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Chapter

Fatty Acids, Gut Microbiota, and the Genesis of Obesity

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Abstract

Obesity is a major public health problem, which is growing around the world. It is a multifactorial disease and a risk factor for other noncommunicable diseases (e.g., cardiovascular diseases, type 2 diabetes mellitus, and hepatic steatosis). Among the etiological factors, gut microbiota and diet, especially lipids, have been highlighted, which seem to have an important potential as a modulator of its composition, being the key factor in the link between microbiota and obesity. Gut microbiota interacts with the host metabolism in the development of this disease through dietary fatty acids or when produced by intestinal bacteria. Short-chain, saturated, and polyunsaturated fatty acids have an impact with respect to gut microbiota and health, presenting central and systemic effects associated with the genesis of obesity. Finally, gut microbiota seems to play a significant role in controlling the endocannabinoid system, and imbalance in this system can be associated with obesity.

Keywords: gut microbiota, obesity, saturated fatty acids, short-chain fatty acids, polyunsaturated fatty acids, endocannabinoid system

1. Introduction

Obesity currently affects around 600 million adults worldwide (13%), being more prevalent among women (15%) than men (11%) [1]. It is described as an increase in the adipose tissue that releases a wide variety of proinflammatory cytokines and chemokines, called adipokines, promoting inflammation, recruitment of macrophages, and insulin resistance [2]. This inflammatory process is manifested systemically and is characterized by a chronic low-intensity reaction [3], which is linked to the pathophysiology of several chronic diseases such as type 2 diabetes mellitus (DM2), cardiovascular diseases, and nonalcoholic fatty liver disease, among others [1, 4]. Although the etiology of obesity is multifactorial, there is often an energy imbalance with an increase in intake and/or absorption of calories and a decrease in energy expenditure or metabolic efficiency, which can be caused by several factors, such as genetics, environment, psychological factors, endocrine disorders, and some drugs. Recently, gut microbiota has been receiving attention [1, 4, 5].

The differences in gut microbiota between lean and obese animals or human subjects suggest a link between gut microbiota and energy homeostasis [7]. In fact, modifications in gut microbiota composition are associated with greater energy breakdown and absorption from food, greater efficiency in storing fat in adipose

tissue, as well as the stimulation of metabolic endotoxemia, low-grade inflammation, and dysbiosis that favors obesity [5, 6]. Dysbiosis leads to increased permeability of the intestinal barrier, allowing for the translocation of lipopolysaccharides (LPSs), toxins that are responsible for the initiation of the inflammatory cascade, affecting mainly adipose tissue, liver, muscle, and brain, which reduce insulin sensitivity in these organs. In addition, LPS also disrupts the endocannabinoid system, further increasing intestinal permeability and allowing greater LPS translocation. The increase in circulating LPS suppresses the fasting-induced adipose factor, thus modulating lipoprotein lipase (LPL) activity, which starts to exacerbate functions in adipose tissue and muscles, favoring the accumulation of triglycerides in these organs [7].

In cell membranes, fatty acids act as phospholipids constituents and may also be released as signaling molecules, regulating energy production and inflammation [8]. Fatty acids are also precursors of endocannabinoids and their structural congeners. The endocannabinoid (eCB) system plays a pivotal role in the regulation of eating behavior and modulation of the immune and inflammatory response [9]. Fatty acids contribute between 94 and 96% of the total weight of different fats and oils and can be classified as saturated fatty acids (SFAs), which contain no double bonds; monounsaturated fatty acids (MUFAs), which feature one double bond; and polyunsaturated fatty acids (PUFAs), which contain multiple double bonds [10]. There are two families of polyunsaturated fatty acids (PUFAs): n-3 (or omega-3 or n-3) and n-6 (omega-6 or n-6). An adequate balance in the dietary intake of n-6/n-3 PUFA is a determining factor in the maintenance of gut microbiota balance, considering the role of this n-6/n-3 ratio in inflammatory response. Over the last decades, there has been a significant modification in the dietary pattern of the western diet, with the increased consumption of industrialized products, generating an increase in the dietary saturated fat and n-6/n-3 ratio [2]. This dietary pattern may increase gut permeability, which results in a greater translocation of LPS from the intestinal lumen to the bloodstream [11]. On the other hand, n-3 fatty acids, e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have an anti-inflammatory effect, which attenuate the endocannabinoid receptor system tone and may contribute to microbiota balance [12]. Therefore, the quality of fatty acids in diet can modulate gut microbiota composition, which in turn may interfere in host metabolic health [10].

Considering that all factors mentioned above are relevant in the context of obesity, the aim of this chapter is to describe the different mechanisms that link the consumption of SFA or PUFA to the composition of gut microbiota and the impact on the regulation of the target inflammation and, consequently, on the insulin resistance and possible risks of type 2 diabetes and cardiovascular disease, among obese individuals.

2. Gut microbiota composition

Microbiota is the set of microorganisms that inhabit the human body in a symbiotic relationship, which can intervene in the digestion process, metabolism, or in the regulation of fatty acid tissue composition. In the gastrointestinal tract of humans, there are approximately 100 trillion bacteria that make up the microbiota in this system. These bacteria are divided into phyla in which the main gut microbiotas are *Firmicutes* (60–65%) and *Bacteroidetes* (20–25%), followed in smaller quantities by *Proteobacteria* (5–10%), *Actinobacteria* (3%), and *Verrucomicrobia* (<1%) [13–15].

The colonization of the human body begins in uterine life, through contact with the bacteria belonging to the maternal microbiota, and is an important health factor for the mother, including nutritional, metabolic, and immunological status.

Both endogenous and exogenous effects can modify the composition of gut microbiota. Other elements that influence the formation of gut microbiota include host genetics, type of birth delivery (vaginal or cesarean section), diet (breastfeeding or infant formula, and dietary introduction), and use of medications (antibiotic, probiotic, prebiotic, and symbiotic) [16].

Gut microbiota composition seems to have different specificities between lean and obese individuals. Regarding the bacterial species, obese individuals present a greater amount of *Lactobacillus reuteri* and smaller concentrations of *Bifidobacterium animalis*, *Lactobacillus casei*, *Methanobrevibacter smithii,* and *Escherichia coli*, with the demonstrated association with adequate body weight only for *L. casei* and, with obesity, the combination of a decrease in *B. animalis* and an increase in *L. reuteri* [17]. Gut microbiota impacts body fat accumulation and insulin resistance in an experimental study with germ-free mice that received transplanted gut microbiota from wild-type mice. In 2005, the first study that identified the difference between the composition of the microbiota of obese and nonobese animals was published [18]. Obese mice (ob/ob) had a 50% decrease in *Bacteroidetes* and an increase, of equal percentage, in *Firmicutes*, when compared with the wild types [19]. Studies have also shown that this change in microbiota acts at the hypothalamic level, promoting a decrease in the secretion of anorectic hormones [peptide YY (PYY) and glucagon-like peptide-1 (GLP-1)], which, associated with low-insulin sensitivity in the hypothalamus, reduce satiety by increasing food intake [7].

Although studies with animal models have defined that with obesity there is an increase in the *Firmicutes/Bacteroidetes* ratio [18–20], in humans, this hypothesis has not yet been verified, as seen in the conflicting results specifically concerning this ratio [21]. A systematic review found 11 interesting studies on humans that connect gut microbiota composition and body mass index (BMI). Among the main findings, a study reported high concentrations of *B. fragilis* and *Lactobacillus* sp. among obese and overweight children when compared with the lean children. In addition, a negative correlation was found between BMI and *Bifidobacterium* spp. The results suggest the differences between the microbial diversity in lean and obese individuals and thus influence the important metabolic pathways [22]. However, studies of differences in gut microbiota between obese and lean people have not always provided consistent results, which is one of the issues requiring further studies.

3. Fatty acids and gut microbiota

3.1 Short-chain fatty acids and gut microbiota

As lipid factors that influence the intestinal balance and the development of obesity, in this chapter, we will first highlight the short-chain fatty acids (SCFAs). SCFAs are metabolites produced by bacterial fermentation in the gut from dietary fermentable carbohydrates. The main SCFAs are acetate, butyrate, and propionate, which play important roles as nutrients for colon epithelium, modulating gut lumen, intracellular pH, cellular volume, and functions associated with ion transport, proliferation, differentiation, gene expression, reduction of oxidative stress, inflammation recovery, and satiety [23].

Propionate has a role as a substrate for hepatic gluconeogenesis, in addition to inhibiting the synthesis of hepatic cholesterol. Acetate is the most abundant SCFA, being absorbed and metabolized rapidly by the liver, where it serves as a substrate for cholesterol synthesis and lipogenesis [24]. It is also involved in the satiety process by inhibiting pro-opiomelanocortin (POMC) in the hypothalamus [25]. As acetate and propionate exert opposite functions in lipid metabolism in the

liver, the proportion of these two SCFAs is important to maintain lipogenic balance and cholesterol synthesis [26]. Butyrate is found in a lower quantity than the other SCFA in the blood circulation. It is the main source of energy for enterocytes. It acts mainly in cell regulation and proliferation, especially in colon intestinal cells, and plays a role in anomalous cell apoptosis. In addition, it has a function in the maintenance of tight junctions and is responsible for preserving the integrity of the intestinal barrier [27].

SCFA can also modulate the endocrine, immune, and nervous system responses. Propionate interacts mainly with G protein-coupled receptors (GPCR) 41 and GPCR43 in enteroendocrine cells, stimulating the secretion of PYY and GLP-1 hormones, respectively, which has anorexigenic effects, thus contributing to the reduction of food intake. Both hormones promote satiety by acting on the hypothalamic arcuate nucleus, suppressing the neuropeptide Y (NPY), which has an orexigenic effect, and stimulating POMC, which is anorexigenic, in addition to delaying gastric emptying [28]. Binding of SCFA to GPCR43 is also related to increased insulin secretion, improving insulin sensitivity and gut immune response. SCFA interacting with GPCR41 and GPCR43 in adipose tissue also stimulates the secretion of leptin, which suppresses adipogenesis. The interaction with GPCR41 can enhance energy expenditure by increasing the activity of the sympathetic nervous system [29].

Propionate and butyrate induce gluconeogenesis in gut cells, thereby regulating food intake and increasing insulin sensitivity. The interaction of butyrate with GPCR109A expressed in the gut reduces the inflammation mediated by interleukin (IL) 8 and IL-10 and promotes lipolysis in adipose tissue. Acetate and propionate can regulate systemic blood pressure by binding to olfactory receptors located in blood and kidney vessels [29].

Acetate plays a role in appetite directly in the hypothalamus. In the brain, acetate is converted into acetyl coenzyme A (CoA) that participates in the cycle of citric acid leading to the accumulation of adenosine triphosphate, which leads to the reduction of the adenosine monophosphate–activated protein kinase (AMPK) and consequent inhibition of acetyl-CoA carboxylase, favoring the accumulation of malonyl-CoA. This, in turn, has been related to the activation of POMC and the suppression of NPY and peptide related to agouti in the hypothalamus, which leads to a suppression of appetite and, consequently, a reduction in food intake [25].

The SCFAs appear to be involved in lipid oxidation and energy expenditure, increasing both and contributing to weight loss [30]. The mechanism by which SCFAs increase fat oxidation was studied in an animal model. Acetate activates AMPK in adipose tissue and skeletal muscles and regulates peroxisome proliferator gene (PPAR), stimulating lipid oxidation in these organs [31]. In addition, SCFAs are responsible for the increase in PYY and mitigation of lipolysis [32].

Acetate and propionate also appear to inhibit intracellular lipolysis. Propionate increases lipidic buffering in adipose tissue through an increase in the uptake of triglycerides by LPL in adipocytes, favoring the adipogenesis in adipose tissue and reducing the circulation of FFA. These effects improve the insulin sensitivity and reduce the accumulation of ectopic fat, especially in muscles and liver [33, 34]. The mechanisms involved in the prevention of fat stores in the liver occur through the inhibition of fatty acid synthesis by propionate and the increase in AMPK activity and PPAR genes by acetate and butyrate, which raise glycogenesis and FA oxidation in the mitochondria, thus reducing fat stores in hepatocytes [35].

In this context, it appears that these metabolites may be the key between the microbiota and the development of obesity, playing an important role in body weight control and insulin sensitivity. Studies *in vitro* and *in vivo* demonstrate that SCFAs regulate energy homeostasis, glucose, and lipid metabolism and have effects on adipose tissue [36, 37]. As discussed above, they act on appetite through

endocrine regulation, stimulating the secretion of leptin by adipocytes, and on neuronal receptors, modulating neural activity and visceral reflexes [26, 36].

Thus, it is possible to assert that SCFAs, produced by gut bacteria, have an impact with respect to gut microbiota and health, presenting central and systemic effects that may contribute to the maintenance of adequate metabolism, in addition to regulating mechanisms that can prevent the development of obesity and its morbidities [36].

3.2 Long- and medium-chain saturated fatty acids and gut microbiota

Based on their structure, saturated fats can be subclassified into short-chain, medium-chain, and long-chain fatty acids. Medium-chain fatty acids have 8–10 carbon atoms, and long-chain fatty acids have, in general, 12 or more carbon atoms [37]. Animal sources are the main sources of saturated fatty acids in the diet: dairy products, meat, butter, margarine, and hydrogenated vegetable oils. These fatty acids are quite heterogeneous in nature, and their potential effects may also vary in relation to their health effects.

A high-fat diet (HFD), predominantly SFA, has been associated with changes in gut microbiota composition and a reduction in diversity [38, 39], independently of the host genotype [40]. A study conducted with subjects at risk of metabolic syndrome showed that SFA intake increased the composition of pathogenic bacteria [41]. A decrease in *Bacteroidetes* and an increase in *Firmicutes* and *Proteobacteria* after the consumption of HFD have also been reported [42]. A HFD significantly reduced levels of *Bacteroidetes* spp., *Eubacterium rectale*/*Clostridium coccoides,* and *Bifidobacterium* spp. These results reflected in insulin resistance, low-grade systemic inflammation, and higher concentrations of endotoxins in plasma [43]. The levels of *Bilophila wadsworthia*, associated with increased gut inflammation, were elevated when mice were fed with a milk fat–enriched diet [44]. Likewise, higher levels of *B. wadsworthia* were observed in mice that were fed a lard diet than fish oil as a lipid source [39].

As previously reported, an imbalance in bacterial population may lead to an increase in intestinal permeability, with a high translocation of bacteria into systemic circulation, inducing an elevation in circulating LPS and metabolic endotoxemia [45]. HFDs are also associated with a reduction in proteins of the narrow junction [45], whose function is to block the intercellular space, preventing the passage of substances through the intestinal epithelium. Additionally, it is relevant to consider that SFAs represent an essential component of the lipid portion of LPS derived from pathogenic bacteria [46].

Studies also demonstrate that SFA can bind to Toll-like receptor 4 (TLR4) and activate inflammatory signaling pathways [47, 48]. The signaling pathway of the TLR4 is recognized as one of the main triggers of the inflammatory response induced by obesity [2]. Subsequent *in vitro* and *in vivo* studies suggest that fatty acids are able to activate proinflammatory signaling pathways mediated by TLR4 and TLR2, leading to insulin resistance [3]. In addition, a normal weight individual who consumed high-calorie meals (910 Kcal), with high lipid (51 g) and carbohydrate content (88 g), demonstrated distinguishable changes in the TLR postprandial stage, implying a greater activation of TLR2 and TLR4 on blood mononuclear cells. A high-fat meal also resulted in a greater activation of NF-κβ in the postprandial stage and an increase in leukocytes' activation, evaluated by surface expression of CD11a, CD11b, and CD62L [49].

The palmitic acid binding to TLR4 also activates the c-jun N-terminal kinase (JNK) and the inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β) proteins and increases the expression and secretion of pro-inflammatory cytokines [50], also causing damage in insulin signaling [51]. It also impairs insulin signaling pathways, inducing the phosphorylation of IRS-1 at the position of the serine residue

307 [52]. This process reduces the interaction with the insulin receptor and, consequently, decreases its action. In addition, SFAs induce insulin resistance due to the antagonistic action of peroxisome proliferator-activated receptor-1 alpha coactivator, promoting the expression of mitochondrial genes that are involved in oxidative phosphorylation and glucose uptake, which is mediated by insulin [51, 53, 54].

Lauric and palmitic FA activates an inflammatory response through TLR4 signaling pathways [55]. It was reported that the lauric, palmitic, and stearic FA could induce inflammation from cyclooxygenase-2 expression by means of a dependent mechanism of NF-κβ in a macrophage cell line, through a TLR4 connection [56]. It was observed that TLR4 was the main signaling pathway to stress the endoplasmic reticulum caused by a high-fat diet among obese mice, increasing inflammation of the adipose tissue even more [57]. NF-κβ can also be activated by the binding of lauric acid with TLR2, as other studies have demonstrated [47, 56]. Mice fed with a high-fat diet (palmitic) demonstrated a greater expression of TLR2 and inflammatory reduction when TLR2 was inhibited [58]. When palmitic acid binds with TLR4, it also activates JNK and IKK-β kinase protein and also increases the expression of NF-κβ [50], impairing insulin signaling [59].

From another perspective, a recent study argues that long-chain saturated fatty acids (lcSFAs) are not direct agonists of TLR4. The authors suggest that the activation of the inflammatory cascade by saturated fats depends on an initial sensitization of the TLR4-dependent macrophages, which can be generated, for example, by a metabolic endotoxemia resulting from LPS infiltration. The authors justify that lcSFAs take several hours to initiate inflammatory signaling, while LPS activates it in minutes. Macrophages of an insulin-sensitive healthy adipose tissue, in the absence of a priming or a sensitizing signal, do not respond to the inflammatory effects of lcSFA. These data demonstrate that further studies are still needed to elucidate, in detail, the signaling pathways involved in this inflammatory process but highlight the interesting interaction of the intestine-inflammation-obesity axis [60].

Medium-chain saturated fatty acids (mcSFAs) are present in coconut oil and breast milk and are known for their antimicrobial properties, preventing LPS-mediated endotoxemia [61]. Rats fed with mcSFA for 1 week prior to an acute intravenous dose of LPS presented a significant improvement of intestinal permeability compared to rats fed with corn oil, which showed increased gut permeability [62]. Medium-chain fatty acids have also been shown to have a direct impact on the gut bacteria of Gram-positive (low LPS) and Gram-negative (high LPS) subdivisions. A change was observed in the population distribution of *Bacteroidetes/Porphyromonas/Prevotella* phyla and in the genus *Clostridia/Streptococcus* with mcSFA consumption [68]. McSFAs also specifically modulated bacterial populations in specific regions, such as jejunum and colon, promoting the growth of *Escherichia/Hafnia/Shigella* bacteria and the genus *Clostridia* [63].

Given this, it is understood that saturated fats play an important role in the development of obesity, either from their influence on the profile of gut microbiota or from their performance in inflammatory processes. The understanding that the immune system and the different metabolic pathways are closely related and functionally dependent is essential for studies that focus on obesity and the possible metabolic repercussions (**Table 1**).

3.3 Polyunsaturated fatty acids and gut microbiota

Linoleic acid (C18:2 n-6; LA) and α-linolenic acid (C18:3 n-3; ALA) are the parent compounds of the n-6 and n-3 polyunsaturated fatty acid families, respectively. Humans do not have enzymes to insert a double bond in the n-6 or n-3 position, which makes n-3 and n-6 fatty acids essential [64]. Many vegetable oils, such as

FA	Sources	Effects on microbiota and Ref.	Systemic effects and Ref.
Saturated fatty acids			
Short chain (<8 carbon atoms)	Bacterial fermentation (fermentable carbohydrates)	Integrity of the intestinal barrier [27]	Regulate energy homeostasis, glucose, lipid metabolism, and appetite [26, 36, 37]
Medium chain (8–10 carbon atoms)	Coconut oil and milk	Preventing LPS-mediated endotoxemia [61, 62]	Regulate energy homeostasis and satiety [64]
Long chain (>12 carbon atoms)	Meat	Increased pathogenic bacteria [39, 41, 44]	Increased inflammation and insulin resistance [43, 47–49]
Polyunsaturated fatty acids			
n-6 Polyunsaturated	Vegetable oils (e.g., corn, sunflower, and soybean)	Increased endotoxemia [69]	Inflammatory precursors [69]
n-3 Polyunsaturated	Fish oil	Regulate the tight junction functioning, intestinal balance [69, 70, 73]	Anti-inflammatory precursors [70]

FA, fatty acids; LPS, lipopolysaccharide; Ref., references.

Table 1.
Studies in vivo and in vitro about the effects of saturated and polyunsaturated fatty acids in gut microbiota.

corn, sunflower, and soybean oils, are rich in n-6 fatty acids, mainly as LA, but linseed is also a rich source of ALA. In humans, dietary LA can be metabolized to arachidonic acid (lcPUFA—AA, 20:4, n-6), and dietary ALA can be metabolized to long-chain n-3 as eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), mainly in the liver [65]. LcPUFAs are synthesized from dietary LA and ALA by microsomal desaturase and elongation enzymes that metabolize both the n-6 and n-3 families of PUFA, and the delta-6 (delta-6) desaturase is the rate-limiting enzyme in this process [66]. Binding affinity for delta-6 desaturase is highest for ALA, high for LA, and lowest for oleic acid [64], and, for this reason, desaturation and elongation of n-9 PUFA are only observed when combined n-3 and n-6 EFA deficiency occurs. This conversion of the dietary ALA to lcPUFA is limited, and, in humans, it is estimated that only 8% of ALA is converted to EPA and even less to DHA (less than 4%) [67].

Dietary sources of preformed n-3 lcPUFA can provide large amounts of these fatty acids and are primarily derived from certain species of fish (and fish oils or marine lipids). These lcPUFAs are part of the structural components of cell membranes and so affect many aspects of membrane functions such as membrane permeability, receptor functions, and membrane-associated enzyme activities [67].

Dietary intake of n-3 PUFA and its role in inflammatory responses is discussed extensively in the literature and is usually associated with fewer inflammatory effects, while PUFA n-6 effects are more inflammatory. PUFAs have the ability to change the composition of gut microbiota [68]. Intestinal dysbiosis has been implicated in obesity pathogenesis, and the supplementation with n-3 led to the increase in *Lactobacillus* species and decrease in *Bacteroidaceae* family bacteria by improving dysbiosis. On the other hand, supplementation with n-6 had a negative association with the abundance of *Akkermansia muciniphila* [69].

Thus, gut integrity appears to be an important factor for n-3 PUFA action because increased permeability is associated with several disorders (e.g., obesity, DM2, and inflammatory bowel disease). n-3 PUFAs are capable of maintaining the integrity of the intestinal epithelium and thus influence inflammatory bowel status. They serve as precursors to anti-inflammatory substances or even regulate the functioning of tight junctions [70]. In a HFD model (high in saturated fat), an increase was observed in the number of *Bacteroides,* which could lead to decreased gut permeability [71]. Using the same diet protocol, a study reported an increase in *Enterobacteria* that elevate gut permeability, and this phenomenon would lead to a systemic elevation of LPS and endotoxemia and also dysbiosis [72]. Furthermore, an imbalance in the gut microbiota environment (dysbiosis) could lead to a low-grade systemic inflammation by increasing gut permeability to LPS and endocannabinoid system activity [6].

Animal studies have demonstrated that n-3 PUFA protects against dysbiosis, reversing bacterial overgrowth induced by n-6 PUFA dietary intake [73]. On the other hand, among healthy humans, the effects of PUFA, especially n-3, on microbiota are less established, and the literature is limited. However, in a study among patients with inflammatory bowel disease, the supplementation with n-3 was able to revert the microbiota to a healthier composition, with a decrease in the genus *Faecalibacterium* and an increase in the *Lachnospiraceae* family, and the *Roseburia* and *Bacteroidetes* genus. In addition, n-3 PUFAs increase the production of anti-inflammatory compounds like SCFA acids that could be associated with disease reversal [74]. Based on the well-established anti-inflammatory effects of n-3 PUFAs (as EPA and DHA) that are related to a reduction in metabolic endotoxemia and positive changes in gut microbiota, further studies are needed to better understand the role of n-3 PUFA dietary intake in preventing diseases associated with dysbiosis, such as obesity (**Table 1**).

4. Endocannabinoid system

The endocannabinoids (eCBs) are a family of biologically active lipids—derivatives of arachidonic acid, an omega-6 PUFA—that bind to and activate CB1- and CB2-cannabinoid receptors, widely distributed throughout the brain areas, in the central nervous system and in peripheral tissues such as liver, adipose tissue, pancreas, and gut. The main types of eCB are anandamide [N-arachidonoyl ethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG)]. This eCB system is a signaling system with a variety of physiological functions, such as the modulation of the immune and inflammatory response, synaptic plasticity and learning, and regulation of metabolism and energy homeostasis [75]. There is growing evidence that the eCB system, high-fat diets, inflammation, and obesity are interconnected [76, 77].

The CB1 appears to be the key factor in this eCB system for the genesis of obesity. Stimulation of CB1 increases the food intake, enhances the reward aspects of eating, and promotes the energy conservation [78]. In fact, obesity is characterized by increased endocannabinoid system tone and the altered expression of CB1 mRNA, accompanied by increased eCB levels in adipose tissues [79]. On the other hand, evidence also suggests that a high-fat diet increases hepatic AEA levels and CB1 density, which leads to increased fatty acid synthesis and contributes to diet-induced obesity [80]. AEA and 2-AG levels are also increased in adipose tissue and pancreas in diet-induced obese mice [76]. At the same time, studies on animals lacking CB1 receptors (CB1−/− mouse model) demonstrate that they are hypophagic, leaner, and lighter in relation to wild types. Another study showed that when CB1 receptor activity is blocked in obese mice induced by diet, an improvement in the

gut barrier and metabolic endotoxemia was observed, including an alteration in gut microbiota composition, a reduction in body fat, and an improvement in obesity-associated parameters [81].

Studies have emphasized that gut microbiota modulates the intestinal eCB system tone, which, in turn, regulates gut permeability and plasma LPS, and is able to stimulate peripheral endocannabinoids in the gut and adipose tissue [76]. This hyperactivity of the CB1 receptor increases the permeability of the gut barrier, favoring the translocation of more LPS into the bloodstream, which will further stimulate the eCB system, generating a cycle in which both remain altered. In adipose tissue, eCB disturbance leads to adipogenesis, contributing to the accumulation of body fat and, consequently, obesity [82]. LPS and eCB regulate, in different ways, the apelinergic system in adipose tissue, reducing the secretion of apelin and the expression of its AP1 receptor. The apelinergic system plays a role in energy and glycemic homeostasis [83]. Thus, gut microbiota seems to play a significant role in controlling the endocannabinoid system and, consequently, as modulators of obesity and energy homeostasis.

A sham-feeding protocol in rats used to identify fatty-acid profile of dietary fat components that could trigger small-intestinal endocannabinoid signaling. Results have shown that sham-feeding emulsions containing oleic acid (18:1) or linoleic acid (18:2) induce a nearly twofold accumulation of jejunal endocannabinoids, whereas emulsions containing stearic acid (18:0) or linolenic acid (18:3) had no such effect [79]. In a mice model, it was observed that increasing the percentage of linoleic acid (18:2 n-6) in the diet led to increased levels of 2-AG and AEA, which are derived from arachidonic acid (20:4 n-6), which, in turn, is formed from linoleic acid in the body. Interestingly, this was associated with a higher body weight but not with an increased food intake [76]. Studies with rodents and human subjects have also shown that increasing the relative proportion of n-3 long-chain PUFA in the diet can lead to a decrease in the formation of the n-6 (arachidonic acid)-derived endocannabinoids AEA and 2-AG [79, 80]. Thus, dietary lipids can modulate eCB system tone.

5. Modulation of gut microbiota and inflammation by fatty acids: the role of diet

As previously discussed, there are several actions of different types of FA in inflammatory pathways and in gut microbiota. Changes in the dietary quality of lipids can improve inflammatory markers and provide an intestinal balance, preventing the development of diseases [84]. In general, therapeutic protocols suggest that a lower intake of foods rich in saturated fats, trans fats, and sugars and an increase in dietary sources of bioactive fiber and lipids are considered beneficial [92]. Also, the intake of bioactive lipids, which include monounsaturated and PUFA, phytosterols, and medium-chain lipids is beneficial [85].

Regarding fat consumption, it has been reported that postprandial endotoxemia is influenced by the fatty acid composition of the diet and not by the fat content as a whole. Subjects consuming meals rich in omega-3 decreased serum levels of endotoxemia, unlike those who consumed omega-6-rich foods. The omega-6 fatty acids can increase serum triglyceride levels and also cause gut hyperpermeability, favoring the accumulation of fat in adipose tissue and stimulating the inflammatory processes [86].

The consumption of sardines and fish enriched in omega-3 caused a decrease in the *Firmicutes* filo and in the *Firmicutes*/*Bacteroidetes* ratio in patients with no DM2 treatment [87]. The adoption of a Mediterranean diet or low-fat and carbohydrate diet by obese individuals resulted in different changes in gut microbiota, with high

levels of the genus *Roseburia* and *F. prausnitzii*, respectively, demonstrating the protective effects of both diets on the development of DM2 [88]. The consumption of extra virgin olive oil enriched with phenolic compounds has been shown to have a cardio-protective effect, which could be mediated by the increase in the population of bifidobacteria, together with the increase in microbial metabolites and phenolic compounds, which has antioxidant activities [89].

Saturated fats, such as palmitic, lauric, and stearic acids, may be related to the activation of inflammatory processes. A study with healthy young people showed that a reduction in the palmitic acid/oleic acid ratio in the diet resulted in lower secretion of IL-1β, IL-18, IL-10, and tumor necrosis factor alpha stimulated by LPS [90]. A study conducted with subjects at risk of metabolic syndrome showed that the consumption of saturated fat increased the composition of pathogenic bacteria [41].

In infants, the percentage of fat in the complementary diet has been reported to be negatively correlated to the diversity of gut microbiota [91]. In infant formulas, lipids are typically added as vegetable oils, with long-chain fatty acids predominating [92]. However, human milk has a low content of n-6 fatty acids and a high content of medium-chain fatty acids, acting as a prebiotic [93]. Sources of SCFA may be useful for remodeling gut microbiota and reducing obesity.

The beneficial role of the fibers in a high-fat (HF) diet on inflammatory markers and gut microbiota was also verified [94]. A decrease in adipocyte size and IL-6 levels was observed when the fibers were administered as part of a HF diet over a period of 6 weeks. These fibers were able to alter gut microbiota and increase fermentation rates, mainly by stimulating the production of SCFA, demonstrating its role in the prevention of intestinal inflammation, and may increase the beneficial forms of microbiota diversity.

6. Conclusion and recommendations

Determination of the fatty acid composition in the diet is essential for two reasons: first, to understand the pathogenesis and responsiveness of some diseases, such as obesity, and second, to address potential therapeutic interventions. In this chapter, we have demonstrated that there is a direct relationship between excessive fat consumption and microbiota composition. Obesity is closely associated to microbiota composition as well. In other words, an overconsumption of fat induces changes in microbiota composition, which, by its turn, becomes influential to obesity. These connections have been demonstrated both in obese people and in rodent models, that consume an excess of fat, have shown alteration in their microbiota composition. Increased intake of saturated fatty acids and LPS is negatively associated with this process, while a higher intake of food sources of short- and medium-chain fatty acids and n-3 PUFA has shown positive effects (**Figure 1**). It is evidently observed the relevant roles of these lipids in inflammatory processes, in the endocannabinoid system, brain functioning, and behavior, influencing the composition of gut microbiota and, therefore, the functioning of the gut-brain axis. All of these factors have significant implications for the reduction of meta-inflammation and, consequently, insulin resistance and the risk of DM2 and cardiovascular diseases in obese individuals.

As most studies have been conducted on animals and cell culture, we strongly recommend well-controlled, long-term clinical studies in humans, so that we can better understand this complex interaction among dietary fatty acids, gut microbiota, and obesity. Due to the strong anti-inflammatory activities of n-3 PUFA, as well as dietary fibers stimulating the production of SCFA and, therefore,

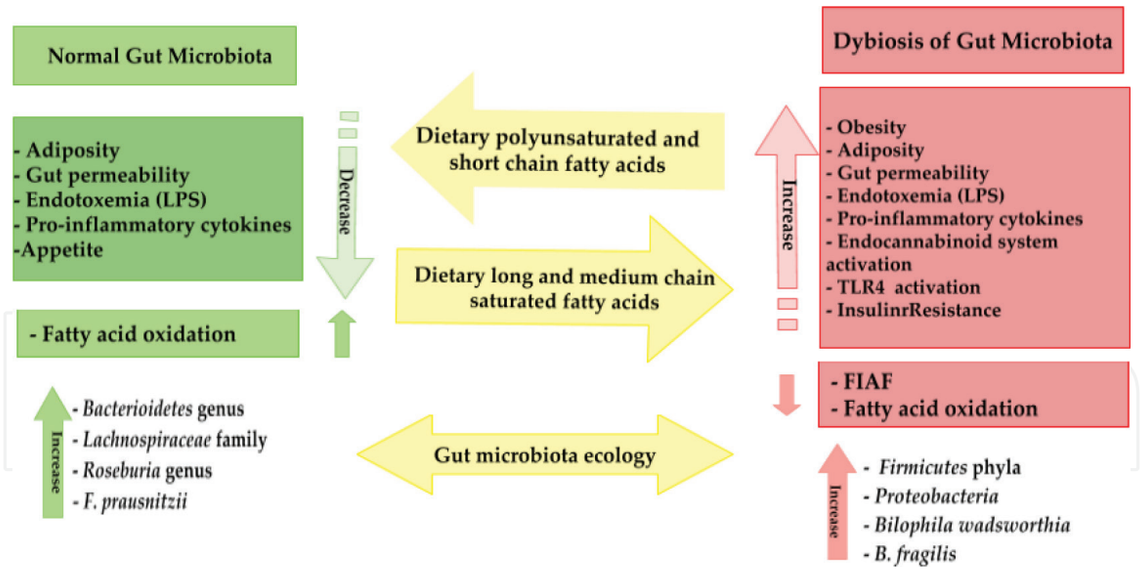

Figure 1.
Impact of dietary fatty acids in the gut microbiota composition and health. A healthy microbiota is associated with the balance between pathogenic and nonpathogenic bacteria that may reflect on systemic consequences. Dietary lipid profile can modulate its composition (yellow arrows). Excessive consumption of SFA (right yellow arrow) will cause negative outcomes to the metabolism and microbiota content (red boxes and arrows). On the other hand, SCFA and PUFA (left yellow arrow) reveal positive effects in inflammation, fat deposition, and microbiota (green boxes and arrows). The two-way arrow (in yellow) represents changes in gut microbiota ecology, depending on what type of FA has been consumed. The equilibrium among these factors seems to be another way to explain the obesity development. FIAF, fasting-induced adipose factor; LPS, lipopolysaccharides; TLR4, Toll-like receptor 4.

influencing the composition of gut microbiota and the host health, we also recommend that dietary fiber and n-3 PUFA should be part of the diet of obese individuals and that dietary SFA and n-6 PUFA should be under control.

Acknowledgements

This work was supported by grants from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro, and Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

2-AG	2-arachidonoylglycerol
AEA	anandamide
AMPK	adenosine monophosphate-activated protein kinase
BMI	body mass index
CB1	type 1 cannabinoid receptor
CB2	type 2 cannabinoid receptor
CoA	coenzyme A
DM2	type 2 diabetes mellitus

eCBs	endocannabinoid
FA	fatty acid
GLP-1	glucagon like peptide 1
GPCR	G protein-coupled receptor
HFD	high-fat diet
IL-1β	interleukin 1β
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IL-18	interleukin 18
JNK	c-jun N-terminal kinase
lcSFA	long-chain saturated fatty acid
LPL	lipoprotein lipase
LPS	lipopolysaccharide
mcSFA	medium-chain saturated fatty acids
NF-κβ	nuclear factor-kappa beta
NPY	neuropeptide Y
POMC	proopiomelanocortin
PPAR	peroxisome proliferator-activated receptor
PUFA	polyunsaturated fatty acid
PYY	peptide YY
SCFA	short-chain fatty acid
SFA	saturated fatty acid
TLR-2	Toll-like receptor 2
TLR-4	Toll-like receptor 4

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