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Gut Microbiota and Body Weight – A Review

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Abstract

The link between gut microbiota and insulin resistance has an important clinical impact, people affected by dysbiosis having a predisposition for developing: obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease, cancers, cardiovascular, neurodegenerative and psychiatric diseases. Dysbiosis may lead through chronic inflammation to obesity and metabolic syndrome. We carried out a systematic review of the studies dedicated to the role of gut microbiota in weight gain and obesity. A systematic literature search of recent data published in electronic databases, was performed, using as search phrase: "gut microbiome and body weight and obesity". Studies that contained no data about the influence of gut microbiota changes on obesity were excluded. Western diet, antibiotic use in childhood, excessive maternal pre-pregnancy weight, Cesarean delivery, and testosterone deficiency are triggers of the alteration of microbiota and subsequently the appearance of obesity. Predominance of *Firmicutes* and anaerobic genera, changes in the mycobiome and viral intestinal population are implied in the etiology of obesity. Prebiotics, polyphenols, different herbs, medication (antidiabetics, calcium), physical exercise, rich fibre intake and bariatric surgery are the most important therapeutic options. Personalized dietary treatments, antiviral agents and mycobiome manipulation would represent the new target in treating obesity. Any change of the quantitative and qualitative composition of microbiota has influence on the components of metabolic syndrome, so any management strategy for the treatment or prevention of obesity in children and adulthood should have the microbiome as target.

*Keywords***:** diabetes, metabolism, microbiota, obesity

Introduction

Gut microbiota actually represents an active biomass, from a metabolic point of view, any change in the composition and/or abundances of different bacterial species may predict the progression toward metabolic syndrome. It has an important role in maintaining homeostasis; although the direct relationship between microbiota and various disorders is still unclear, predominance of some phyla and quantitative and

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both qualitative imbalance of different species has an important impact on creating a chronic inflammatory state, which leads to obesity and diabetes. The human gastrointestinal microbiota consists of 10^{14} microorganisms/ml of luminal content, belonging to over 5000 bacterial species, 90% of them belong to the *Bacteroidetes phyla*. The link between gut microbiota and insulin resistance has an important clinical impact, people affected by dysbiosis have a predisposition for developing: obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular, neurodegenerative and psychiatric diseases (mental illness, dementia, depression), cancers (gastric, colorectal, esophageal, liver and pancreatic carcinomas) (Bruce-Keller et al., 2015; Koh et al., 2016; Saad, Santos, & Prada, 2016). The aim of this paper is to review the mechanisms of implication of microbiota in obesity, as well as the possible therapeutic strategies beneficial to lose weight, and to prevent/treat the components of metabolic syndrome by acting on the microbiome. The importance of microbiota implication in obesity has been described in different reviews up to now, among them the most important are: Saad et al. (2016), Oh, Ahn, and Cho (2016), Nehra, Allen, Mailing, Kashyap, and Woods (2016), and Ghazalpour, Cespedes, Bennett, and Allayee (2016).

Methods

A systematic literature search of recent data published in electronic databases, including PubMed and ISI Web of Science, was performed for all studies assessing the influence of gut microbiota changes on obesity (from 1st January 2015 to 1st October 2017). The search strategy included text terms and Medical Subject Headings (MeSH) for microbiota and obesity: "gut microbiome and body weight and obesity". The "related articles" function in PubMed was also used to identify articles not found in the original search.

Inclusion Criteria

The inclusion criteria used were: abstracts and full-text journal publication, including data about pathogenetic mechanisms of gut microbiota in inducing obesity, and treatment options in the metabolic syndrome. Papers in English, French, German and Polish were included in the study, or in any other language, but with an English abstract. The titles and abstracts of all identified studies were reviewed and then confronted by independent authors (between 1st January 2015 to 31st December 2016 by: ID and FR, and between 1st January 2016 to 1st October 2017 by: AC and DLD) according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) criteria.

Exclusion Criteria

Studies were excluded if they were editorials or letters to the editor, or did not meet the inclusion criteria; these were papers containing general literature data about gut microbiota and obesity, but without mentioning any study or any precise therapeutic option for weight gain.

Results

The first search resulted in a total of 201 articles. After reviewing the abstracts, we kept 184 studies, which described the mechanisms of the gut microbiota implication in obesity and therapeutic options and thus met our inclusion criteria. Included articles were published between 1st January 2015 and 1st October 2017. The 17 excluded articles mentioned the implication of gut microbiota in obesity in general, or did not mention anything about the treatment, or did not have an available abstract.

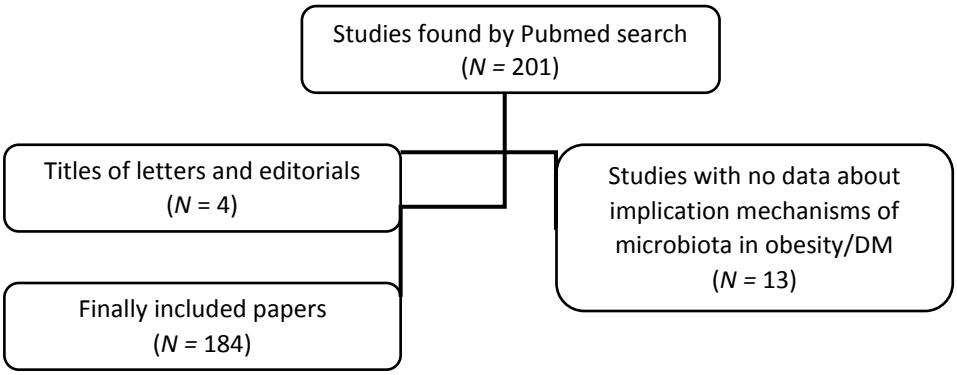

Figure 1. The Selection of Papers for this Analysis.

Implication of Microbiota in Human Obesity

Etiopathogenesis

Davis, Yadav, Barrow, and Robertson (2017) showed that Westernized diet proved to be a more severe factor in causing dysbiosis as compared to an overweight or obese body mass index (BMI). One of the important triggers of childhood obesity is the antibiotic use, which increases the adipogenesis and alters the microbiota composition (Li, Wang, et al., 2017).

Table 1

Obesity Studies on Humans

Study	*No. of patients*	*Microbiota spp.*	*Outcome*	*Influence/ modulation on/of microbiota*
Miller et al. (2017)	355 per- and postmenopausal women		ODMA non-producer phenotype	
Menni et al. (2017)	1632 healthy females (TwinsUK)	Ruminococcaceae Lachnospiraceae Bacterioides	high microbiome diversity, high-fibre intake and OTUs	16S ribosomal RNA gene sequence
Bergeron et al. (2016)	52		cardiovascular risk	TMAO
Betancourt-Garcia et al. (2017)	NR		NAFLD	
Davis et al. (2017)	81	Bacteroidetes-Firmicutes ratio	Westernized diet	
Prescott (2016)	NR		early-nutrition	
Palleja et al. (2016)	13 morbid obesity	E. coli, Klebsiella pneumoniae, Veillonella spp., Streptococcus spp., Alistipes spp., Akkermansia muciniphila	Roux-en-Y gastric bypass	microbiota diversity increase
Mueller et al. (2016)	74 neonates	Bacteroides Enterococcus, Acinetobacter, Pseudomonas, Hydrogenophilus	vaginal vs. Cesarean birth	
Mayorga Reyes et al. (2016)	young adults	Bacteroides thetaiotaomicron Prevotella, Faecalibacterium prausnitzii, Clostridium leptum Bifidobacterium longum	diet rich in unsaturated fatty acids and fibre	high abundance of B. longum and Bacteroidetes
Emoto et al. (2016)	119	high Lactobacillales low Bacteroidetes (Bacteroides＋ Prevotella)	coronary artery disease	

Study	*No. of patients*	*Microbiota spp.*	*Outcome*	*Influence/ modulation on/of microbiota*
Barczynska et al. (2016)	5 children	Firmicutes, Bacteroidetes, Actinobacteria	fibre preparations	
Radilla-Vázquez et al. (2016)	64 young Mexicans	Clostridum leptum Lactobacillus Prevotella Escherichia coli	endotoxemia	body temperature elevated
Moreno-Indias et al. (2016)	NR	bifidobacteria Lactobacillus F. prausnitzii Roseburia	red wine polyphenols	prebiotic
Ignacio et al. (2016)	84 children	Bacteroides fragilis Clostridium Bifidobacterium Escherichia coli	BMI-phyla correlation	
Angelakis et al. (2015)	10	Firmicutes Actinobacteria	duodenal microbiota	anaerobiotic genera
Kasai et al. (2015)	56 Japanese	Blautia hydrogenoto-rophica Coprococcus catus Eubacterium ventriosum Ruminococcus bromii Ruminococcus obeum		high Firmicutes/ Bacteroidetes ratio
Bernardi et al. (2015)	2063 young Brazilian adults		Cesarean delivery	BMI
De Lorenzo et al. (2017)	60 women		psychobiotics	SIBO, orocecal transit time
Cassidy-Bushrow et al. (2015)	639		delivery mode-BMI relationship	pets

Note. NR = not reported; ODMA = O-desmethylangolensin; OUT = operational bacterial taxonomic units; IMAO = trimethylamine-N-oxide; MUFA = mono-unsaturated fatty acid; PUFA = polyunsaturated fatty acids.

Table 1 described human studies that concerned different types of species of microbiota and their change in children and adults, but also their impact on weight gain, diabetes mellitus and cardiovascular diseases.

O-desmethylangolensin (ODMA) non-producer phenotype (individuals that are not capable of metabolizing the soy isoflavone daidzein to ODMA) was associated with obesity in peri- and post-menopausal women (Miller et al., 2017).

Non-alcoholic liver fatty disease (NAFLD) combined with portal vein toxins secondary to an altered microbiota led to early occurrence of non-alcoholic steatohepatitis (NASH) in children, through the following mechanisms: increasing obesity in children, gut-liver-axis-dysfunction, perturbations of trace element homeostasis, and oxidative stress due to genetic changes – allele substitution in the PNPLA3 gene (Betancourt-Garcia et al., 2017; Clemente, Mandato, Poeta, & Vajro, 2016).

Gut Changes in Pregnancy

Excessive maternal pre-pregnancy weight associated with vaginal delivery leads to altered microbiota of the child and consequently an altered metabolism (Mueller et al., 2016). Cesarean delivery was associated with a higher BMI but there was no correlation found with glucose, insulin resistance, cholesterolemia and triglyceridemia levels in a Brazilian study (Bernardi et al., 2015). Caesarean section-born children without a pet animal at home had a higher risk of obesity at the age of 2 years, without knowing the exact mechanism (Cassidy-Bushrow et al., 2015). Higher risk of neurodevelopmental disorders in children, including autism, has been associated with maternal obesity during pregnancy (Buffington et al., 2016). Dietary strategies including early nutritional exposures, with more tolerogenic conditions during early immune programming in small children reduces the risk of allergies and many inflammatory diseases (Prescott, 2016).

Gut Compositional Changes in Humans

Ignacio et al. (2016) showed that lean individuals have higher abundance of *Bifidobacterium spp.* compared with obese persons. Rich diet in unsaturated fatty acids and fibre induces in young adults abundant beneficial microbiota population, like *B.longum* and *Bacteroidetes* (Mayorga Reyes et al., 2016). Predominance of *Firmicutes* and anaerobic genera over the *Bacteroidetes* and *Actinobacteria* strains were found in obese children (Angelakis et al., 2015; Barczynska, Slizewska, Litwin, Szalecki, & Kapusniak, 2016). Central adiposity in young obese people had a corresponding subclinical endotoxemia (measured by serum lipopolysacharides concentration) with small amount of *E.coli* and hypertrygliceridemia (Radilla-Vázquez et al., 2016). Not only bacterial population is implied, but specific fungal composition of microbiota (mycobiome) was proven also to have importance in weight gain, *Mucor racemosus* and *M. fuscus* being more abundant in lean people (Mar Rodríguez et al., 2015).

Therapeutic Options

High diversity of microbiota, together with fiber intake and operational bacterial taxonomic units (OTUs), like *Ruminococcaceae* and *Lachnospiraceae*, proved to be associated with lower risk of weight gain in humans, independently of the caloric intake (Menni et al., 2017). Moreno-Indias et al. (2016) showed that moderate intake of red wine improved weight gain. Recent studies revealed that intake of selected psychobiotics modulated microbiota in preobese and obese women, but further research is needed in order to establish exact correlations (De Lorenzo et al., 2017). For children and adults, fecal transplantation represents a new way of managing severe obesity (Jayasinghe, Chiavaroli, & Holland, 2016).

Bariatric surgery represents the main option in morbid obesity. Gut microbioma diversity increased within the first 3 months after Roux-en-Y-gastric bypass surgery in obese patients, remaining high even one year later (Palleja et al., 2016).

Implication of Microbiota in Obesity – Experimental Studies on Animals

Etiopathogenesis

Noble et al. (2017) showed that especially early-life sugar consumption alters in rats the microbiota, independently of caloric intake, body weight or adiposity index. Artificial sweeteners, like saccharin and acesulfame-potassium disturbs the gut microbiota in mice inducing glucose intolerance, raising questions about their possible contribution to the epidemic of obesity and diabetes (Bian et al., 2017). Hypogonadism and androgen deprivation (castration) altered the cecal and fecal microbiota, increased plasma adiponectin irrespective of diet, and increased the risk factors for cardiovascular disease (obesity, impaired fasting glucose, high triglyceride amount in liver, muscle weight loss) in high-fat diet-fed mice (Harada, Hanaoka, Hanada, et al., 2016); testosterone deficiency altered the intestinal microbiome in mice, inducing abdominal obesity (Harada, Hanaoka, Horiuchi et al., 2016).

Table 2 described animals' experimental studies that concerned several types of species of microbiota and the change induced by different types of diet, but also the impact of pre/probiotics on weight gain and obesity reduction.

Experimental studies on mice showed that deficiency of intestinal mucin-2 and higher IL-22 levels offer protection from diet-induced NAFL and obesity (Hartmann et al., 2016). In line with human studies, hypogonadism represents also in mice a responsible factor for inducing cardiovascular diseases (Harada, Hanaoka, Hanada et al., 2016).

Table 2

Obesity Experimental Studies on Animals

Study	*Animal*	*No. of animals*	*Microbiota spp.*	*Outcome*	*Influence/ modulation of microbiota*
Xu et al. (2017)	mice	30	Blautia bacteria Desulfovibrio bacteria	Montmorillonite	prebiotic
Li, Lauber, et al. (2017)	dogs	63	Cl. hiranonis, Cl. perfringens, Ruminococcus gnavus	HPLC diet	decrease Bacteroidetes/ Firmicutes increase Bacteroides/ Prevotella
McGavigan et al. (2017)	mice	14		Vertical sleeve gastrectomy	incr. Gammaproteo-bacteria + Enterococcus, decr. Adlercreutzia
Noble et al. (2017)	rats	42	Prevotella Lachnospiraceae incertae sedis Bacteroides Alistipes Lactobacillus Cl. sensu stricto Bifidobacteriaceae Parasutterella	early life sugar consumption	alteration independent of caloric intake, BMI
Wang et al. (2016)	mice	NR		green tea polyphenols	
Ansari et al. (2017)	mice	18	Bacteroidetes/ Firmicutes ratio	Chowiseungcheng -tang (CST)	anti-obesity effect
Kieffer et al. (2016)	mice	29		High-amylose-maize resistant starch type 2	incr. fecal nitrogen
Harada, Hanaoka, Hanada, et al. (2016)	mice	29	Firmicutes/ Bacteroidetes ratio Lactobacillus	hypogonadism, high CV risk	
Tung et al. (2016)	mice	NR		Piceatannol	anti-obesity effect
Yan et al. (2016)	rats	15	Lactobacillus, Bifidobacterium, Tenericutes, Ruminococcaceae	sitagliptin; anti-diabetic effect	correction of dysbiosis

Study	*Animal*	*No. of animals*	*Microbiota spp.*	*Outcome*	*Influence/ modulation of microbiota*
Basso et al. (2016)	rats	60	low Ruminococcus high Lactobacillus+ Collinsella	glandular gastrectomy	remodelling
Perry et al. (2016)	mice	NR		acetate production, parasympath. activation	
Wang et al. (2016)	mice	48		accelarated postna neonatal growth	increased risk for adult MS
Oh et al. (2016)	rats	NR	Gammaproteo-bacteria	ileal transposition surgery	
Park et al. (2015)	dogs	14	Proteobacteria	leptin, adiponectin, low serotonin	
Li, Wang, et al. (2017)	mice	30	high Firmicutes /Bacteroidetes	florfenicol and azithromycin	
Welly et al. (2016)	rats	30	Streptococcaceae, Rikenellacea	exercise vs. diet	
Harada, Hanaoka, Hanada, et al. (2016)	mice	NR	Firmicutes/ Bacteroidetes, Lactobacillus	castration	
Jiang et al. (2016)	rats	40	Bacteroidetes Firmicutes	apple-derived pectin	
Garcia-Mazcorro et al. (2016)	mice	21	Ruminococcaceae Lactobacillus spp	whole-wheat consumption	
Gooda Sahib Jambocus et al. (2016)	rats	36		Morinda citrifolia L. Leaf Extract	anti-obesity
Rajpal et al. (2015)	mice	30	Bacteroidetes Firmicutes	ceftazidime, vancomycin	
Yadav et al. (2016)	mice	18		viral fecal content	
Cluny et al. (2015)	mice	32	Methanobrevi-bacter spp	Tetrahydrocanna-binol	
Xie et al. (2015)	rats	NR	Lactobacillus Enterococci	Ligustrum robustum	anti-obesity
Zhang et al. (2015)	rats	134		berberine and metformin	decr. microb. diversity
Paul et al. (2016)	rats	104	Bifidobacterium Clostridium	prebiotics	pregnancy, lactation
Chaplin et al. (2016)	mice	NR		calcium- prebiotic	

Study	*Animal*	*No. of animals*	*Microbiota spp.*	*Outcome*	*Influence/ modulation of microbiota*
Hartmann et al. (2016)	mice	NR		intestinal mucin-2	NAFLD
Schneeberger et al. (2015)	mice	46	Akkermansia muciniphila		
Garidou et al. (2015)	mice	NR		ileum microbiota	
Chang et al. (2015)	mice	25	Firmicutes/ Bacteroidetes	Ganoderma lucidum	prebiotic
Bruce-Keller et al. (2015)	mice	30		dementia, depression	
Bian et al. (2017)	mice	20		saccharin	
Kang et al. (2017)	mice	24		chilli pepper	
Li, Wang, et al. (2017)	mice	NR	Rikenella	florfenicol, azithromycin	
Kulecka et al. (2016)	rats	64		fecal transplant	

Note. NR = not reported; MS = metabolic syndrome.

Gut Composition Changes in Animals

Greater abundance of *Firmicutes* and lower of *Bacteroidetes*, decreased *Bacteroidetes/Firmicutes* ratio and increased *Bacteroides/Prevotella* ratio were found in high-protein, low-carbohydrate (HPLC) diet-fed dogs; microbial gene networks were enriched by using HPLC diet, maintaining weight in dogs (Li, Lauber, Czarnecki-Maulden, Pan, & Hannah, 2017). Another beneficial bacteria, implied in metabolism, is *Akkermansia muciniphila*; its abundance is affected by age and high-fat diet (Schneeberger et al., 2015). It was proven that obese subjects have an increased viral fecal population (Yadav, Jain, & Nagpal, 2016).

Therapeutic Options

Many substances targeting the microbiota, like probiotics (live bacteria), prebiotics (oligosaccharides) and synbiotics (pre- and probiotics) have been found to have the capability of acting in order to prevent/treat obesity (Kieffer et al., 2016).

Studies on mice proved that Berberine, a Chinese herb, has lipid lowering effect, through several mechanisms: inhibition of bile salt hydrolase activity, increasing the taurocholic-acid, activation of intestinal farnesoid-X receptor and reduction of long-chain-fatty acid-uptake in the liver (Ziętak, Chabowska-Kita, & Kozak, 2017). Beneficial effects, obtained in rats by reduction of microbial diversity of the host, can be achieved by administration of Berberine in combination with Metformin (Zhang

et al., 2015). Among prebiotics, dietary lipid absorbent-montmorillonite (DLA-M) seems to prevent dysbiosis and obesity-related metabolic disorders by absorbing free fatty acids and endotoxins (Xu et al., 2017). Another prebiotic, the Chinese mushroom with anti-diabetic effect, Ganoderma lucidum, reduced obesity, inflammation in high-fat diet fed mice (Chang et al., 2015). Polyphenols from green tea (Wang, Zeng, et al., 2016) improved metabolic syndrome markers in mice, such as: reduced weight gain, adipocyte hypertrophy and liver steatosis in a dose-dependent manner, increasing the number of butyrate-producing bacteria (*Faecalibacterium prausnitzii, Roseburia*), *Bifidobacteria* and *Lactobacillus*, acting as a prebiotic. A significant reduction of body and liver weight, glucose levels and dyslipidemia (total cholesterol, LDL and HDL-chlolesterol) was achieved in mice by using piceatannol, an analog of resveratrol (Tung et al., 2016). Herb formulas, like Chowiseungcheng-tang (CST) have anti-obesity effect by modulating the metabolism-related neuropeptides, adipokines and microbiota composition in mice (Ansari et al., 2016). Yan et al. showed that intestinal flora changed after oral gavage-administration of Sitagliptin in rats, leading to improvement of glucose metabolism and moderate correction of dysbiosis in T2DM (Yan, Feng, Li, Tang, & Wang, 2016). Exercise vs. diet alone improved in rats the insulin resistance, reduced LDL-cholesterol and significantly increased the abundance of cecal *Streptococcaceae*, having a weight-loss independent metabolic benefit (Welly et al., 2016). Improvement of metabolic endotoxemia, weight, steatosis and insulin resistance was achieved also by apple-derived pectin supplementation in diet-induced obese rats (Jiang et al., 2016) and by red pitaya fruit (Hylocereus polyrhizus) betacianins in mice (Song et al., 2016). Experimental studies on rats, showed that administration of Morinda citrifolia L. leaves extract had significant anti-obesity effect after 9 weeks of treatment (Gooda Sahib Jambocus et al., 2016). Composition and diversity of microbiota suffered beneficial changes in obesity control, both *in vivo* and *in vitro*, by administration of Ligustrum robustum in high-fat diet rats (Xie et al., 2015). Certain antibiotics, like Ceftazidime, improved the metabolic variables (glucose, insulin, glucagon-like peptide-1) in a dose-dependent manner in obese mice (Rajpal et al., 2015); co-administration of azithromycin with intestinal alkaline phosphatase early in life prevented the development of metabolic syndrome (Economopoulos et al., 2016). Similar to the frequent cannabis users, it was proven that chronic administration of Tetrahydrocannabiol reduced weight gain and fat mas gain in diet-induced obese mice (Cluny, Keenan, Reimer, Le Foll, & Sharkey, 2015). Calcium supplementation acted also in a prebiotic manner on microbiota in obese mice (Chaplin, Parra, Laraichi, Serra, & Palou, 2016). Treatment of Helicobacter pylori infection, although the exact mechanism of action is not known yet, had a benefic effect on insulin resistance in mice (He et al., 2016). Dietary capsaicine, the major pungent bioactivator in chili peppers, prevents dysbiosis, having anti-obesity effect in mice (Kang et al., 2017). Prebiotic intake during lactation and pregnancy in obese mothers improves the metabolic profile of the offspring in rats (Paul, Bomhof, &

Vogel, 2016). Fecal transplant from obese to lean mice led in the latter to adopting the obese phenotype (Kulecka et al., 2016).

Improvement of insulin resistance has been achieved in rats by glandular gastrectomy (resection of 80% of the glandular portion), even if obesity persists (Basso et al., 2016). Among the surgical variants of bariatric treatment, ileal transposition surgery showed obvious improvement of weight loss, glucose tolerance, increased insulin sensitivity, being a revolutionary method for obesity and T2DM (Oh et al., 2016). Vertical sleeve gastrectomy-induced reduction in blood pressure in mice shifts in gut microbiotal population, by inducing increases in the relative abundance of *Gammaproteobacteria* and *Enterococcus* and decreasing *Adlercreutzia* (McGavigan et al., 2017).

Discussion

Although other reviews have already searched for possible correlations between microbiota and obesity, the distinct character of our review is that it comprises not only recent studies in human (including small children and pregnant women) and animal models but also therapeutic methods of treating weight gain.

The appearance of obesity, T2DM and atherosclerosis is influenced by the intestinal mircrobiota (Wegielska & Suliburska, 2016). Alteration of microbiota is linked with a high incidence of coronary artery disease (Emoto et al., 2016); biomarkers of cardiovascular risk, like TMAO (trimethylamine-N-oxide) are dependent on microbiota (Bergeron et al., 2016). Association of dysbiosis, obesity and diabetes is also a higher risk of osteoporosis (Ejtahed, Soroush, Angoorani, Larijani, & Hasani-Ranjbar, 2016) and asthma (obesity-related asthma by alteration of both gastrointestinal and lung microbiota) (Cho & Shore, 2016). Dysbiosis has been recently demonstrated to have a role in the development and progression of kidney disease in obese people, so pre- and probiotics were shown in some studies to have benefits in improving the kidney injury (Wanchai et al., 2017).

Alterations in the composition of microbiota can be caused by different agents like: industrialized food (especially higher fried food intake), combined with use of antibiotics, low-fiber-diets, especially lack of soluble fiber (inulin), low-bacteria diets (Zschocke, 2016). There have been controversies regarding azithromycin use: early abusive antibiotic exposure in childhood represents a damage of microbiota, increasing the adipogenesis (Li, Wang, et al., 2017); on the other hand, targeted use of simultaneous administration of azithromycin with intestinal alkaline phosphatase early in life prevents the development of metabolic syndrome (Economopoulos et al., 2016). So healthy high-fiber diet, well established meal rhythms and strategic intake of bacteria could reestablish the microbiota balance. Early onset of obesity increases the risk of obesity in adulthood.

Mechanisms that are involved in microbiota changes in obesity are following: chronic inflammation, activation of TLR4, insulin resistance, effects on bile acids, branched-chain amino acids (Saad, Santos, & Prada, 2016), decreased 5HT levels (increasing appetite) (Park et al., 2015), gastrointestinal vagal signaling (Kentish & Page, 2015). Pathogenesis of obesity implies changes regarding molecular mechanisms, including hormones like: glucagon like peptide-1, pancreatic polypeptide, increased ghrelin secretion (Basso et al., 2016; Perry et al., 2016) and cholecystokinin (Mishra, Dubey, & Ghosh, 2016). The ileal microbiota was proven in a study by Garidou et al. to give the outcome of metabolic disease by regulating Th17 cell homeostasis (Garidou et al., 2015). Another role was attributed to the brown fat based thermogenesis, in order to stimulate energy expenditure to reduce obesity (Ziętak et al., 2017). Accelerated postnatal growth in low birth-weight humans, with dysbiotic microbiome, leads to a higher risk of metabolic syndrome in adulthood than in normal birth-weight individuals (Wang, Tang, et al., 2016).

During pregnancy, significant changes inside the microbiome take place, therefore alterations at this level are important to be avoided in order to have a healthy pregnancy (Neuman & Koren, 2017).

It has been noticed that there are quantitative and qualitative compositional differences regarding gut microbiota in obese patients and healthy people; the latter proved to have higher abundance of *Bifidobacterium spp.* compared with overweight persons (Ignacio et al., 2016), while obese subjects have reduced numbers of *Bacteroidetes* and increased numbers of *Firmicutes* compared to lean people.

Controversies regarding the implication of diversity of intestinal microbiota in weight gain and obesity appeared between studies on humans and animals: ***lower*** diversity of microbial species was shown by Park et al in a study on obese beagle dogs (Park et al., 2015), while another study proved by terminal restriction fragment length polymorphism a ***greater*** bacterial diversity and a specific composition (*Blautia hydogenotrophica, Coprococcus catus, Ruminococcus bromii, Eubacterium ventriosum*) in obese Japanese patients (Kasai et al., 2015).

Experimental studies on humans and animals revealed discrepancy regarding implication of *Lactobacillus spp*. in weight induction: higher abundance of Lactobacillus spp. in mice was associated with whole-wheat consumption, vs. lean and obese mice with standard diet (Garcia-Mazcorro, Ivanov, Mills, & Noratto, 2016); on the other hand, Ignacio et al. showed that *Lactobacillus spp.* were in higher number (p = .02) in obese and overweight children compared to the lean ones (Ignacio et al., 2016).

Regarding effective strategies in order to lose weight, HPLC diets have proved to be for many years effective (Li, Lauber, et al., 2017), and personalized dietary treatments represent the future aim (Goni, Cuervo, Milagro, & Martínez, 2016). Many herbs proved to have prebiotic effect in order to prevent and even reduce obesity, physical exercise had a weight-loss independent metabolic benefit vs. diet, and last, but not least the bariatric surgery should be taken into account with its

positive results both on microbioal composition and weight loss changes. Antiviral agents and mycobiome manipulation would represent a new target in the therapy of obesity (Mar Rodríguez et al., 2015).

High dietary polyphenol intake included in Mediterranean diet, induces a low risk for neurodegenerative diseases, DM, CV diseases, hypertension, obesity and early death (Anderson & Nieman, 2016). Parasympathetic activation can be a therapeutic option for obesity (Perry et al., 2016). Regular coffee consumption (3-4 cups/day) proved to reduce the risk of developing T2DM, due to caffeine and chlorogenic acid content (Santos & Lima, 2016). Gallagher and LeRoith (2015) showed, that intentional weight loss protects against carcinogenesis, and antidiabetic therapy may be effective in cancer progression.

In conclusion, implication of weight gain, obesity and gut microbiota represent a bidirectional effect. Any change of the quantitative and qualitative composition of microbiota has influence on the components of metabolic syndrome, therefore any management strategy for treating or preventing obesity in children and adulthood should have the microbiome as target. Any imbalance of microbiota composition, even starting from delivery mode, food diversification in children and weight gain in early years of life, have been proved to affect the adult's homeostasis, leading to obesity, and other metabolic diseases. Personalized diets, avoidance of antibiotic abuse, physical exercise and prebiotics would represent the most important options for the prophylaxis of obesity.

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Microbioma intestinal y peso corporal – revisión

Resumen

La relación entre la microbioma intestinal y la resistencia a la insulina tiene un impacto clínico importante dado que la gente afectada por disbiosis tiene predisposiciones para desarrollar la obesidad, la diabetes mellitus tipo 2, la enfermedad de hígado graso no alcohólico, cánceres, enfermedades cardiovasculares, neurodegenerativas y psiquiátricas. La disbiosis puede convertirse en una inflamación crónica, obesidad o síndrome metabólico. Hemos hecho una revisión sistemática de los estudios dedicados al papel de la microbioma intestinal para el aumento de peso y la obesidad. Una búsqueda sistemática de datos recientes publicados en las bases de datos electrónicas se ha llevado a cabo usando la frase "gut microbiome and body weight and obesity". Se ha excluido a los estudios que no contenían informaciones sobre la influencia de los cambios de la microbioma intestinal en la obesidad. La dieta occidental, uso de los antibióticos en la niñez, peso excesivo antes del embarazo, parto por cesárea y deficiencia de testosterona provocan la alteración de la microbioma y por consiguiente la apariencia de la obesidad. El predominio de firmicutes y géneros anaeróbicos, cambios en el microbioma y población intestinal viral están implícitos en la etiología de la obesidad. Prebióticos, polifenoles, diferentes hierbas, medicamentos (antidiabéticos, calcio), ejercicio físico, consumo de fibras y cirugía bariátrica son las opciones terapéuticas más importantes. Tratamientos dietéticos personalizados, agentes antivirales y manipulación de la microbioma representarían nuevas metas en el tratamiento de la obesidad. Cada cambio en la composición cuantitativa o cualitativa de la microbioma influye en los componentes del síndrome metabólico, así que todas las estrategias para el tratamiento o prevención de la obesidad en niños o adultos deberían tener microbioma como su meta.

Palabras clave: diabetes, metabolismo, microbioma, obesidad

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