mechanisms of action, such as changing the composition of the microbiota, changes that increase the functioning of enteroendocrine cells, glucose homeostasis and leptin sensitivity, in addition to increasing sensib glp-2 (16). The anti-obesogenic role of Lactobacillus and Bifidobacterium strains, alone or combined, as well as Pediococcus pentosaceus, was well established in obese adults, leading to a reduction in weight gain, BMI, abdominal circumference and body fat index (16).

A higher amount of Bifidobacteria has been described in children with normal weight compared to obese children. Reduced levels of S. aureus were linked to normal weight, indicating that changes in the microbiotamay pre-cede overweight. Diet and breastfeeding seemed to play a determining role in obesity. The increase of Bacteroidetes and Firmicutes in obese adults may be a result of dysbiosis (17).

A review of clinical trials (18) showed that the use of yogurt usingprobiotics is a promising tool for the management of obesity, diabetes and nonalcoholic fatty liver disease (NAFLD), with results such as reduced BMI and abdominal fat. There is evidence that the microbiota can influence the greater absorption of energy of short-chain fatty acids (FCS), an extra energy source beyond food, and may affect the development of obesity (19). SFCAs promote an extra gain of 10% of daily calories and regulate energy expenditure, fasting-induced adipose factor, lipogenesis, glucose homeostasis regulation, leptin secretion and satiety modulation (19). The report of obese children with more SFCAs in feces than non-obese children correlated with higher BMI z score and more Firmicutes and fewer Bacteroidetes. There is evidence that prebiotics increased GLP-1 and PYY and reduced ghrelin, increasing satiety and decreasing energy absorption (20).

The microbiota is also related to endotoxemia and decrease of the intestinal barrier, which leads to levels of inflammation associated with obesity comparable with the consumption of a fatty diet (20). With loosening of the intestinal barrier (tight junctions), more intestinal bacteria reach the host's immune system. The principalities of changes in the microbiota associated with obesity are increased Firmicutes/Bacteroidetes ratio, increased pathogenic microorganisms and reduction of SFCO producers. The use of probiotics is linked to mechanisms of increased satiety (decreased lina,increased PYY, lower plasma glucose) that are very important for obesity.

Among the mechanisms of the microbiota in obesity, the stimulation of bacteria in the endocannabinoid system stands out, affecting host metabolism, functional barrierand control of homeostatic and hedonic appetite (21). Torres-Fuentes et al, 2017 (21) also identified a relationship between diet components, such as carbohydrate fibers, proteins, saturated and unsaturated fats and polyphenols with the microbiota by different mechanisms.

In addition to the mechanisms of the microbiota in the production of SCFAs and intestinal inflammation, the microbiota also contributes to the increase of TIR3 and SGLT1 receptors, regulating CCK and PYY and acting on motility and food perception (22).

The aim of this review is to find what is known up to the moment of the relationship between microbiota and obesity. In addition, we seek to understand what are the gaps in this relationship.

2 METHOD

On 03/21/2021, pubmed research was conducted with the terms "gut microbiota and obesity", resulting in 4,857 results. As of 05/06/2022, 98 reviews were found in the search for "gut microbiota and obesity" in the literature. Inclusion criteria were systematic reviews in English that addressed data from the intestinal microbiota related to obesity in human studies. Animal studies or no direct relationship between obesity and microbiota were excluded.

Excluding 54 articles after reading, 44 systematic reviews resulted.

3 RESULTS / DISCUSSION

Table 1: Summarized results of selected articles.

Title	Authors and year of publication	Number subjects	Age	Intervention	Control	Primary results	Secondary results
Childhood Obesity and Firmicutes/Bacteroidetes Ratio in the Gut Microbiota: A Systematic Review	Indiani et al, 2018	1707	3 without - 13 years	Evaluation of fecal microbiota	-	Association between evaluated microbiota species and overweight/obesity: ↑BMI, ⌈A. muciniphila, ⌈F. prausnitzii, Bacteroidetes/Prevotella. ^B. fragile, ⌈C. difficile, ↑Firmicutes, ↑Lactobacillus, ⌈B/F	-

Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review	Seganfredo et. al., 2017	522 + 213 + 709		Diet + bariatric surgery (BS) + microbiota manipulation	-	- Restrictive diets reduced Lactobacillus, Firmicutes and Bfidobacterium, higher correlation with nutrient deficiency than weight loss. - Surgery (Bariatric Surgery - BS) had similar reduction and increase of Proteobacteria - Use of probiotics with tendency to decrease BF	- All interventions had animpact on the microbiota, although not all of them impacted on weight loss
The Gut Microbiome Profile in Obesity: A Systematic Review	Castaner et al., 2018	2509 + 50 (BS)	3 - 16 years + adults for BS	Trials of observational obese + BS	Not obese	- Significant difference between obese and thin: ↑F/B, ⌈ Bacteroidetes - Difference between BS and non-BS: ⌈Firmicutes, Bacteroidetes, Actinobacteria and Cyanobacteria	-
Profile of the gut microbiota of adults with obesity: a systematic review	Crovesy et al., 2020	-	20- 60 years (approx.)	Observational studies and trials without intervention	-	- ↑F/B, Firmicutes, Fusobacteria, Proteobacteria, Mollicutes, Lactobacillus reuteri, - -Akkermansia muciniphila, Faecalibacterium, Bacteroidetes, Methanobrevibacter, Lactobacillus plantarum and paracasei	- Some bacteria with positive correlation and others negative with obesity.
Gut microbiota-derived metabolites in obesity: a systematic review	Ejtahed et al., 2019	1328	schoolchildren and adults	-	N=201	- ↑BCAAs and ↑AAAs in obese - obesity-related glutamate - Arg, Met Ornit related to bacteria - Firmicutes ratio, Bacteroidetes and SCFAs - Blautia increased in ↑BMI - ^biosynthesis at primary =obesity - xanthena in obese	- Differences between insulin-sensitive and insulin-resistant individuals
Impact of a Moderately Hypocaloric Mediterranean Diet on the Gut Microbiota Composition of Italian Obese Patients	Pisanu et al., 2020	23	adults > 18	Diet in patients BMI > 25, diet-free	46 healthy subjects	- Weight reduction in obese patients after 3 months - F/B reduction in obese patients after intervention	-
Probiotics have minimal effects on appetite-related hormones in overweight or obese individuals: A systematic review of randomized controlled trials	Cabral et al., 2021	1282+410+94	obese/overweight	intervention with probiotics	placebo	•fasting insulin after intervention	no leptin difference, ↑Adiponectin in the intervention group
Probiotic Strains and Intervention Total Doses for Modulating Obesity-Related Microbiota Dysbiosis: A Systematic Review and Meta-analysis	Moreno et al., 2020	329	obese adults and adolescents, thin adults, obese postmenopausal women	analysis of probiotic dosagens given for effect in obesity	No	Benefits in obesity, satatosis, hepatic fibrosis, NASH, NAFLD and GLP-1 after use of VSL#3	^BMI, but maintenance lipid profile and glucose, after L. reuteri
Probiotics for weight loss: a systematic review and meta-analysis	Park et al., 2015	94	obese adults	evaluate clinical trials on the effectiveness of probiotics in weight loss	102	Long-term treatment with Lactobacillus may facilitate weight and body fat reduction	Meta-analysis result showed no positive effects of probiotics on weight, BMI and body fat
Effects of Probiotics and Synbiotics on Weight Loss in Subjects with Overweight or Obesity: A Systematic Review	Arraño et al., 2021	2413		evaluate the effect of probiotics and symbiotics on RCTs on weight loss in obese/overweight people	yes	- L. gasseri → decrease in weight, abdominal circumference andvisceral and subcutaneous fat (higher dose). - L. curvatus with L. plantarum → body weight, BMI and abdominal circumference reduction, reinforcing previous results in rats - L. acidophilus + L. casei + Bifidobacterium → weight reduction, although some species of Lactobacillus have been associated with weight gain, but most studies have found results in weight loss	-

Gut microbiota in patients with obesity and metabolic disorders - a systematic review	Xu et al., 2022	4761	Obese	review cases of obese and associated microbiota to facilitate treatment	yes	- significant changes in FIrmicutes, Bacteroidetes and Proteobacteria (not made clear whether changes associated with lean or obese profile) - Bacilli classes, Gammaprotheobacteria and family Coriobacteriaeae associated with obesity - Proteobacteria associated with obesity and inflammation - A. muciniphila modulating gut barrier - generos Bifidobacterium, Roseburia, Prevotella and Ruminococcus consistently associated with "lean" microbiota	- reduction of alpha diversity in obese (compared with controls) - contradictory difference between studies with beta diversity
Gut Microbiome Composition in Obese and Non-Obese Persons: A Systematic Review and Meta-Analysis	Pinart et al., 2021	12385	obese (compared to non-obese)	assess diversity, F/B ratio and differences in composition	yes	- contradictory results in Firmicutes and Bacteroidetes in the evaluated studies - genera Acidaminococcus, Anaerococcus, Catenibacterium, Dialister, Dorea, Escherichia-Shigella, Eubacterium, Fusobacterium, Megasphera, Prevotella, Roseburia, Streptococcus and Suterella more abundant in obese compared to non-obese - Bifidobacterium and Eggerthella increased in non-obese	- many studies have notincluded significant differences between obese and lean microbiota by fecal analysis
The association of weight loss with changes in the gut microbiota diversity, composition, and intestinal permeability: a systematic review and meta-analysis	Koitoukidis et al., 2022	1689	adults	quantitatively synthesize changes in microbiota and permeability after interventions for weight loss and possible relationship with dose-response	-	- weight loss related to ↑Akkermansia, ↑Bacteroides, ⌈ Bifidobacterium - weight loss associated with significantintestinal permeability - weight loss increased alpha diversity with dose-response pattern	-
Benefits and Implications of Resveratrol Supplementation on Microbiota Modulations: A Systematic Review of the Literature	Inchingolo et al., 2022	13th	20 - 50 years old	evaluate resveratrol supplementation in microbiota and human metabolism	yes	- no effective results in insulin sensitivity - reduction of sulfated androgen metabolites - reduction of F/B ratio, which high is associated with obesity	-
Effects of Non-insulin Antihyperglycemic Agents on Gut Microbiota: A Systematic Review on Human and Animal Studies	Cao et al., 2020	-	obese adults	use of anti-hyperglycemic agents, glucose control	-	DM2 patients treated with Liraglutide had increased Akkermansia, a decrease in Bacteroidetes.	-
Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review	Grabia et al., 2021	1771	Children DM1	assess prevalence of metabolic syndrome	No	^Bacteroidetes and ↑Streptococci and ⌈Clostridium can contribute to progression of DM1	Metabolic syndrome should include microbiome criteria, inflammation, and metabolic control.
Influence of Maternal Prepregnancy Obesity and Excessive Gestational Weight Gain on Maternal and Child Gastrointestinal Microbiome Composition: A Systematic Review	Dreisbach et al., 2020	1363	obese/overweight pregnant women	collection of microbiota from the mother, babies and both	-	⌈C. cocoides in obese mothers, ↑S. aureus in obese mothers, ↑S. aureus in 6m babies - positive associations of obesity in pregnancy and other bacteria	-
Effect of Probiotic Supplementation on Newborn Birth Weight for Mother with Gestational DiabetesMellitus or	Wang et al., 2020	-	obese pregnant women/ MgD	- Administration of probiotics Bifidobacteri	yes	There was no significant difference	-

Overweight/Obesity: A Systematic Review and Meta-Analysis				um and Lactobacillus			
Maternal exposures and the infant gut microbiome: a systematic review with meta-analysis	Grech et al., 2021	17509	pregnant women and their babies	review evidence of maternal exposures and infant microbiota	yes	- overweight/obese mothers had babies withmicrobiota d iferença - ^Bacteroidetes and Proteobacteria and Enterococcus - changes were not significant at 6 months of age - no difference in mother's weight and diversity in babies born in cesarean section	- pregnant women DM had the same change
Modulation of the gut microbiome: a systematic review of the effect of bariatric surgery	Guo et al., 2018	150	adults	Changes in post-BS microbiota	-	-↑ richness microbiota post RYGB - ↑Bifidobacterium related to BMI, weight, caloric intake, [leptin]	Clostridium more related to insulin in BIB patients
Adaptation of human gut microbiota to bariatric surgeries in morbidly obese patients: A systematic review	Ejtahed et al., 2018	112	obese adults	Microbiota analysis	(genetic sequencing)	•Firmicutes, ()'Clostridia and Γ Verrucomicrobia pós RYGB - ↑Gammaproteobacteria, ↑Prevotellaceae, ↑Enterobacteriaceae, ↑Fusobacteriaceae	-
Comparison of methodological approaches to human gut microbiota changes in response to metabolic and bariatric surgery: A systematic review	Marroquin et al., 2020	221	obese adults	analysis of microbiota after different bariatric methods	-	RYGB surgery led to ↑Bacteroidetes, ↑Proteobacteria	^IMC~Firmicutes
Altered gut microbiome after bariatric surgery and its association with metabolic benefits: A systematic review	Davies et al., 2019	308	obese adults	caloric, bariatric restriction	yes	^microbial richness after RYGB, Γ Firmicutes and ↑Bacteroidetes and ↑Proteobacteria post surgery	surgery actually changes the microbiota, more potent than the diet just
The role of bile acids in reducing the metabolic complications of obesity after bariatric surgery: a systematic review	Penney et al., 2015	534	obese adults (with and without DM2)	bariatric RYGB, VSG	314	•weight, Γhedonic response to hunger	•IR, liver fat after 3 months
The Importance of the Microbiome in Bariatric Surgery: a Systematic Review	Luijten et al., 2019	631	obese patients	RYGB/LSG/ VBG	yes	- ↑Gammaproteobacteria associated with Γweight after RYGB - ↑Bacteroidetes ↑Proteobacteria Γ Firmicutes post RYGB	F. prausnitzii had a direct association with systemic inflammation
Effect of Lactobacillus on body weight and body fat in overweight subjects: a systematic review of randomized controlled clinical trials	Crovesy et al., 2017	-	adults	Lactobacillus supplementation with cheese, yogurt and fermented milk or capsules	placebo	- weight gain after Lactobacillus and weight loss after L. gasseri	-
Microbiota manipulation for weight change	Dror et al., 2017	7930	adults, children and babies	- Administration of probiotics/symbiotics/antibiotics	yes	- significant weight loss with robotic p- Lactobacillus in children's weight gain	- Azithromycin in children led to weight gain in the intervention group
Prebiotics may reduce serum concentrations of C-reactive protein and ghrelin in overweight and obese adults: a systematic review and meta-analysis	Borges et al., 2020	639	obese with or without DM2, 18 - 65 years)	Foods supplemented with prebiotics	-	•ghrelin and ΓPCR, •leptin post prandial	-
A comprehensive systematic review of the effectiveness of Akkermansia muciniphila, a member of the gut microbiome, for the management of obesity and associated metabolic disorders	Roshanravan et al., 2021	-	obese adults	supplementation with A. muciniphilaa nd m obese adults	yes	supplementation led to body weight, fat mass, circumf abd	•white céll in DM2 - brought some possible mechanisms of obesity

Effects of probiotics on body adiposity and cardiovascular risk markers in individuals with overweight and obesity: A systematic review and meta-analysis of randomized controlled trials	Pontes et al., 2021	901	obese adults	probiotic supplementation in yogurts/capsules/powder	1055	•body fat, weight and visceral fat	⌈TNF alpha and ⌈ CRP after probiotics
Systematic review on intervention with prebiotics/probiotics in patients with obesity-related nonalcoholic fatty liver disease	Tarantino et al., 2015	1099	adults and obese children	prebiotics/probiotics	-	•weight (and maintenance of loss) in adults, inflammation in obese adults, abdominal adiposity	significant changes in children, prevention of gestational DM with use of probiotics (540 ♀ Australians)
Effects of pro-/synbiotic supplementation on anthropometric and metabolic indices in overweight or obese children and adolescents: A systematic review and meta-analysis	Mohammadi et al., 2019	215	obese children and adolescents	supplementation with symbiotics and probiotics	195	•BMI with symbiotics	•weight in adults and 'weight in children with Lactobacillus - beneficial in lipid profile and glucose in postmenopausal ♀
The effect of ultra-processed very low-energy diets on gut microbiota and metabolic outcomes in individualiduals with obesity: A systematic literature review	Lane et al., 2020	130	-	VLED Diet	-	Improvement in BMI after intervention	Improvement in biochemical markers
Gut microbiota modulation as a possible mediating mechanism for fasting-induced alleviation of metabolic complications: a systematic review	Angoorani et al., 2021	398	adults	evaluate literature on fasting and relationship with microbiota	yes	- Buchinger fasting led to decrease of Lachnospiraceae and Ruminococcaceae and increase of Bacteroidetes and Proteobacteria - increase of Proteobacteria and decrease in F/B ratio - after fasting of Ramadan, there was decrease in Firmicutes and Enterobacteriaceae	- Maintaining a correct feeding schedule and increasing fasting periods can positively affect the microbiome, reducing intestinal permeability and increasing health
The Role of the Gut Microbiota on the Beneficial Effects of Ketogenic Diets	Attaye et al., 2021	-	adults	evaluate effect of ketogenic diet	-	- ketogenic diet promoted reduction of alpha diversity and increase Akkermansia muciniphila	data compared to animal studies
Efficacy and safety of fecal microbiota transplantation for the treatment of diseases other than Clostridium difficile infection: a systematic review and meta-analysis	Green et al., 2020	104	obese adults with metabolic syndrome.	fecal transplantation, compared with control group	42	Metabolic changes	^insulin sensitivity
Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials	Proença et al., 2020	154	obese with or without metabolic syndrome	fecal transplantation (FMT) in the treatment of obesity	placebo	FMT group with ⌈HbA1C, ↑HDL, no difference in weight and BMI (low quality of studies)	late results: ⌈BMI, hip and weight after FMT (some moderate quality evidence)
Therapeutic mechanisms of traditional Chinese medicine to improve metabolic diseases via the gut microbiota	Zhang et al., 2021	-	-	-	-	-	-
The effect of Berberine on weight loss in order to prevent obesity: A systematic review	Ilyas et al., 2020	405	patients with DM2, dyslipidemia	1g berberine/ Berberine + Metformin	-	•HbA1C in DM2 patients - does not talk about weight/obesity	-
Targeting obesity management through gut microbiota modulation by herbal products: A systematic review	Ejtahed et al., 2019	376	obese adults	Herbal products	-	Actinobacteria change, controversial data on Firmicutes and Bacteroidetes	-

Short Chain Fatty Acids and Fecal Microbiota Abundance in Humans with Obesity: A Systematic Review and Meta-Analysis	Kim et al., 2019	249	adults	Analysis of case-control studies	not obese	- Obese with concentr acetate in blood and feces - Obese with bacteroidetes and firmicutes	-
Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis	Rasmussen et al., 2018	527504	24 months - 12 years	-	-	Antibiotic treatment did not increase risk of obesity/overweight, but repeated exposure was associated with mild increase in	-

Influence of Microbiota on Obesity

Direct role in obesity: Indiani et al 2018 (23) showed the association between species present in the microbiota and obesity in children from 3 weeks to 13 years of age. Seganfredo et al 2017 (24) also showeddifferences in the microbiota with restrictive diets and bariatric surgery, and use of probiotics with a tendency to decrease body fat - showed impact on the microbiota, but not necessarily on weight. Castaner et al (25) brought data from children aged 3 to 16 years and obese adultos who did bariatric, compared with non-obese individuals, and showed a significant difference between obese and thin and between BS and non-BS. Crosvesy et al 2020 (26) showed correlations between bacteria and obesity, as higher F/B ratio and increase of Firmicutes, Fusobacteria, Proteobacteria, Mollicutes and Lactobacillus reuteri in obese, and decrease of Akkermansia muciniphila, Faecalibacterium, Bacteroidetes, Methanobrevibacter, Lactobacillus plantarum and Lactobacillus paracasei. Ejtahed et al 2019 (27) brought dados on increased BCAAs and AAAs in obese individuals, glutamate ratio with obesity and insulin resistance in school-age children and middle-aged adults, compared with control. An article by Pisanu et al, 2020 (28) brought data from 23 adults submittedto the diet and compared it with 46 healthy individuals, showing weight reduction and decreased F/B ratio in obese patients after the intervention. Cabral et al, 2021 (29) reviewed data from probiotic interventions in obese/overweight and found a decrease in insuli in fastingin the intervention group when compared with placebo. As a secondary result, the intervention group showed an increase in Adiponectin, but with no difference in leptin concentration. Several side effects of supplementation have been reported to work, something previously unreported. Moreno et al, 2020 (30) conducted a systematic review of the probiotic doses needed for microbiota modulation in obesity-related dysbiosis. The study included thin and obese adults, obeseelders and obese postmenopausal obese women, showing benefits in obesity, stalatosis, hepatic fibrosis, NASH and GLP-1 concentration after use of VSL#3. The formula VSL#3 contains Streptococcus thermophilus, Bifidobacterium (B. breve, B. infantis, B. longum), Lactobacillus acidophilus, L. plantarum, L. paracasei, and L. delbrueckii subsp. bulgaricus. As a secondary result, supplementation with L. reuteri was associated with increased BMI with maintenance of lipid profile and glucose. The systematic review by Park et al, 2015 (31), evaluated randomized clinical trials on the effectiveness of probiotics in weight loss. The result was that long-term lactobacillus treatment may facilitate weight and body fat reduction. Nevertheless, the meta-analysis of the articles showed no positive effects of probiotics on weight, BMI and body fat. Arraño et al., 2021 (32), sought to evaluate randomized controlled clinical trials on the effect of probiotics and symbiotics on weight loss of people with obesity/overweight. In the study, l. gasseri was influenced on the decrease in weight, abdominal circumference and areas of visceral and subcutaneous fat (a higher dose was required); of L. curvatus with L. plantarum in reducing corpórweight and waist circumference, reinforcing previous results in rat studies; of L. acidophilus, L. casei and Bifibacteridoum combined in weight reduction, although some species of Lactobacillus have been associated with weight gain, but most of the studies foundresults in weight loss. The review by Xu et al., 2022 (33), sought an association between the microbiota and obesity in control case studies. Significant changes were found in Firmicutes, Bacteroidetes and Proteobacteria, but there werecontradictory associations: while some studies associated with thinness, others associated with obesity. Classes Bacilli, Gammaproteobacteria and the family Coriobacteriaceae were associated with obesity, while Proteobacteria was associated withobesity and also inflammation. There was evidence of A. muciniphila modulating the intestinal barrier. Genera Bifidobacterium, Roseburia, Prevotella and Ruminococcus were associated with consistency with a lean microbiota. As secondary results, the andall presented reduction of alpha diversity in obese (compared with controls) and a contradictory difference in the aspect of beta diversity. Pinart et al., 2021 (34) conducted a systematic review focusing on high-rend imento sequencingtechnologies. The results were contradictory in Firmicutes and Bacteroidetes. In the genera Acidaminococcus, Anaerococcus, Catenibacterium, Dialister, Dorea, Escherichia-Shigella, Eubacterium, Fusobacterium, Megasphera, Prevotella, Roseburia, Streptococcus and Suterella were more abundant in obese patients compared to non-obese individuals. Bifidobacterium and Eggerthella were increased in non-obese individuals. However, many studies did not find statistically significant differences between "lean" and "obese" microbiota after fecal analysis. The review by Koitoukidis et al, 2022 (35) sought changes in the microbiota and a possible dose-response relationship. With weight loss, there was an increase in Akkermansia, Bacteroides and decreased Bifidobacterium, and weight loss was associatedwith reduced intestinal permeability, with no difference between interventions with diet or bariatric surgery. In obese individuals, interventions for weight loss showed an increase in intestinal diversity and improved permeability, with a dose-resposta pattern. The study by Inchingolo et al, 2022 (36), brought data on resveratrol supplementation in obesity, showing a reduction in the F/B ratio after supplementation. This proportion, when high, is associated with obesity.

Diabetes Mellitus (DM): A study by Cao et al, 2020 (37) reviewed the use of anti-hyperglycemic agents in obese adults and showed that DM2 patients treated with Liraglutide had increased Akkermansia. Bacteroidetes decreased in newly diagnosed patients with DM2 who started metformin treatment. Grabia et al, 2021 (38), sought to evaluate the prevalence of metabolic syndrome in children and adolescents with DM1. The result was that higher concentrations of Bacteroidetes, Streptococci and lower concentrations of Clostridium may contribute to the progression of DM1. In addition, according to the authors, metabolic syndrome should have as additional criteria microbiome data, inflammation and metabolic control.

Metabolic syndrome: Oneand all of Grabia et al., 2021 (38) evaluated the prevalence of metabolic syndrome in children and adolescents with DM1, finding that increased Bacteroidetes and Streptococci and clostridium decrease may contribute to the progression of DM1 in children. The study also points out that metabolic syndrome should include microbiome analysis, inflammation and metabolic control as criteria for the syndrome.

Pregnancy: Dreisbach et al, 2020 (39) reviewed articles that analyzed the microbiota of obese pregnant women and their babies, showing reduction of C. cocoides and increase of S. aureus in obese mothers, increase of S. aureus in 6-month-old babies and associations between obesity in pregnancy with bacterial species. Wang et al, 2020 (40) reviewed articles with obese pregnant women with gestational diabetes who received probiotics from the Bifidobacterium and Lactobacillus groups, compared with placebo. The result was that there was no significant difference between the intervention and the placebo group or that it treated only with diet. Grech et al., 2021 (41) reviewed data on the relationship between maternal exposure and infant microbiota, analyzing both pregnant women and their babies. It was found that overweight/obese mothers had babies with differences in the microbiota. These babies hadincreased Bacteroidetes and decreased Proteobacteria and Enterococcus, but the changes did not persist beyond 6 months of age. Pregnant women with diabetes had the same pattern of change in the microbiota. However, babies born from cesarean section did not have this association between microbial diversity and maternal weight.

Interventions and their effects on microbiota and obesity

Bariatric surgery in the microbiota and obesity: Guo et al, 2018 (42) conducted a systematic review of changes in the microbiota after bariatric surgery, finding increased richness of the microbiota after RYGB, increased Bifidobacterium correlated with BMI, weight, caloric intake and leptin concentration. The review also showed a positive correlation between Clostridium and insulin in the blood. Ejtahed et al, 2018 (43) reviewed microbiota analysis data of obese adults after RYGB, through genetic sequencing. Comparison after surgery with the control group showed a decrease in Firmicutes, Clostridia and Verrucomicrobia and increased Gammaproteobacteria, Prevotellaceae, Enterobacteriaceae, Fusobacteriaceae, Bacteroides. It was not clear whether changes in the microbiota are the cause or consequence of weight loss after surgery. The study by Morales- Marroquin et al, 2020 (44) brought an analysis of the microbiota after different bariatric methods, showing an increase in Bacteroidetes and Proteobacteria after RYGB, while the sleeve method showed increased Lactobacilli and decreased Firmicutes. There was a positive correlation between the phylum Firmicutes and BMI, and a negative correlation between Prevotella and BMI. Davies et al, 2019 (45) reviewed data on caloric restriction and bariatric surgery in obese adults, showing increased microbial richness after RYGB, decreased Firmicutes and increased Bacteroidetes and Proteobacteria after surgery. The authors concluded that surgery is actually able to alter the microbiota, being more potent than just diet. Penney et al, 2015 (46) brought data on bariatric surgery (RYGB, VSG) in obese adults (with or without DM2), showing decreased weight and response to hedonic hunger after surgical intervention, compared with placebo. The study also demonstrated decreased insulin and liver fat resistance after 3 months in the intervention group participants. Luijten et al, 2019 (47) brought data from bariatric surgery in obese patients, showing a correlation between gammaproteobacteria increase and weight reduction after bariatric surgery. There was also an increase in Bacteroidetes, increased Proteobacteria and decreased Firmicutes after RYGB, and direct association of F. prausnitzii with decreased systemic inflammation.

Probiotic supplementation: Crovesy et al, 2017 (48), evaluated by means of a system supplementation with Lactobacillus (cheese, milk, fermented yogurt, capsules) in adults and concluded that there was weight gain after lactobacillus consumption and weight loss after L. gasseri. Dror et al, 2017 (49), conducted a systematic review of work in childrenand adults with the administration of probiotics, symbiotics and antibiotics, showing significant loss with probiotics and infant weight gain with the use of Lactobacillus. There was a comparison with the control group and, as a secondary result, the use of azithromycin in children led to weight gain in the intervention group. Borges et al, 2020 (50) showed lower levels of ghrelin, C-reactive protein and post prandial leptin in obese patients after consumption of foods supplemented with probiotics in obese adults. The study by Roshanravan et al, 2020 (51) showed that supplementation with A. muciniphila in obese adults decreased body weight, fat mass and abdominal circumference when compared with placebo. In addition, there was a decrease in whitecells as a predictor of DM2 in obese patients, improvement in IR and TOG. The study also provided details of some possible mechanisms. Pontes et al, 2021 (52) did a systematic review on probiotic supplementation in obese adults. There was a decrease in body fat, visceral fat and weight in interventions compared with placebo, in addition to a decrease in C-reactive protein and TNFalfa after the use of probiotics. Tarantino et al, 2015 (53) brought a review on the intervention with prebiotics/probiotics in patients withnafld related nafld patients. The article showed weight loss (and maintenance of weight lost) in adults, decreased inflammation and decreased abdominal adiposity in obese adults in the intervention group. Tarantino et al also brought significant changesin children (long-term effects on body composition, growth and metabolic markers) and prevention of gestational DM in obese women with the use of probiotics. Mohammadi et al, 2019 (54) conducted a systematic review of supplementationwith symbiotics and probiotics in children and adolescents, reporting decreased BMI with the use of symbiotics, comparing with the control group. The use of Lactobacillus was associated with decreased weight in adults and weight gain in children. In addition, there was benefit in lipid and glucose profile in postmenopausal women. The systematic review by Moreno et al, 2020, also sought to investigate the dosages of probiotics with effect on obesity in adults after the use of the formula VSL#3. Wang et al, 2020 (40) showed that there was no difference between obese pregnant women who supplemented with probiotics and obese pregnant women who dieted.

Diet: Seganfredo et al, 2017 (24) found that restrictive diets reduced Lactobacillus, Firmicutes and Bifidobacterium and had a higher correlation with nutritional deficiency than with weight loss. Lane et al, 2020 (55) evaluated the impact of very low energy diets (LeV) in obese individuals, showing improvement in BMI and biochemical markers, while the microbiota presents or controversial results among the studies evaluated. Pisanu et al, 2020 (28) also reviewed data from obese adults, showing weight reduction and f/b ratio after 3 months. Wang et al, 2020 (40) conducted a study with the administration of probiotics Bifidobacterium and Lactobacillus pregnant obese and with Gestational Diabetes Mellitus (MgD). The result was that there was no statistically significant difference between control group and intervention. Davies et al, 2019 (45) studied changes in the microbiota intestinal after bariatric surgery, showing that surgery actually alters the microbiota more than just the isolated diet. Angoorani et al, 2021 (56) conducted a review on the types of fasting and its influence on the intestinal microbiota. The change of microbiota promoted by fasting may be responsible for converting white adipose tissue into brown, increasing energy expenditure and contributing to improve obesity. The study found that Buchinger fasting contributed to the decrease of Lachnospiraceae and Ruminococcaceae and increased Bacteroidetes and Proteobacteria, in addition to a decrease in the Bacteroidetes/Firmicutes ratio, leading to decreased hepatic steatosis and metabolic syndrome. After fasting in the Ramadan period, there was a decrease in Firmicutes and Enterobacteria, which led to decreased blood glucose, fat mass and weight. Fasting alternate days led to increased SCFA and decreased weight and blood pressure. Maintaining meal times and increasing fasting time can positively affect the microbiota and health. Attaye et al 2021 (57) conducted a review focusing on the effect of ketogenic diet on the microbiota and obesity was one of several conditions analyzed. The study concluded that the ketogenic diet led to decreased alpha diversity (associated with worse metabolic results) and relative increase in Akkermansia muciniphila (scfas producer and associated with metabolic improvement).

Fecal transplantation: Green et al, 2020 (58) sought data on the efficacy and safety of fecal transplantation in diseases other than C. difficile, comparing FMT in obese adults with a control group. The result was increased insulin sensitivity and metabolic changes after transplantation. Proença et al, 2020 (59) conducted a systematic review on fecal transplantation (FMT) in obese patients (with or without metabolic syndrome), finding a decrease in HbA1C and an increase in HDL as primary results. In the results of late-term, a decrease in BMI, weight and hip was found after fmt, compared to the group receiving placebo, but the evidence had moderate to low quality. Zhang et al, 2019 (60) conducted a systematic review on FMT in adults from lean donors, finding increased Roseburia and Clostridium after FMT.

Heterogeneity in the data found: Some studies brought experiments without much scientific basis, such as berberine supplementation (Ilyas et al, 2020 (61)), products herbais (Ejtahed et al 2019 (62)), teas (Bond et al, 2019 (63)). Studies with fecal transplantation also had moderate quality data. In addition to these, the analysis of short-chain fatty acids by Kim et al, 2019 (64) showed that obese individuals had larger acetate concentration in feces and lower concentration of Bacteroidetes and Firmicutes in relation to non-obese individuals. The article by Lane et al, 2020 (55) showed improvement in BMI, weight and waist circumference after vled diet with ultra-processed products, in addition to dand improvement in biochemical markers (glycemia and fasting insulin, RI, HbA1c, LDL, HDL, total cholesterol, triglycerides and plasma leptin), but with a decrease in bacteria producing butyrate and Bifidobacterium. Antibiotic exposure in children aged 24 months to 12 years, assessed by Rasmussen et al, 2018 (65), showed that single antibiotic treatment did not increase risk of overweight or obesity, but repeated exposure was associated with a slight increased risk.

4 DISCUSSION

The reading of this article allowed us to elucidate a little better the relationship of the microbiota in obesity. The methodologies found were diverse, hindering practical conclusions. When I started the search, I imagined that I would find a scenario of greater practical possibilities, but everything is still inconclusive. It is certain that these conclusions are a difficult task, because human beings are very different. There are many variables to be taken into account in the relationship between microbiota and weight gain, such as dietary patterns, ethnic origin and influence of environmental stress. In addition, data on the amount and time that supplementation with symbiotics, probiotics or association should last. It is also difficult to extrapolate how the effect of this supplementation occurs because obesity improves. Are probiotics/prebiotics/symbiotics indispensable? Or just amplifiers of current treatments for obesity, such as lifestyle change, medications and bariatric surgery?

There is also a lack of data on which bacterias are indispensable. Some studies have shown controversial results, which may be due to individual differences in the microbiota. Is it really worth supplementing the microbiota with selected species? Or can "general" probióticas measures, such as consumption of probiotic-rich foods such as yogurts and fermented, make more sense? Can associating already probiotic foods with extra probiotic supplementation help? Does all this only work in a context ofnon-inflammatory feeding, without sugars and farinaceous, made from natural foods? There are many questions that still need to be answered in new studies in the future. For now, we know that microbiota supplementation can help in the conditions of overweight and obesity.

5 CONCLUSION

The rise in obesity in the world has led to increased research to solve this problem. The search for the relationship between the intestinal microbiota and obesity has emerged in recent years as a possible alternative for treatment. Several articles showed that there is direct influence of the microbiota on obesity. There are still not so clear data on the relationship of the intestinal microbiota with diabetes and metabolic syndrome. Some studies have also dealt with pregnancy and microbiota. As for surgical interventions, some studies have shown clear changes in the microbiota after bariatric surgery, with different bacteria associated with different surgical methods (bypass, Roux Y, balloon). Supplementation with probiotics also had interesting results. The influence of diet on the microbiota has also been shown in the studies, although it has not yet been fully elucidated. It is possible to conclude that the intestinal microbiota plays a still not very clear role in the pathophysiology of obesity. Further studies are needed to qualitatively elucidate these changes.

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