In the history of medicine, only recently has obesity been recognized as a disease. We know now that it is a pandemic condition, partly explained by the so-called Western lifestyle and related to multiple other comorbidities in various systems. This lifestyle includes eating large portions, rich in saturated fats and refined sugar, all coupled with sedentary habits. In recent years, the gut microbiota has been indicted as a new culprit in pathophysiological aspects involved in obesity. From studies with animals free of bacteria in the digestive tract, known as “germ-free animals”, the relevance of intestinal microbiota in the regulation of body fat became evident and its importance has also been extended to the pathophysiology of diseases such as diabetes mellitus and coronary heart disease. Characterization of Toll-like receptors led to the discovery of mechanisms that link the immune system with some metabolic pathways and opened new avenues to a previously unknown world to biological sciences. Increased knowledge about interactions between gut microbiota and the host can certainly reveal, in a not too distant future, new therapeutic perspectives for obesity and its related diseases.

**KEYWORDS:** obesity; gut; microbiota


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**INTRODUCTION**

Obesity is a condition known for millennia in humans, but only recently it started to be considered as a disease. It is estimated that genetic factors may account for 25% to 40% of body mass index (BMI) variance, by determining factors such as differences in basal rate of metabolism and response to overfeeding. It is believed that changes in eating habits and sedentary lifestyle acting on susceptibility genes are the main determinants in the growth of obesity worldwide. The theory of “economic genotype” was introduced by Neel et al. in 1962, according to which individuals with greater ability to accumulate energy during periods of food scarcity would be more likely to survive in such conditions. This concept reinforces the theory of Darwin’s natural selection, according to which the fittest individuals are selected by nature to maintain their offsprings.

According to recommendations of the World Health Organization for health maintenance, at least 150 minutes of moderate intensity physical activity or 75 minutes of high intensity activity per week must be performed in populations aged 18 to 64 years; however, anthropological studies have shown that isolated African tribes in regions of Kenya and Ethiopia, who keep living habits to very similar those of their ancestors maintain their BMI ranging from 17.8 to 19.1 kg/m² due to an estimated 8 hours of daily physical activity; this is up to 16 times more than the above mentioned recommendation.

Such observations have led to a search for genes that may be related to weight gain. Thus, the so-called genetic map of human obesity is in constant process of evolution as new genes and chromosomal regions associated with obesity are identified. In its latest version, this map reports more than 430 genes, markers...
and chromosomal regions associated with human obesity phenotypes.

From the observation of *Drosophila*, in which the same tissue is responsible for providing energy and defense against invading microorganisms, emerged the hypothesis of a “memory” ancestor that connects the immune system and the development of obesity. Actually, we already know that the adipose tissue is capable of producing many substances previously associated solely with the immune system. A family of membrane proteins called Toll-like receptors (TLR) may be the link between the immune system and body metabolism. These receptors are capable of recognizing pathogens, of initiating the immune response and to respond to both lipopolysaccharide (LPS) present in *Gram*-negative bacterial cell walls and to some types of fatty acids.

Accumulation of excessive adipose tissue is due to hyperplasia and hypertrophy and the latter is more susceptible to lipolysis, which broadens the pool of circulating fatty acids to bind to the subtype 4 of TLR (TLR-4); this triggers an immune response that results in a low-grade inflammatory state even in the absence of any infection. This low-grade or subclinical inflammation is often asymptomatic and closely related to insulin resistance. One of the clearest evidences of the importance of TLR-4 in obesity and diabetes has been demonstrated by experiments with TLR-4 knockout mice, which have been shown to be protected from developing diabetes or obesity-related morbidities when exposed to a high-fat diet.

The human gastrointestinal microbiota has been physiologically recognized as a true organ that produces local and systemic mediators, which may contribute or cause damage to host metabolism. Among the main signaling molecules, LPS is present in the outer membrane of *Gram*-negative bacteria; in addition to being involved in pyrogenic mechanisms in sepsis, LPS was recently related to low level systemic inflammation present in obesity and metabolic diseases.

This review article aims to discuss the main links between obesity and gut microbiota and how they can change the perspectives of treatment of this disease that has a huge impact on Western civilization.

**MATERIALS, METHODS AND RESULTS**

A search was conducted in Pub Med using the terms [gut microbiota] and [obesity] on 06/08/2017, producing 1691 hits. We included 110 articles, after evaluating the clinical relevance of each article as well as the availability of access to the article in its entirety.

**DISCUSSION**

**Gut microbiota**

Until birth, the gastrointestinal tract of a normal fetus is sterile. During labor and shortly after delivery, bacteria from the mother and surrounding environment colonize the gut of the newborn. The type of delivery seems to influence decisively in this colonization: the gastrointestinal tract of normally delivered babies appears to be colonized predominantly by the mother’s gut microorganisms that seem to influence its microbiota up to about one month after birth; in contrast, the gastrointestinal tract from babies delivered by cesarean section appears to be preferentially colonized by bacteria of the surrounding environment, the air, other children and medical staff, and may have its composition changed until the sixth postnatal month. By the second year, the intestinal flora is similar to that found in adults.

The gastrointestinal tract is initially colonized by aerobic bacteria, including facultative aerobic bacteria. Their expansion consumes oxygen and creates a favorable environment for the growth of strictly anaerobic organisms, most of them belonging to the genera *Bifidobacterium*, *Bacteroides*, *Clostridium* and *Ruminococcus*.

The pioneer microorganisms may act to induce or modulate the expression of genes in epithelial cells of the host, which may create a favorable environment while preventing the growth of bacteria introduced later in this ecosystem. Thus, the initial colonization is of fundamental importance in establishing the permanent flora of adults.

Colonization in the gastrointestinal tract diverges according to its segments. Among the microorganisms, bacteria are the majority with over 90% of the species belonging the phyla Firmicutes and Bacteroidetes. The colonization of gastrointestinal tract has an impact in energy use of non-digestible food such as cellulose and in the synthesis of short chain fatty acids, such as propionic acid that serves as substrate for gluconeogenesis and acetate, a substrate for *de novo* lipogenesis in hepatocytes and adipocytes. Furthermore, the gastrointestinal tract microbiota acts as a barrier against colonization of pathogens and stimulates the development of the immune system. Therefore, the intimate contact between commensal bacteria and the intestinal epithelium seems to play a key role in regulating host-commensal bacteria against pathogens (Figure 1).

**Obesity and gut microbiota**

The intestinal microbiota of obese subjects is characterized by a higher Firmicutes/Bacteroidetes ratio when compared to lean individuals. Weight loss programs
are associated with changes in the proportion of both phyla related to how much weight was lost and not with lower calorie intake.\textsuperscript{15}

Animals with sterile intestines (e.g., germ-free mice) are protected from diet-induced obesity and its associated comorbidities, whereas when colonized by the intestinal microbiota of other mice, they show significant weight gain 2 weeks after colonization. Interestingly, the weight gain of these colonized animals varies from 40% when the microbiota came from lean mice, to 60% when it came from genetically obese mice (ob/ob mice). Germ-free animals have reduced ability to extract dietary energy associated with reduced energy supply in the liver and skeletal muscle.\textsuperscript{16,17} These findings link the germ-free condition to caloric restriction regimen in which there is resistance to develop obesity. Furthermore, caloric restriction is associated with longevity due to improvements in general health.\textsuperscript{17,18} However, this resistance to become obese induced by feeding seems to be dependent on specific interactions between diet and microflora.\textsuperscript{18}

The greater ability to obtain energy from nutrients observed in the ob/ob mouse appears to be related to genes that encode enzymes that process indigestible polysaccharides, causing an increase in the production of fermentation products, mainly short chain fatty acids. Some authors observed that the amount of calories in the feces of these animals was smaller than what is found in lean animals\textsuperscript{19} while others found no differences in the amount of fecal energy of germ-free mice compared to controls.\textsuperscript{17} These observations suggest that other mechanisms underlying food energy extraction capacity could be responsible for weight gain related to intestinal microbiota composition. It has also been reported that intestinal colonization of germ-free animals resulted in significant changes in hormone levels with increased plasma levels of insulin, leptin and glucose, in capillary density and, especially, in the expression of genes that regulate lipogenesis and “energy sensing”.\textsuperscript{16} An example of such changes is that germ-free animals, when colonized, had reduced expression of the fasting-induced adipocyte factor (FIAF) in the gut epithelium, which is capable of inhibiting the activity of lipoprotein lipase, thus reducing the release of fatty acids from triglycerides.\textsuperscript{16,20} Furthermore, higher expression of FIAF stimulates $\alpha$ coactivator peroxisome proliferator-activated receptor, which causes up-regulation of genes encoding regulators of mitochondrial fatty acid oxidation.\textsuperscript{17} In contrast, lower levels of FIAF lead to higher lipoprotein lipase activity, causing an increase in storage of triglycerides in the adipocytes.

Another feature that makes germ-free animals more resistant to western diet-induced obesity appears to be related to higher expression of phosphorylated AMP-activated protein kinase (AMPK) in skeletal muscle and liver,\textsuperscript{17} since AMPK upregulates fatty acid oxidation and glucose uptake in muscle tissue and inhibits the synthesis of fatty acids and hepatic gluconeogenesis. In adipose tissue, AMPK inhibits fatty acid synthesis and lipolysis; it also inhibits insulin secretion mediated by fatty acids, playing an important role in body weight maintenance and reduction of lipotoxicity.\textsuperscript{21} In summary, the protection from diet-induced obesity in germ-free animals occurs through two complementary mechanisms. Even though high levels
of fasting-induced adipocyte factor and increased AMPK activity work independently, they result in reduced storage of triglycerides.

Taken together, the results of the study conducted with germ-free animals directs attention to the active role of the microbiota in oxidation and storage of nutrients and not only to an increased absorption of nutrients by the gut. Contrary to what was believed, germ-free animals fed with a high-fat diet did not become fat and, according to the study, it is likely that dietary fat alone is not enough to cause obesity.17

Data from clinical studies (table 1) that investigated changes in the composition of the intestinal microbiota in obesity have been, in general, in agreement with animal models; although these clinical studies are more heterogeneous, this could be attributed to the increased complexity of human lifestyles when compared to experimental animals.

Lipopolysaccharide – clinical features

Lipopolysaccharide glycolipids are large molecules formed by covalent bonds between lipid fractions and polysaccharides. They are found in the outer membrane of Gram-negative bacteria; they are also known as endotoxins due to their ability to trigger intense immune responses. The basic structure consists of lipid A associated with an antigenic group O which is probably the molecule responsible for triggering the inflammatory response and low-grade metabolic disorders.7

High fat diets appear to favor the uptake of lipopolysaccharides by the intestinal epithelium, but the exact mechanism remains under discussion.29,30 It has been shown that chylomicron formation promotes absorption of LPS in human colorectal carcinoma model in vitro. Chylomicron formation is associated with secretion of LPS by the cells.31

Other reports,32,33 however, showed that an increase of about 10 times in the concentration of fatty acids can harm the integrity of the intestinal mucosal barrier. In animals, the endotoxemia that follows high-fat diet has been associated with reduced expression of genes that encode two proteins, namely zonula occludens-1 and occludin, both important in keeping the selective permeability of the intestinal mucosa.34

An alternative route for LPS absorption has been described:35,36 internalization through intestinal microvilli by a TLR4 dependent mechanism of protein and myeloid differentiation protein type 2; once inside enterocytes, LPS can be transported to the Golgi site of synthesis of chylomicrons.

Upon reaching the bloodstream, LPS is transported by a specific acute phase protein, the LPS binding protein and by lipoproteins into hepatocytes where it is cleared by excretion in bile.37,38 All classes of plasma lipoproteins can sequester LPS and it seems to be dependent on the amount and by lipoproteins into hepatocytes where it is cleared by excretion in bile.37,38 All classes of plasma lipoproteins can sequester LPS and it seems to be dependent on the amount of phospholipids on their surface.39

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<table>
<thead>
<tr>
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<th>Brief Outcomes</th>
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<td>Ley et al.15</td>
<td>Obese adults</td>
<td>Diets with fat or carbohydrate restriction. Monitoring of microbiota for 1 year (sequencing of the 16S rRNA gene)</td>
<td>As weight loss was increased, there was absolute reduction in Firmicutes and increase in Bacteroidetes, regardless of the type of diet.</td>
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<tr>
<td>Nadal et al.24</td>
<td>Obese and overweight adolescents</td>
<td>Longitudinal study intervention (diet and increased caloric expenditure) for 10 weeks</td>
<td>Reduction in the species C. histolyticum, C. coccoides and E. rectale in those who lost weight.</td>
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<tr>
<td>Santacruz et al.25</td>
<td>Overweight adolescents</td>
<td>Longitudinal study intervention (diet and increased caloric expenditure) for 10 weeks</td>
<td>In the group with the highest weight loss, there was an increase of B. fragilis and Lactobacillus and reduction B. longum and C. coccoides</td>
</tr>
<tr>
<td>Duncan et al.26</td>
<td>Obese adults</td>
<td>Individuals submitted or not to the weight loss program for 4 weeks Longitudinal study intervention (diet) for 4 weeks</td>
<td>Significant reduction of Firmicutes in the feces of those who underwent weight loss</td>
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<td>Turnbaugh et al.27</td>
<td>Identical twin adult women or not corresponding to obesity or eutrophic mothers Adult female monozygotic and dizygotic twin pairs concordant for leanness or obesity</td>
<td>Sequencing of the 16S rRNA gene to characterize the microbiome.</td>
<td>Microbiome is shared among family members, with some variation between twins, but maintained a &quot;core microbiome&quot;. Obesity was associated with changes in phyla and lower bacterial diversity.</td>
</tr>
<tr>
<td>Kasai et al.28</td>
<td>Japanese population, obese and non-obese</td>
<td>Stool samples, T-RFLP polymorphism</td>
<td>Reduced Bacteroidetes and higher Firmicutes to Bacteroidetes ratio in obese subjects.</td>
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Table 1 - Main studies evaluating changes in intestinal microbiota composition in humans
in conditions of acute inflammation and infection, plasma HDL is reduced, while triglycerides and chylomicrons are increased. Thus, in this scenario, the LPS binding protein seems to transfer LPS preferentially to low-density lipoprotein (LDL cholesterol) and promote the formation of complexes of LPS with HDL and LDL. By increasing and redistributing phospholipids between different lipoproteins, the immuno-stimulatory effect of LPS can be attenuated. This mechanism may represent part of the innate defense system against endotoxemia caused by gram-negative bacteria.

At least three mechanisms have been proposed by which dietary lipid could promote greater absorption of LPS: (a) compositional changes in the intestinal microbiota, (b) increased availability of chylomicrons and (c) changes in the permeability of the intestinal epithelium. Therefore, a diet rich in lipids may contribute to greater absorption of LPS, a fundamental molecule for the process of chronic subclinical inflammation associated with many obesity-related diseases, especially atherosclerosis.

Endotoxemia and its importance in cellular metabolism

A new hypothesis, illustrated in Figure 2, has linked intestinal microbiota and metabolic homeostasis. Based on evidence that obesity and type 2 diabetes are both associated with systemic low-grade inflammation in the liver, adipose tissue and hypothalamus, Cani et al. suggested that bacterial LPS derived from gut bacteria could trigger inflammation that would lead to diabetes induced by high fat diet and obesity.

In the same study, Cani et al. examined the relationship of a diet rich in lipids and circulating LPS and noted that, after the ingestion of fat, LPS levels were approximately 1.4 times higher than observed in animals receiving standard diet, demonstrating a direct relationship between absorption of fat and endotoxin.

The same authors endeavored to demonstrate an in vivo relationship of cause and effect between systemic exposure to slightly increased levels of endotoxin and development of weight gain, insulin resistance and low-grade inflammation, which some authors call “metabolic endotoxemia”. It seems that endotoxemia exacerbates and accelerates the pro-inflammatory, pro-diabetogenic stage promoted by fatty acids that, in turn, modulate activation of TLR4 by LPS.

Another effect of LPS on adipose tissue is its influence upon adipocyte size, because chronic infusions of LPS were associated with reductions in the average size of adipocytes. The balance between hypertrophy and hyperplasia could influence individual risk of fat mass gain and development of insulin resistance and cardiovascular diseases.

Another interesting fact is that the amount of LPS administered in the study performed by Cani et al. would be enough to cause anorexia, which was not observed. Chronic exposure to endotoxin probably causes tolerance despite the already known anorexigenic mechanism of LPS. The reasons behind this observation are not completely understood but may be related to genotypic differences between species, hormonal factors such as leptin and ghrelin or biochemical characteristics of LPS.

LPS influences insulin signaling

The induction of the inflammatory response by LPS can establish an intersection with insulin signaling at various stages, and may even inhibit it. Insulin acts on target cells through binding to cell surface receptors inducing receptor autophosphorylation and activation of tyrosine kinase receptor activity that phosphorylates various substrates, such as members of insulin receptor family substrates (IRS), triggering its well known effects at the end of the cascade.

It is also now well documented that phosphorylation of serine residues by the insulin receptor reduces ability of IRS-1 to associate with the receptor and thus inhibits the remainder of the cell signaling cascade. TNFα and IL-6 are responsible for the inhibitory phosphorylation of IRS-1.

The key point in the integration of metabolic and immune pathways occurs at the level of the c-Jun N-terminal kinase. Inflammatory signals lead to hyperactivation of the c-Jun N-terminal kinase, resulting in serine phosphorylation of IRS-1. However, other points of overlap between immune and metabolic pathways occur at the levels of protein kinase C, the family of suppressors of cytokines such as SOCS-1, 3 and 6 and the induced nitric oxide synthase.
At the adipose tissue level, two other mechanisms also contribute to insulin resistance induced by LPS. First, activation of TLR4 in LPS-induced preadipocytes alters the expression of several cytokines, including TNFα and IL-6 by a paracrine route that inhibits insulin signaling in adipocytes. Moreover, LPS promotes the expression of NF-κB and activation of the MAP kinase pathway in adipocytes, leading to target gene expression, such as glucose transporter stimulated by insulin-4 (GLUT-4), adiponectin, fatty acid synthase and perilipin. In adipocytes belonging to the 3T3-L1 cell line; LPS also promotes the expression of inducible nitric oxide synthase.

It was observed that low doses of LPS induce a biphasic response in glucose uptake in non-obese individuals. In the early hours, there was an increase in insulin sensitivity, with subsequent reduction. This biphasic effect on insulin sensitivity during experimental endotoxemia and sepsis may be due to expression of inducible nitric oxide synthase. LPS increases the uptake of glucose by myocytes through inducible nitric oxide synthase induction. On the other hand, excessive production of nitric oxide (NO) causes a reduction in glucose uptake by muscle cells. The effect of NO on insulin action may be perturbed by release of TNFα and IL-6 induced by LPS. Furthermore, excessive production of NO may worsen insulin resistance by increasing the levels of circulating fatty acids, due to loss in lipoprotein lipase activity, which favors lipolysis.

The behavior of blood glucose during sepsis demonstrates this biphasic effect, as shown by the evolution of hypoglycemia to hyperglycemia. LPS-induced hypoglycemia is associated with a reduction in glucose synthesis. In addition, increased activity of NF-κB results in an increase in the expression of inducible nitric oxide synthase and reduced expression of genes that encode limiting enzymes for glucose synthesis such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase.

Down-regulation of adiponectin receptor expression on surface of monocytes probably also contributes to the reduction in insulin sensitivity. The release of counter-regulatory hormones such as cortisol and growth hormone following the administration of low doses of LPS can contribute to reduction of peripheral and hepatic glucose uptake.

**Type 2 diabetes, hyperinsulinemia and endotoxemia**

LPS stimulates insulin secretion and, reciprocally, chronic hyperinsulinemia causes reduction of LPS clearance by reducing the function of hepatic Kupffer cells. However, this mechanism that, in theory, would protect against microorganisms of gastrointestinal tract reaching the blood stream, may become exaggerated in the presence of adiposity, hyperinsulinemia, high fat diet, and smoking. As result, LPS concentration in plasma increases by about 50% after high-fat diet or when associated with smoking.

Hyperinsulinemia with hyperglycemia may be intensified by endotoxemia, since they reduce jejunal motility and intestinal transit and may facilitate bacterial overgrowth and loss of mucosal integrity, which occurs quite frequently in patients with type 2 diabetes mellitus. Since hyperglycemia and hyperinsulinemia are usually accompanied by a diet rich in lipids and dyslipidemia, they can act as synergistic factors. It has been reported that individuals with type 2 diabetes have serum levels of LPS that are 76% higher than those found in healthy individuals.

**Endotoxemia links dyslipidemia and cardiovascular disease**

To our knowledge, the first study to demonstrate the relationship between LPS and cardiovascular risk was published in 1999 by Wiedermann et al., showing that individuals with LPS levels above 50 pg/ml had a threefold higher risk of developing atherosclerosis. The positive association between increased levels of LPS and metabolic syndrome suggests a possible clinical utility of endotoxin in serum as a marker of low-grade inflammation and increased cardiovascular risk. This might add power to the classic markers of cardiovascular risk, by providing information about damage to tissues such as the liver endothelium. Through its connection to TLR4 in endothelial cells, monocytes and macrophages, LPS causes the release of pro-inflammatory cytokines, leading to severe endothelial dysfunction, atherosclerotic plaque formation, oxidation of LDL and thrombogenesis. LPS is not expressed in a constitutive manner in the endothelium, but their expression depends on mechanical and non-mechanical stimuli, which include blood flow disorders, oxidized LDL, endogenous nonlipid ligands, free fatty acids, stress factors (heat shock proteins), advanced glycosylation end products, as well as fibrinogen, heparan sulfate and hyaluronic acid.

By interacting with the endothelial surface of TLR4, LPS promotes direct endothelial damage by generation of reactive oxygen species. Furthermore, when stimulated by LPS, endothelial cells release pro-inflammatory factors, chemotactic and cell adhesion molecules, which cause transmigration of monocytes, differentiation into macrophages and atherosclerotic plaque formation. Among these cytokines, IL-8 is chemotactic for T lymphocytes, directed to the fibrous cap of atherosclerotic plaque; very low concentrations of endotoxin (<1 ng/ml) can promote this process. An interesting aspect is the reduction of cardiovascular risk by statins due to their ability to reduce the effects of endotoxin both on endothelium and macrophages.
Immunity in obesity triggered by TLR

LPS, when not fully eliminated by hepatocytes, binds to TLR4 present on surface of Kupffer cells, preadipocytes and adipocytes, causing upregulation of CD14 and expression of TLR2. Preadipocytes, adipocytes and macrophages present in visceral adipose tissue appear to respond synergistically to inflammatory stimuli. Considerable potential has been assigned to pro-inflammatory visceral adipose tissue, when compared to non-visceral adipose tissue, because it is more readily mobilized during stress. Due to its features, visceral adipose tissue seems to be decisive in determining the inflammatory response triggered by TLR activation.

The change in the content of protein CD36 which, in turn, regulates the uptake of plasma free fatty acids in adipose tissue, in muscle, and probably in the liver, might show an association between ectopic fat distribution and metabolic obesity-related disease.

LPS and adipose tissue

Adipose tissue is composed of about 50-70% adipocytes, 20-40% of vascular stroma components, which include pre-adipocytes, fibroblasts, and mesenchymal stem cells, and 1-30% of infiltrating macrophages. Endotoxin in nanograms per milliliter levels induce the release of proinflammatory molecules of macrophages and pre-adipocytes, which in turn trigger insulin resistance in mature adipocytes. The trigger for the development of insulin resistance occurs in adipocytes via activation of NF-κB and MAP Kinase signaling, reducing the activity of peroxisome proliferator-activated receptor gama and sensitivity to insulin. Moreover, LPS inhibits adiponectin expression in preadipocytes, whereas addition of LPS to cultures containing adipocytes alone did not adversely affect insulin mediated glucose uptake or adiponectin gene expression.

Under normal conditions, adipocytes regulate lipid metabolic homeostasis, whereas macrophages are responsible for the inflammatory response. However, under special conditions, such as obesity and overeating, pre-adipocytes act as immune cells, displaying phagocytic and anti-microbial activities and differentiating into macrophages.

The proinflammatory effect of LPS on preadipocytes can be partially mediated by induction of TLR2 expression. Although TLR4 expression is constitutive in both preadipocytes and adipocytes, expression of TLR2 is induced by either LPS or TNFα and CD14. It seems that the TLR2 receptor is converted into a high molecular weight form, which may be due to recruitment of TLR4, with the formation of a complex. Alternatively, activation of TLR4 can induce the formation of intracellular effectors to form a complex with TLR2.

Evidence supports the concept that fatty acids, more particularly lauric and palmitic acids, can promote insulin resistance and weight gain, being associated with low-grade inflammation through activation of TLR2 and TLR4. TLR4 activation mediated by fatty acids has been demonstrated in several cellular models. However, Erridge et al. in their study attributed this activation to other molecules in their preparation and not to fatty acids.

Thus, fatty acids appear to induce activation of TLR4 through formation of "lipid rafts" understood as membrane microdomains that help to bring together receptors, co-receptors, adapters and distal cascades of signaling molecules. Although saturated fatty acids have the ability to activate this process, polyunsaturated fatty acids inhibit the dimerization and recruitment of TLR4.

In type 2 diabetes mellitus, a condition in which we have a stimulated lipolysis, increased free fatty acids can promote activation of TLR in various tissues. In fact, it has been shown that high glucose levels and LDL oxidized particles, can strengthen expression and activation of TLR4, supporting the crucial role of fatty acids in the relationship between nutrition and immunity.

Therapeutic prospects in the modulation of intestinal microbiota and microbiota-host mutualism

In animal models of insulin resistance (ob/ob mouse and diet-induced obesity), intestinal microbiota composition was modulated by administration of antibiotics. The combination of norfloxacin and ampicillin suppressed the number of aerobic and anaerobic cecal bacteria in mice with insulin resistance. After 2 weeks of antibiotic treatment, there was a significant improvement in fasting plasma glucose and oral glucose tolerance in ob/ob mice, independently of food intake or adiposity. A reduction in the amount of liver triglycerides and increased hepatic glycogen in animals treated with antibiotics was also observed. In addition, there was a decrease in LPS plasma levels and an increase in adiponectin levels, supporting the anti-diabetic effects of treatment with antibiotics in ob/ob mouse.

The use of prebiotics (oligosaccharides and derivatives of inulin, soluble fibers) may be justified by their ability to stimulate growth of beneficial bacteria such as Lactobacilli and Bifidobacteria in the intestines, as well as generation of fermentation products and short chain fatty acids with anti-inflammatory action by binding to leukocyte receptors, reducing appetite and inhibiting adhesion and infection of pathogens to intestinal epithelial cells.

Although the use of prebiotics and probiotics has yielded encouraging results in experimental models of liver steatosis, results in human studies of obesity and cardiovascular disease are not consistent.

Recently, Plovier et al. observed improved metabolism in obese and diabetic mice treated with
Obesity and microbiota

Akermansia muciniphila either as a purified membrane protein or in pasteurized form, with better results when pasteurization was performed.

CONCLUSION

Gut microbiota has an enormous potential to become one of the most important features in the fight against obesity, type 2 diabetes and cardiovascular disease worldwide. However, much remains to be investigated in this fascinating field of science. As further studies are conducted, important new discoveries will be added to our scant current knowledge, so that in near future, we can have more effective ways to modulate the microbiome with possible beneficial effects on human health.

AUTHORS CONTRIBUTIONS

VLSJ, FAML (literature review and writing of the manuscript); RMA and EB (revised the manuscript); MGCS, CMLB and PAM (literature review); LGKA (conceived the review, revised the manuscript and edited the final version).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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