Insight about Colonic Microbiota Imbalance and Obesity

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Abstract

Since the 1990s, nutritionists have concluded that poor food hygiene, as well as environmental and food pollution, are the cause of the major serious diseases affecting humanity: overweight and obesity, which induce persistent systemic pro-inflammatory status, and hence all complications metabolic disorders, cancers, joint diseases, skin disorders, psychological disorders. The human body hosts a large number of microbes, including bacterial, fungal and protozoal microorganisms, which together constitute our microbe. Dysbiosis, generated by a sedentary lifestyle, consuming highly industrialized food, and non-compliance with the mass program, can lead to obesity, with a decrease in quality of life and shortening it. Obesity and metabolic disorders related to obesity are characterized by specific changes in the composition and function of the human intestinal microbe. Among the possible strategies for preventing and/or treating obesity, the microbiota is intended to restore or modulate its composition by consuming probiotics, prebiotics or both (synbiotics).

Keywords: dysbiosis, diet, microbiota, obesity

Introduction

The consumer's acceptance of food is of a subjective nature, based in particular on the pleasure of eating. The pleasure of consuming certain foods is conditioned mainly by their sensory qualities, the culture and physiological state of the consumer, as well as by other contextual factors (Savona et al., 2017).

Today, more and more people suffer from a severe imbalance of intestinal microflora, dysbiosis, with serious health effects, and appearance of overweight and obesity. The whole organism is affected by the alteration of this microbiota, which is multifactorial (changes in the human diet, now too rich in ultra-processed foods, smoking, lifestyle, stress, pathogens, antibiotic use, radiation, etc) (Singh et al., 2017).

Obesity is a metabolic abnormality, manifested by an increase in body fat mass as a result of a positive energy balance, with the prevalence of lipogenesis relative to lipolysis[7]. However, recent evidence suggests that obesity is a more complicated disease associated with intestinal dysbiosis in both mice and humans (Arslan, 2014).

In 2016, more than 1.9 billion adults, 18 years and older, were overweight, and of these over 650 million were obese. 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. Most of the world's population live in countries where overweight and obesity kills more people than underweight. 41 million children under the age of 5 were overweight or obese in 2016. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 (WHO, accessed: January 2019).

Based on the latest estimates in European Union countries, overweight affects 30-70%

and obesity affects 10-30% of adults. (WHO, accessed: May 2019). For Romania, the available epidemiological data estimate a prevalence of overweight to be 31% of the adult population and the prevalence of obesity to be of 21.3% (Roman el al., 2015).

Obesity is a serious public health problem because, in addition to lowering the quality of life (Taylor et al., 2013) and life expectancy, there is an increased risk of chronic diseases such as type 2 diabetes, cardiovascular disease, hypertension, coronary artery disease (Nuberg et al., 2018), certain cancers (Lauby-Secretan et al., 2016), and psychological problems. For society as a whole, obesity has direct and indirect costs that burden the health system and social resources (Tremmel et al., 2017).

In obese individuals, there is a general decrease in bacterial diversity in the intestines (De Gruttola et al., 2016). In most studies, both in humans and animal models, obesity appears to be associated with a modified ratio between *Bacteroidetes* and *Firmicutes*, showing a decrease in the number of *Bacteroidetes* while *Firmicutes* increased (Turnbaugh et al., 2006; Hildebrandt et al., 2009).

Microbial colonization of the human intestine since the early days of life is a complicated complex process, resulting in a symbiotic relationship with the host that maintains its health and homeostasis.

The four dominant bacterial phyla in the human gut are *Firmicutes*, *Bacteriodetes*, *Actinobacteria* and *Proteobacteria*. Most bacteria belong to the genera *Bacteroides, Clostridium, Faecalibacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus*, and *Bifidobacterium*. Other genera, such as *Escherichia* and *Lactobacillus*, are present to a lesse extent. Species from the genus *Bacteroides* alone constitute about 30% of all bacteria in the gut, suggesting that this genus is especially important in the functioning of the host (Guarner et al., 2003). In the healthy young intestine, the microbiome has the following dominant composition: *Bifidobacterium, Escherichia coli, Clostridium, Bacteroides, Streptococcus, Enterococcus,* and *Actinomycetes*. Bifidobacteria are the first to colonize the human intestine, constituting the dominant microbial of the infant. The newborn is exposed to beneficial bacteria when passing through a natural canal of birth and then through breast milk. Communal microorganisms can enter maternal breast milk from the mammary skin of area or through the bloodstream after translocation from the maternal intestine to mammary glands (Le Doare et al., 2018).

Obesity and its triggering factors

Gestation and early life. Among the factors criminalized in an individual's predisposition to obesity are the environmental and nutritional influences in critical developmental periods. Maternal body weight during pregnancy can influence the body size, shape and body composition of the fetus. Infants born to mothers with type 2 diabetes or who have smoked during pregnancy are at greater risk of being overweight as children and adults. Breastfeeding is associated with a lower risk of overweight (Lifschitz et al., 2015).

Childhood and adolescence. The predictive value of childhood obesity varies with age at the onset of obesity. Obesity during childhood, usually prevalent in adulthood, especially in obese families. Obesity during adolescence is associated with severe obesity in adults with its metabolic complications (You et al., 2016).

Adults. In spite of the importance of childhood and adolescent weight, most overweight people develop their problem in adult life through changes in global food supply, including the availability of cheap, palatable, convenient, energy-dense foods, sedentary lifestyle, sleep deprivation, cessation of smoking. The relationship between diet and obesity may also involve the gut microbiome. Epidemiological data suggest that a diet high in fat and sugar is associated with obesity. In a prospective evaluation of three cohorts (120,877 men and women), increased consumption of potato chips, potatoes, sugar-sweetened beverages, unprocessed red meat and processed meats was directly associated with weight gain (Mozaffarian et al., 2011).

Physiological critical periods such as puberty, pregnancy, menopause - may be accompanied by obesity.

Genetic factors. Their importance lies in the family aggregation of cases of obesity. There are monogenic conditions that lead to obesity, some associated with dysmorphic features (Prader-Wili S, Bardet-Biedl S, etc.), most of which are due to mutations in genes of the leptin-melanocortin

system (POMC, MC4-R, leptin and its receptor). However, obesity occurs in most cases due to subtle alterations of interactions between genetic and environmental factors (multifactorial determinism). Heritability ranges from 0.6 to 0.9. The newest "whole genome scan" population identifies certain common polymorphisms in the population as associated with an increased risk of obesity: a SNP (mononucleotide polymorphism) near the INSIG2 (insulin-induced gene 2) gene revealed at 10% of the population, a variant of the FTO gene (fat mass and obesity associated) may explain 22% of common obesity, according to a study. Mutations in the heterozygous form of the MC4-R (melanocortin-4 receptor) gene in the β3-adrenergic receptor or PPARγ2 (Peroxisome proliferator-activated receptor) gene, a nuclear transcription factor having a key role in differentiating adipocytes, are other examples of genes involved in simple obesity (Huvenne et al., 2016).

Psychogenic and nervous factors such as "binge eating" (psychiatric condition characterized by uncontrolled excess food, especially in the evening) or night feeding episodes.

Drugs. Some drugs administered over a longer period of time cause obesity. These include the following: contraceptives, antidepressants (amitriptyline, doxepin, lithium, imipramine), antipsychotics (chlorpromazine, risperidone, clozapine), antiepileptics (carbamazepine, valproate), steroids (glucocorticoids, estrogens), serotoninergic (ciproheptadine) antagonists, insulin, thiazolidinediones (administered inappropriately). The mechanisms by which they produce obesity are those that stimulate appetite.

Metabolic and endocrine factors, such as: hypothyroidism; insulinoma in which hyperinsulinism and excessive food intake promotes the accumulation of fats; the hypercorticism that actually causes a redistribution of adipose panicle and a moderate weight gain; excess cortisol favors adipocyte hypertrophy hypertrophy and fat redistribution, plus muscle protein destruction that emphasizes the appearance of obesity, the activity of lipoprotein lipase is more pronounced under the action of cortisol in visceral tissue than in the subcutaneous tissue in women, as well as to the man; hypothalamic disorders - traumas, tumors, inflammations are often accompanied by obesity due to the hunger, satiety and energy consumption control centers; hypogonadism is often accompanied by obesity; weight gain occurs mainly after puberty; polycystic ovary syndrome associates a firm obesity without creases, associating signs and symptoms of ovarian virilism; adult GH deficiency is accompanied by visceral obesity.

Intestinal microbiota is influenced by several factors: ability of bacteria to bind to specific enterocyte receptors, altering the functions and morphology of intestinal villitis; food spectrum and diet: a permanent intake of meat favors the growth of a microflora of putrefaction, while a fiber and vegetable-rich regime determines a fermentative microflora; gastric acidity: in the case of hypoacidity/achlorhydria the number of bacteria multiplies by about 10,000 times in the upper intestine (duodenum); this microflora becomes anaerobic, rich in lactobacilli, so a pathological state; active peristalsis of the upper small intestine tends to move microflora towards the terminal end of the digestive tract; interactions between bacteria, either stimulatory or inhibitory have tendency to modify species structure of the microbiota; IgA secreting antibodies produced by intestinal wall plasma cells inhibit microbial proliferation and prevent the adhesion of bacteria to the mucosal epithelium; mucus prevents the action of bacteria, while protecting other bacterial species against the destructive action of hydrochloric acid, digestive enzymes, and digestive enzymes (Thursby and Juge, 2017).

One of the roles of colon microbiota is to ferment the substances from the diet that could not be digested in the small intestine. Non-digested components are starch-resistant, non-ammonium polysaccharides (cellulose, hemicellulose, oligosaccharide, protein, etc.).

Intestinal Microbiota

The intestinal microbiota consists of a complex ecosystem of microorganisms, a number of which grows from 10^3 germs/ml in the stomach to 10^4-10^6 germs/ml in the small intestine, up to 10^{12} germs/ml in the colon, belonging to over 500 different species (Alberoni et al., 2018). The human digestive system contains about 10^{14} bacteria, that is, ten times more bacterial cells than its own cells. For each human gene, there are 100 bacterial genes that makeup metagenome (Grice and Segre, 2012).

When born naturally, a newborn's intestine is populated with a mother's natural birth microflora, thus borrowing the characteristics of the family microbe, being extremely important for the future development of the child's microbiota, maturation of the immune system, resistance to infections, autoimmune diseases, and generally for his health for the rest of his life. It seems that each family develops a specific microbiota that is inherited, so an obese mother will transmit a microbiota that predisposes the child to obesity (Neu et al., 2011). Natural breast milk stimulates the strong growth of *Bifidobacteria*, while artificial feeding stimulates the development of *Clostridium, Bacteroides, Streptococcus* genes. With aging, the intestinal microbial structure changes, decreasing *Bifidobacteria*, while *Lactobacilli, Enterococci, Enterobacteria* and *Clostridia* increase in number. This stimulates the development of pathogen-toxic processes that increase the risk of overweight, cancer and liver dysfunction (Mueller et al., 2015).

Microflora varies quantitatively depending on segments of the digestive system: oral microflora has an average abundance; gastric acid is relatively low because gastric acid destroys about 99% of germs; microflora being more numerous in the thin lower intestine, 10^6-10^7/ml and extremely abundant in the large intestine, 10^9-10^{11}/ml, so that bacteria represent more than half the weight of the feces. Microflora varies qualitatively depending on the segmental digestive tract: in the upper part of the digestive tract (the oral cavity) there are exclusive aerobic germs, which will be replaced by anaerobic germs, the predominant colon (over 99%); in the duodenum and jejunum there are aerobic germs: *Enterococci, Streptococci, Staphylococci, Enterobacter, Klebsiella, Citrobacter, Pseudomonas*; the anaerobic germ predominates in the ileum portion, and in the colon the microflora is strictly anaerobic (Cooper, 2018). It is estimated that the microbiota consists of over 400 bacterial species (Grice and Segre, 2012).

Microbiota, in terms of bacterial colonization capacity, can be:

- passage microbiota, including bacteria that are unable to attach to the intestinal structures and to develop in this environment;
- resident microbiota able to colonize and develop in intestinal structures. This microflora is found in the terminal intestinal tract and in the colon (Jandhyala et al., 2015).

Every day, 60-80 g of non-digested foods, which are partially degraded by lactic acid fermentation and short chain fatty acids (SCFAs), mainly represented by acetate, propionate, and butyrate, reach the adult colon. It results from the fermentation process and carbon dioxide, hydrogen, methane, phenolic compounds, amines, ammonia. In the first part of the colon, mainly lactic acid and short chain fatty acids are produced, while in downstream and sigmoid colon phenolic and nitrate compounds are generated, causing colon cancer, ulcerative colitis and other gastrointestinal diseases. Short-chain fatty acids produced by fermentation have an important local beneficial effect, providing energy to epithelial cells (colonies), lowering pH, increasing calcium, iron and magnesium absorption, with positive influences on glucose and lipid metabolism in the liver (Besten et al., 2013).

Intestinal microbiota can be found in two physiological states:

- Physiological status: when microflora is saprofit type and between it and the intestines establishes a symbiosis relationship, providing the human host with various benefits: completing digestion of food, degrading biliary pigments, participating in vitamin K biosynthesis, inhibiting growth of yeasts (*Candida Albicans*) and fungi, providing polyamines that in physiological doses feed enterocytes (children contribute to maturation of the digestive system).
- Pathological-dysbiosis status: when microflora becomes pathogenic, by proliferation in excess of pathogenic germs that release toxins (*Staphylococci, Colibacilli*) or damage the mucosal epithelium, crossing it as in case of *Salmonella, Shigella*; aerobic microorganisms developed in duodenal excess are responsible for diseases such as ankylosing spondylitis (*Klebsiella*), rheumatoid arthritis (*Proteus Mirabilis*), Basedow-Graves disease (*Yersinia enterocolitica*), gastroduodenal ulcer and some cancers (*Helicobacter Pylori*).

Dysbiosis-related diseases

Diseases strongly associated with intestinal microbial imbalance are irritable bowel syndrome, colon inflammatory diseases, colon cancer, gastroenteritis, neonatal enterocolitis, pseudomembranous colitis, intestinal cystitis pneuma-

tosis, overweight, and obesity (Carding et al., 2015).

Microbiota has an essential role in shaping oral tolerance. Bacterial lipopolysaccharides facilitate induction of oral tolerance and mediate the differentiation of intestinal Th cells into cells with Th2 phenotype and possibly Th3. It is known that antibiotic prescription for children is associated with the occurrence of mediated IgE allergies due to the adverse effects of antibiotics on normal intestinal microflora. Antibiotics interfere with the installation of oral tolerance and allergy development. Recent studies have shown that food-specific IgG antigens circulate in the blood of children and adults. IgG antibodies appear early, before the age of 3 months and grow up to 5 years of age. Interestingly, over the same period of time, food-specific IgE antibodies are significantly decreasing. IgG1 and IgG4 antibodies, specific isotypes for eggs, wheat and cow's milk can be detected in both healthy individuals and those suffering from food allergies (Castener et al., 2018).

These antibodies become dangerous when intestinal mucosa suffers lesions produced by pathogenic microflora, viruses, bacteria. Thus, a condition of inflammation that increases intestinal permeability (permeable intestinal syndrome) occurs and allows partially digested proteins, peptides to reach sub-mucosal microcirculation. Immune system exposure GALT = lymphoid tissue associated with intestine, to soluble food antigens, normally induces oral tolerance. If oral tolerance is compromised by dysbiosis, more than 5% of the population develop IgE, IgG and TGF-β mediated adverse immunological reactions. Thus, the compromise of immune regulation of pathogenic microorganisms response in microbiota degenerates into the occurrence of pathologies spread today: irritable bowel syndrome, Crohn's disease, ulcerative colitis, obesity (Cox et al., 2015).

In overweight / obese humans, low fecal bacterial diversity is associated with more marked overall adiposity and dyslipidemia, impaired glucose homeostasis and higher low-grade inflammation (Davis, 2016). Bacteroidetes prevalence is lower in obese people, with this proportion increasing along with weight loss based on a low-calorie diet. Lactobacillus and Clostridium species are associated with insulin resistance, with Lactobacillus positively correlated with fasting glucose and glycated hemoglobin levels, whereas Clostridium showed a negative correlation with these parameters (Sun et al., 2018).

Certain bacteria secrete enzymes that act as hydrolyses of bile salts (for the formation of primary bile acids), being able to activate signaling pathways and gene expressions involved in the metabolism of lipids, carbohydrates and cholesterol in the body. The global bile acid signaling capacity is currently unclear. Bile acids are natural ligands for a nuclear receptor, the farnesoid X receptor, and the plasma membrane-bound bile acid receptor TGR5. By activating these receptors, bile acids regulate glucose, lipid and energy homoeostasis. Mechanisms of the interaction between microbiota and host that have been characterized thus far include an increase in energy harvest, modulation of free fatty acids—especially butyrate—of bile acids, lipopolysaccharides, gamma-aminobutyric acid (GABA), an impact on toll-like receptors, the endocannabinoid system and "metabolic endotoxinemia" as well as "metabolic infection" (Harsch et al., 2018).

Most of the human microbiota is composed of *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria,* and *Verrucomicrobia*, and 90% of all bacterial species are *Bacteroidetes* and *Firmicutes* (Tang et al., 2017). The composition of bacterial diversity appears to change between the weak and the obese, increasing the number of *Firmicutes* at the expense of *Bacteroides* in obese patients (Karlsson et al., 2013).

The composition of the intestinal microbiota is strongly affected by dietary patterns. A high fat, high-sugar diet "in Western-style" increases the relative abundance of *Firmicutes* at the expense of *Bacteroids* (Turnbaugh et al., 2009).

Manipulation of the microbiota may present new pathways for therapeutic interventions designed to prevent or treat obesity and associated metabolic disorders. These strategies include dietary manipulation, such as the use of prebiotics, probiotics or synbiotics, as well as transplantation of fecal microbial communities.

Prebiotics - are the food ingredients that selectively stimulate the development and activity of *Lactobacilli* and *Bifidobacteria*. Prebiotics are low-grade carbohydrates (n=2-60), which are indigestible because the human intestines do not contain the specific enzymes needed to depolymerize them. Prebiotics are

unchanged in the colon where they form the nutritional substrate for beneficial probiotic bacteria, giving them competitive advantages, stimulating their development, to the detriment of pathogenic bacteria. The most common prebiotics in human food is inulin, oligosaccharides, fructooligosaccharides (FOS), galactooligosaccharides, xilo-oligosaccharides, maltodextrin, polyfructosans. Daily consumption of 15 g fructo-oligosaccharides for 2 weeks significantly changes the balance of beneficial species in the human colon. FOS determines the increase in the number of beneficial *Bifidobacteria* and inhibits the development of pathogenic and rotting microflora of *Clostridia, Fusobacteria,* and *Bacteroids* (Slavin, 2013). Gut hormones, such as peptide-1 (GLP-1), play a critical role in transmitting nutritional and energy status signals from the gut to the central nervous system to control food intake (Lutz, 2016). In a double-blind, placebo-controlled study in 16 adults, administering an inulin-like prebiotic fiber was associated with a significant decrease in hunger and significantly higher satiety after a meal and an increase in GLP-1 in the comparator plasma with a similar placebo (dextrin/maltose) tasting (Cani et al., 2009).

Probiotics - are living microorganisms, such as *Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacteria*, found in fresh fermented milk products (white sugar-free yogurt and added fruit or flavor, sour, kefir, beaten milk, undeclared) of probiotic or lyophilized food in nutritional supplements able to colonize the colon with antibacterial action on pathogenic microflora (eg *Helicobacter Pylori*), inducing beneficial effects on the health of the host organism (Shi et al., 2016). A randomized controlled trial in humans demonstrated that the consumption of fermented milk containing *Lactobacillus Gasseri* probiotic for 12 weeks resulted in a significant reduction in abdominal visceral area compared to the control subjects (Kadooka et al., 2013). In contrast, other studies have shown no benefit of probiotics for the prevention/treatment of obesity (Guine et al., 2016).

Synbiotics - Foods or dietary supplements that contain both probiotic microorganisms and prebiotic fibers are synbiotic functional foods needed to prevent disease and the health of the body. Studies suggest that synbiotics may be effective in altering the composition of the microbiota. The symbiotic combination of oligofructose (SYN1) and *Lactobacillus Rhammnosus* GG and *Bifidobacterium Lactis* Bb12 enginavirinum inulin for 12 weeks resulted in a 16% and 18% increase in *Lactobacillus* and *Bifidobacterium* and a 31% decrease in the number of *Clostridium Perfringens*.

The composition of human intestinal microbiota is in a state of dynamic evolution, suffering qualitative and quantitative changes with age. After birth, the gastrointestinal tract is sterile, being progressively colonized by *Bifidobacteria, E. Coli, Streptococci*, optionally anaerobic. In the upper part of the colon, microflora is predominantly anaerobic, consisting of *Enterobacteria, Streptococci, Staphylococci, Lactobacilli, Propionylbacteria* and *Bacilli.* In the lower part of the colon, microflora becomes strictly anaerobic, consisting of *Bacteroides, Eubacterium, Peptococci, Bifidobacterium, Fusobacterium, Clostridium species* (Shi et al., 2016). Food is the main bearer of information taken from the environment, interacting with its own genetic information of the body. Dysbiosis as a pathological condition is today unconscious and therefore undiagnosed and untreated. Ignoring dysbiosis, however, has serious health and long-term consequences, generating a polymorphic pathology such as irritable bowel syndrome, Helicobacter pylori infection, hepatic cirrhosis, non-alcoholic steatohepatitis, ankylosing spondylitis, Alzheimer's disease, eating disorders, obesity, metabolic syndrome and type 2 diabetes.

Whole grains

Cereals are the basis of the diet of the planet's inhabitants, being represented by eight basic cereals: wheat, corn, rice, barley, sorghum, oats, rye, millet. The change in lifestyle lifestyle has led to a high consumption of grain as well as industrially deficient in the vitamin B group.

Whole grains have great nutritional and bioactive properties due to their fractions, bran and germ, which contain unique health-promoting bioactive components exhibiting significant antioxidant activity [18] with ferulic acid as its major antioxidant. Grain bran is a major source of phenolic acids - antioxidants, fibers and minerals (Calinoiu et al., 2018). Whole grains has been shown to reduce the risk of metabolic disease, possibly via modulation of the gut microbiota.

A recent meta-analysis concluded that adults consuming more than three servings of whole grain had a consistently lower risk of obesity (Ye et al., 2012). Consuming whole grains is postulated to decrease chronic disease risk, in part due to beneficial effects on body weight regulation (Jonnalagadda et al., 2011). Observational studies strongly suggest that consuming ~3 servings/d whole grain (~48 g) is associated with lower BMI and central adiposity relative to low or no whole grain consumption, and higher WG intakes may attenuate weight gain (Calinoiu et al., 2018). There have been several studies that report changes in the gut microbiota following a whole grain intervention. Most studies report only modest to no changes in gut microbiota composition (Cooper et al., 2017).

Diet therapy is the treatment of choice for dysbiosis. Changing dietary habits sustain by a proper educational community intervention (Guine et al., 2016) and adopting a diet rich in live foods with high levels of active food enzymes, fruits, vegetables, seeds, nuts, germs, and herbs, consumed in the raw state and in their emergence season can restore a physiological microbiota (Badau et al., 2018).

Conclusion

In conclusion, negative influence of the microbiota by consumption of industrially-added food, especially with artificial preservatives, but also by inadequate antibiotic treatments, leads to an imbalance in microbiota concretized in the state of dysbiosis. The human body now comes in contact with over 40,000 different "toxins" (heavy metals, pesticide residues, chemical fertilizers, antibiotics, hormones, genetically modified organisms, plastics, motor vehicle emissions, food additives, artificial flavors, cosmetic compounds, products of chemical-industrial activity, artificial electromagnetic fields, etc.). Thus, digestive system, liver, kidneys, or immune system are overstretched and often overcome, leading to general intoxication, enzyme blocking, and ultimately disease.

In order to return to the normal state of oral-gastrointestinal microflora, a healthy lifestyle must be followed, consuming raw, less processed foods, incorrect use of antibiotics, mouth disinfectants and other substances or foods that can affect their balance.

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