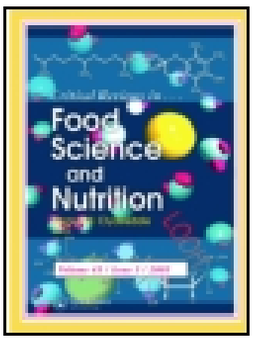

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Dietary fat and gut microbiota: mechanisms involved in obesity control

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Abstract

Obesity is a serious global health problem that is directly related to various morbidities manifestation. Intestinal dysbiosis has been implicated on obesity pathogenesis. Diet composition can alter gut microbiota, regardless of energy intake. Dietary fatty acids quality may affect gut microbiota composition, which in turn may affect host metabolic health. The mechanisms by which the different type of FFA modulate gut microbiota is yet poor elucidate and there is a lack of studies regard to this. Fatty acids may act in cell membrane, interfere with energy production, inhibit enzymatic activities, impair nutrient absorption and generate toxic compounds to cells, leading to growth inhibition or even bacterial death. The beneficial effect of the consumption of n-3 polyunsaturated fatty acids (PUFA) and conjugated linoleic acid (CLA) on microbiota, unlike n-6 PUFA and saturated fatty acids has been suggested. n-3 PUFA consumption promotes desirable changes on obese intestinal microbiota making it similar to that of normal weight individuals. More studies are needed to better understand the effect of CLA on microbiota and host health. Long term human controlled clinical trials must be conducted to allow us to understand the complex interaction between dietary fat, intestinal microbiota and obesity.

Key words: Free fatty acids, dysbiosis, diet, microrganims, antimicrobial.

Introduction

Obesity is a serious global health problem, which is directly related to the manifestation of many morbidities due to mechanisms that involve subclinical inflammation, considered a link between obesity and associated disease (Gomes, Costa, and Alfenas 2015; Swinburn et al. 2011). Intestinal dysbiosis plays a role on obesity pathogenesis by mechanisms that involve, in part, its action on systemic inflammation. Therefore, gut microbiota modulation may be a potential target for obesity therapeutic interventions (Tagliabue and Elli 2013).

Modulation of gut microbiota through the use of antibiotics, prebiotics, probiotics, besides microbiota transplantation are some of the emerging obesity therapies (O'Flaherty et al. 2010; West et al. 2015). However, the high cost, difficulty of maintaining a desirable microbiota in long term basis and the possible health risks affect the applicability of these strategies. Diet, on the other hand, is one of the main determinants of obesity, and may be an accessible target for dysbiosis therapeutic interventions (Cotillard et al. 2013).

Dietary fat is the food component that has the highest antimicrobial action (Desbois and Smith 2010), which is also able to modulate systemic inflammation (Angelakis et al. 2012). Its efficacy to increase the shelf life of food products (Lucera et al. 2012), its use on oral hygiene products (Shino et al. 2016) or for topical infections treatments (Verallo-Rowell, Dillague, and Syah-Tjundawan 2008) have been demonstrated. However, the antimicrobial activity and potential use of dietary fat to control obesity dysbiosis through gut microbiota modulation has been neglected. In the past it was once believed that the small amounts of free fatty acid (FFA) that reached the colon was not enough to affect intestinal microbiota (Salonen and de Vos 2014). However, recent findings indicate that 7% of dietary fat reach the colon in FFA form, even after the consumption of normofat diets by healthy people (Gabert et al. 2011). The influence of dietary fat on gut microbiota has been confirmed by an increasing number of scientific evidences (Chaplin et al. 2015; David et al. 2014; Devkota et al. 2012; Fava et al.

2013; Mujico et al. 2013; Wu et al. 2011). Nevertheless, the mechanisms by which the different type of FFA modulate gut microbiot is yet poor elucidate and there is a lack of studies regard to this.

The undesirable effect of high fat diets on obesity microbiota modulation was recently confirmed in a robust study (E. A. Murphy, Velazquez, and Herbert 2015). Thus, the objective of this review is to critically evaluate the studies in which the role of different dietary fat types on obesity control through gut microbiota modulation, as well as to elucidate the possible mechanisms involved.

Methodology

We searched the electronic Medline/PubMed, Science Direct, Scientific Electronic Library Online (SCIELO) and Latin American and Caribbean Health Sciences Literature (LILACS) databases to identify published studies related to the effects of dietary fat on obesity control through gut microbiota modulation. The following terms were used on the search: intestinal/gut microbiota/microbioma/microflora, dietary fat/fatty acids, obesity/overweight, antimicrobial/antibacterial activity/effect. The terms were used alone or in association and the selected languages were Portuguese, English and Spanish. Original articles and review have been selected according to the titles and abstracts and published in the last 10 years. Articles published before this period were included if justified by their scientific revelation. All articles were read and critically analyzed.

Effects of dietary fat types on gut microbiota

The gastrointestinal tract (GIT) microbiota composition differs along its length. While there is a small diversity and low abundance of microorganisms in the stomach, there is a wide variety and high number of microorganisms in the large intestine. Bile and pancreatic juice limit the number of bacteria present in the small intestine, ranging from ~ 104 / ml in the proximal region to ~ 106-108 / ml in the ileo-cecal region (Walter and Ley 2011). Aerobic and

aerotolerant anaerobic species are prevalent in the small intestine, while strict anaerobes predominate in the colon where there is low oxygen tension (Mowat and Agace 2014).

The largest and most studied human microbial community resides in the colon and it is composed of approximately 1100 distinct species. More than 90% of the bacteria found in the human intestine belong to the *Firmicutes* phylum (including the genera *Clostridium, Enterococcus, Lactobacillus* and *Ruminococcus*), or to the phylum *Bacteroidetes* (including *Bacteroides* and *Prevotella*) (Power et al. 2014). In smaller proportions are the phyla *Actinobacteria*, *Fusobacteria*, *Proteobacteria* and *Verrucomicrobia* (Brahe, Astrup, and Larsen 2013).

The microbiota imbalance (dysbiosis) observed in obese favors the passage of endotoxins, such as lipopolysaccharide (LPS) derived from Gram-negative cell wall (Moreira and Alfenas 2012) from the intestinal lumen to systemic circulation (Yang and Rose 2014). Increased LPS in circulation results in metabolic endotoxemia and consequent low grade inflammation (Kaliannan et al. 2015). Although there is still no consensus on overweight individuals gut microbiota composition, most authors point out a decrease in phylum *Bacteroidetes* and increase of *Firmicutes* (Armougom et al. 2009; Ley et al. 2006). In addition, these people present gut microbiota lower diversity (Clarke et al. 2012).

Many factors such as eating habits, environment and antibiotics use may affect gut microbiota composition (Chen et al. 2016). Gender, age and race also affect microbiota formation (Hullar and Fu 2014). Diet composition, regardless of the consumed calories (Cox and Blaser 2013) or fatty acid (FA) type, carbon chain size and the degree of saturation can also influence microbiota composition (Mujico et al. 2013), acting as a link between intestine and host metabolic health. However, it should be noted that FA only exert this function after being digested and released as FFA within the intestine (Brahe, Astrup, and Larsen 2013). Fat digestion begins in the mouth through the action of lingual and gastric lipases (Mu and Høy 2004). However, pancreatic lipase is primarily responsible for dietary fat hydrolysis, releasing the FFA in the small intestine (Di Maio and Carrier 2011).

Animal studies evidences

The consumption of high fat diet negatively affects the microbiota composition in animal models (Table 1). In general, saturated fat has been supplied as the fat source in high-fat diet studies (Cani et al. 2008; Hildebrandt et al. 2009; E. F. Murphy et al. 2010; Parks et al. 2013; Turnbaugh et al. 2008; Turnbaugh et al. 2009), although the purpose of these studies were not to evaluate the specific effect of this type of fat.

The consumption of high-fat diet (high in saturated fat) by animal models for 3 to 25 weeks, often used to induce obesity, reduces the population of the phylum *Bacteroidetes* and increases *Firmicutes* (Cani et al. 2008; Hildebrandt et al. 2009; E. F. Murphy et al. 2010; Turnbaugh et al. 2008; Turnbaugh et al. 2009). Regarding genera, the dynamics is still controversial, but saturated fatty acids (SFA) appear to decrease *Bacteroides*, *Prevotella*, *Lactobacillus ssp.* and *Bifidobacterium spp.* (Cani et al. 2008; E. F. Murphy et al. 2010; Zhang et al. 2010), making the microbiota profile similar to the one of overweight people and animals.

However, the consumption of diet supplemented with 0.5% of *trans*-10, *cis*-12 conjugated linoleic acid (CLA-t10c12) for 8 weeks resulted in increased *Bacteroidetes* and decreased *Firmicutes* compared with the non-supplemented group. Microbial fermentation in the cecum was also enhanced, resulting in higher concentrations of the short chain fatty acids (SCFA) isobutyrate, acetate and propionate (Marques et al. 2015). These SCFA modulate host metabolism, promote intestinal health, cell differentiation, exerting anti-inflammatory effect (Macfarlane and Macfarlane 2012; Power et al. 2014). On the other hand, supplementation with CLA, although caused beneficial changes in the microbiota, it culminated in hepatic steatosis in the animals (Marques et al. 2015). Thus, more studies with CLA are necessary to know better its effects and adequate dosage.

Animals CLA supplementation (6 mg/day, 50:50 cis-9, trans-11 and trans-10, cis-12 active isomers) caused beneficial changes on microbiota by increasing bacteria population that may favor obesity control, from *Bacteroidetes* filo and *Akkermansia muciniphilia* (Chaplin et al. 2015). *A. muciniphilia* resides in the intestinal mucus layer, it is responsible for degrading mucin, and it is associated with a healthy mucosa. The number of these bacteria reduced in

obesity (Chaplin et al. 2015), besides being negatively correlated with body fat (Parks et al. 2013). These changes verified after supplementation with CLA confirm its beneficial effect in the microbiota of animals (Chaplin et al. 2015). These results may be relevant in the development of strategies for managing body weight, once CLA has been used for body fat loss in humans (Gaullier et al. 2007).

Ghosh and contributors demonstrated that polyunsaturated fatty acids (PUFA) *n*-3 protected rats from dysbiosis, reversing bacterial overgrowth caused by *n*-6 PUFA intake (Ghosh et al. 2013). Bacterial overgrowth is a condition characterized by an up-regulated growth of bacteria in small intestine and causes abdominal pain, swelling, besides of vitamins (such as a B12), fat and protein malabsorption. This condition is not only a quantitative change in gut microbiota, but dysbiosis is frequently presente (Ierardi et al. 2016). Futhermore, *n*-6 PUFA consumption by laboratory animals resulted in *Bacteroidetes* and *Firmicute*s phyla depletion, increased BMI, and infiltration of inflammatory cells into ileum. In contrast, *n*-3 PUFA turned teh infiltration occurrence similar to observed in response to control diet (Ghosh et al. 2013). It was also observed that in rats fed a high-fat diet, *n*-3 PUFA supplementation for 19 weeks increased *Lactobacillus* abundance (Mujico et al. 2013). However, *Lactobacillus* strains were not specified, which is a limitation of that study, since different species associate in different ways with obesity. While *Lactobacillus reuteri* is positively associated with obesity (M Million et al. 2012) and *Lactobacillus acidophilus* with weight gain, *Lactobacillus gasseri* have been associated with weight loss in humans (Matthieu Million et al. 2012).

Human studies evidences

Regarding the effects of dietary fat types on human gut microbiota, data are still scarce. In a controlled study involving 10 subjects (nutritional status not indicated by the authors), fecal microbiota was altered 24h after the initiation of a high-fat/low-fiber or low-fat/high-fiber diet, without affecting the enterotypes (Wu et al. 2011). On the other hand, according to the authors of a cross-sectional study, in which the fecal microbiota composition of 98 subjects was

assessed, the enterotypes are associated with long-term eating habits. Consumption of a diet rich in animal protein and fat, a typical diet of western societies, favors the *Bacteroides* enterotype, while the *Prevotella* enterotype prevails among people with higher fiber, fruit and vegetable consumption (Doré and Blottière 2015; Wu et al. 2011). It is noteworthy that both enterotypes are contemplated in *Bacteroidetes* phyla, which appears to be decreased overweight and obese individuals (Armougom et al. 2009).

Considering the results obtained all the studies presented (animal and human evidences), it seems that there is still no consensus regarding the ways in which different dietary fat types modulate gut microbiota composition. However, there is strong evidence from animal studies that it affects microbiota, since the consumption of *n*-3 PUFAs and CLA was beneficial, unlike *n*-6 PUFA and SFA. Next, we will elucidate possible mechanisms that involves fat antibacterial capacity and consequently its effects on gut microbiota modulation.

Mechanisms involved in obesity control

Among the environmental factors that influence microbiota composition, diet is the easiest to modify and the most accessible form of therapeutic intervention (Wu et al. 2011). Therefore, dietary fat can modulate gut microbiota and play a role on obesity control. Fat regulates the pro/anti-inflammatory diet capacity, in addition to increasing the abundance of beneficial bacteria (Brahe, Astrup, and Larsen 2013), increasing SCFA production by favoring a healthier microbiota (Ríos-Covián et al. 2016).

Antimicrobial activity and gut microbiota modulation

Antibiotics inhibit enzymes involved in specific parts of the bacterial life cycle, increasing the chance of obtaining resistant strains (Ling et al. 2015). On the other hand, fat acts on the cellular envelope (Jackman et al. 2016), reducing mutations frequency that can result in resistant strains. since it This may be another positive point regarding the use of fat as strategies to control the growth of intestinal bacteria related to obesity. . In a study conducted by our research group we confirmed that FFA, even in very small doses, have high antibacterial

activity (data not published yet). Thus, fat seem to be promising agents against the growth of undesirable bacteria,

Dietary fat may decrease the number of some species and genera that are related to body weight excess (Chaplin et al. 2015; David et al. 2014). Fat antibacterial activity depends on its FA composition, as well as its structure and shape, such as carbon chain size and the presence, number, position and orientation of double bonds. The -OH group of the carboxyl group appears to be relevant for the FFA antibacterial activity (Zheng et al. 2005). In order to realize its activity, FFA need to be digested. Pancreatic lipase and colipase digests from 50 to 70% of dietary fat. These enzymes hydrolyze TAG and diacylglycerol (DAG) at the sn-1 and/or sn-3 positions, resulting in 2-monoacylglycerol (2-MAG) molecules and free fatty acids (Birari and Bhutani 2007). 2-MAG is the main form of MAG absorbed in the small intestine. These 2-MAG are rearranged resulting in MAG complete degradation, releasing glycerol and FFA. It seems that about 7% of FA resulting from digestion, after the consumption of normofat diet by healthy subjects, are not absorbed and are excreted through feces (Gabert et al. 2011). This fraction of FFA will pass through the small and large intestines, where it may exert antimicrobial effects, modulating the microbiota.

In general, FA and MAG have a broad spectrum of antibacterial activity because they cause bacterial cell membrane lysis (Jackman et al. 2016), solubilizing it (Shilling et al. 2013) or by indirectly affecting cellular metabolism (Sheu and Freese 1972) (Figure 1). They work as light surfactants that disrupt the bacterial cells membranes, causing bacteriostatic or bactericidal effects (Heerklotz 2008).

The amphipathic structure of FA exert a detergent effect , which may lead to the solubilization of the cell membrane leading to cellular lysis (Desbois and Smith 2010). Medium chain fatty acids (MCFA) and long chain fatty acids (LCFA) both saturated and unsaturated Fas may also prevent regulation of metabolism and/or energy production by the cell, inhibiting bacterial growth (Jackman et al. 2016). When they access cytoplasmic membrane of Gram-positive and Gram-negative bacteria, FAs impair electrons transference, reduce ATP production

and deprive the cell of its essential energy source (Sheu and Freese 1972), affecting its survival.

Among the SFA, lauric acid (C-12) shows the best antimicrobial activity, followed by capric acid (C-10) (Kabara et al. 1972). *In vitro* and *in vivo* (humans) studies showed lauric acid efficacy against *Staphylococcus aureus* (Nakatsuji et al. 2009). Obesity, as well as hyperglycemia and high adiposity related to overweight were associated with increased *S. aureus* population (Olsen et al. 2013). Lauric acid antimicrobial effect can be potentiated when glycerol is esterified, resulting in monolaurim, the medium chain MAG with higher antibacterial activity. Monolaurim is active against pathogenic Gram-positive bacteria and deteriorating bacteria (Batovska et al. 2009), but we could not identidy studies assessing its effect against GIT bacteria. Such studies are extremely relevant due to the relationship between gut microbiota and obesity. Considering the strong antimicrobial activity of lauric acid, it is assumed that if it acts against bacteria that are prevalent in the overweight people GIT, this FFA can modulate the gut microbiota of these people and thus it can help to control obesity. In addition, synergistic interactions may occur between monolaurim and food compounds such as phosphates, antioxidants and acidulants (Batovska et al. 2009), intensifying the antimicrobial effect. Lauric acid and capric acid also reduce the growth of *S. aureus* (Sado Kamdem et al. 2008) and FA *de novo* biosynthesis (Sado-Kamdem, Vannini, and Guerzoni 2009). FA biosynthesis is essential for bacteria because they produce essential fat compounds, including their cell membranes (Zheng et al. 2005).

Unsaturated FA (medium and long chains) tend to be more effective against Gram-positive bacteria than Gram-negative bacteria and are generally more potent than SFA presenting the same carbonic chain (Kabara et al. 1972). The Gram-negative outer membrane behaves as a barrier for FA entry, while the Gram-positive cell wall allows the passage of FA through cytoplasmic membrane (Sado-Kamdem, Vannini, and Guerzoni 2009), facilitating antimicrobial agents action. The presence of double bonds directly increase the efficacy of the unsaturated FA. The naturally occurring double bonds in FA typically exhibit *cis* orientation and these tend to have higher antibacterial activity than those with double bonds in *trans* orientation (Kabara et al. 1972). This is probably because the structures of these trans

unsaturated FA resemble those of the saturated AG (Desbois and Smith 2010). Furthermore, Zheng et al. (2005) demonstrated that PUFA, similar to SFA, also hinder bacterial FA biosynthesis *in vivo* (Zheng et al. 2005), which, in turn, affects cell membrane composition, altering its function and impairs nutrientes uptake (Desbois and Smith 2010).

Alpha-linolenic (C-18: 3), linoleic (C-18: 2) and oleic (C-18: 1) acids also exert antimicrobial effects (Batovska et al. 2009; Huang and Ebersole 2010; Maia et al. 2007). The antibacterial effect of unsaturated FA is mainly mediated by inhibition of membrane or the cytosol enzymes, which are crucial for bacterial survival and growth (Sado-Kamdem, Vannini, and Guerzoni 2009; Zheng et al. 2005). Another possible explanation for unsaturated FA toxicity is related to their auto-oxidation or peroxidation products, which are derived from the metabolic processes and which are antibacterial by themselves (Desbois and Smith 2010).

The insertion of unsaturated FA into bacteria cytoplasmic membrane makes it more fluid and permeable, leading to loss of internal cellular content, inhibiting growth or causing cell death. If the membrane fluidity increases excessively, it becomes unstable, culminating in cellular lysis, which often occurs within minutes (Zhang et al. 2010). On the other hand, SFA may induce bacterial cell wall autolysis in some species, possibly by reducing membrane fluidity. Using a lipid bilayer model, a recent study demonstrated how SFA destabilizes the membrane, altering its morphology and consequently bacterial metabolism (Yoon et al. 2015).

The specific interaction between antimicrobial fats and bacterial cell membrane still needs to be better understood. In fact, fats have a broad spectrum of mechanistic behavior, with inherent details of chemical structure and concentration of each compound. A few studies evaluated this potential against GIT microrganisms perhaps neglecting that effect, since the highest concentration of bacteria is found in the large intestine (Mowat and Agace 2014) and most FA are absorbed in the small intestine (Iqbal and Hussain 2009). Similar mechanism was observed in ruminants, through an *in vitro* study with *n*-3 and *n*-6 PUFA, which showed that these FA were effective against rumen bacteria (Maia et al. 2007). Limitations such as FA solubility and distribution of microrganisms along the GIT may make it difficult to precisely determine how much FA come into contact with specific types of bacteria *in vivo* (Maia et al.

2007). Extrapolation of such results to humans, suggest that these FA are also effective against human GIT bacteria, being able to modulate gut microbiota of overweight people, and thus contribute to control obesity.

SCFA: microbiota metabolite

The ingestion of different fat types can increase SCFA production, regardless of the amount of carbohydrates and proteins ingested (Cox and Blaser 2013). SCFA are energy sources for colonic epithelium (Power et al. 2014). Gut microbiota acts on dietary fiber and protein that were not completely hydrolyzed by enzymatic reactions. Fibers fermentation by colonic bacteria results in SCFA formation (Kimura et al. 2013), like acetic acid (C-2), propionic acid (C-3) and butyric acid (C-4) (Ríos-Covián et al. 2016). The latter, in particular, exerts beneficial effects on intestinal health (Power et al. 2014) by favoring the maintenance of a healthy intestinal barrier (Cox and Blaser 2013). The barrier integrity prevents LPS translocation into circulation, preventing weight gain, body adiposity and insulin resistance (Cox and Blaser 2013).

There is a positive association between SCFA production by gut bacteria and obesity control showing positive health impacts (Ríos-Covián et al. 2016). Recent evidence suggests that higher SCFAconcentration are associated with lower body fat content in animals (Marques et al. 2015).

Besides supplying energy to enterocytes, SFCA transmit signals via G-protein-coupled receptors GPR41 and GPR43 (or free fatty acid receptors-FFAR 3 and 2, respectively). GPR41 is also activated by propionate, butyrate and pentatonate, while GPR43 prefers propionate to other SCFA (Ichimura et al. 2009). SCFA activate enteroendocrine cells GPR41, which, in turn, induce peptide YY secretion, hormone responsible for reducing intestinal transit time and increasing satiety (Cox and Blaser 2013). SCFA also activate GPR43 receptors, expressed in adipose, immune and intestinal tissues. When SCFA bind to GPR43, they regulate energy uptake by the adipose tissue and prevent fat accumulation in adipocytes by promoting their use by the liver (Kimura et al. 2013). The activation of GPR43 by acetate reduces lipolysis and

activates adipogenesis, indicating a potential role of this FA on plasma fat profile regulation (Ichimura et al. 2009). Adipocytes treated with acetate and propionate had reduced lipolytic activity. This inhibition of lipolysis occurred due to FFAR2 activation, because this effect was suppressed in adipocytes of animals without this receptor (Ichimura et al. 2009). Furthermore, a study conducted in overweight adults has shown that increased concentrations of propionate prevented body weight gain. Propionate significantly stimulated the secretion of the peptide YY and glucagon-like peptide 1 (GLP-1), reducing food intake (Chambers et al. 2015). Taken together, these endocrine signals sent by the SCFA contribute to control obesity.

Dietary supplementation with butyrate protected rats against obesity induced by saturated fat consumption. This effect was associated with increased energy expenditure, fat oxidation and maintenance of normal blood glucose levels (Gao et al. 2009). The improvement in glycemic control was also observed by a 50% decrease in fasting insulin concentration, an improvement in the response to intraperitoneal insulin tolerance test and a lower HOMA-IR in comparison to control group. These results suggest that butyrate prevented obesity and insulin resistance in animals (Gao et al. 2009).

Finally, SCFA production reduces luminal pH, which in turn can inhibit undesirable microorganisms growth and increase absorption of some nutrients, contributing to host health (Macfarlane and Macfarlane 2012). The production of SCFA seems to play an important role in the maintenance of intestinal barrier, in microbiota composition (Ríos-Covián et al. 2016) and consequently in obesity treatment.

Anti-inflammatory effects and others benefits

Intestinal dysbiosis is associated with metabolic endotoxemia and low grade inflammation, both observed in obesity (Ley et al. 2006). In overweight subjects, the microbiome diversity was considered a predictive factor of weight loss and improvement of metabolism and inflammatory profile in response to hypocaloric diets (Cotillard et al. 2013). The connection between gut microbiota and low grade inflammation with infiltration of macrophages in the adipose, muscular and hepatic tissues characterizes the progression of obesity to metabolic disorders (Brahe, Astrup, and Larsen 2013).

The metabolism of propionate and butyrate has gained the researchers attention in recent years due to the connection between low concentration of bacterial populations producing these compounds in some diseases in which the inflammatory process is present (Ríos-Covián et al. 2016). It was observed a lower abundance of butyrate producing bacteria in feces of patients with type 2 diabetes compared with control group of healthy people (Qin et al. 2012), suggesting a protective role of butyrate on metabolic diseases related to obesity. In addition, butyrate has anti-inflammatory properties. Butyrate is able to regulate intestinal barrier function and prevent LPS passage from the intestinal lumen into systemic circulation (Yang and Rose 2014), preventing the occurrence of metabolic endotoxemia and low-grade inflammation associated with obesity (Kaliannan et al. 2015).

Diet affects cell membrane FA composition of several tissues, with PUFA w-3 being of most interest among researchers. An increase MUFA and PUFA diet content tends to increase the content of these FAs in most membrane phospholipids (Abbott et al. 2012; Andersson et al. 2002). In contrast, changes in SFA consumption do not interfere on FA membrane content. Adipose tissue FAs are the most responsive to dietary modifications of both SFA, MUFA and PUFA (Abbott et al. 2012). Dietary FA composition influences inflammation by transforming FA profile of cell membranes and adipose tissue, thus altering availability of substrates for pro-inflammatory eicosanoids (such as arachidonic acid, C20:4 n-6) or antiinflammatory agents (eicosapentaenoic acid - C20: 5 n-3- and docosahexaenoic acid-C2:6 n-3) (Calder 2011). In summary, the excessive consumption of n-6 PUFA, such as in Western diets, leads to n-3/n-6 ratio imbalance. That imbalance culminates in arachidonic acid concentrations increase, and hence to the manifestation of chronic inflammation and its associated diseases, such as obesity (Abbott et al. 2012).

In addition, the interaction between tissues FA composition and gut microbiota plays an important role on anti-inflammatory effect exerted by n-3 PUFA. An increase in tissues n-3 PUFA content increases the production and secretion of alkaline phosphatase intestinal enzyme, which induces changes in microbiota composition. This leads to decreased LPS production and gut permeability, reducing metabolic endotoxemia and inflammation (Kaliannan et al. 2015).

Intestinal alkaline phosphatase is an endogenous antimicrobial peptide with numerous physiological functions (Lallès 2010). It is highly expressed in the small intestine, being secreted by apical enterocytes into the lumen and goes to the large intestine (Kaliannan et al. 2015). That enzyme also inhibits Gram-positive bacteria growth by dephosphorylation of ATP, to prevent *Escherichia coli* and other Gram-negative overgrowth due to its ability to dephosphorylate the LPS located on the outer membrane (Koyama et al. 2002) and promote TGI commensal bacteria growth (Malo et al. 2014). Thus, n-3 PUFA (as EPA and DHA) stand out for their anti-inflammatory properties (Coelho et al. 2016), which are related to reduction of metabolic endotoxemia (Kaliannan et al. 2015) and positive changes in gut microbiota (Pusceddu et al. 2015).

In addition to SCFA, human gut microbiota also synthesizes vitamin K in the menaquinone form (OHSAKI et al. 2006). Vitamin K reduces triglycerides concentration, body fat, and LPS induced inflammation favoring obesity and comorbidities control (Sogabe et al. 2011) and (OHSAKI et al. 2006). High vitamin K consumptio was also associated with improved insulin sensitivity, lower waist circumference, lower BMI and systemic arterial blood pressure (Dam et al. 2015). Overweight people usually present a microbiota composition that impairs vitamin K production by gut bacteria. Thus, indirectly, the modulation exerted byfat on colonic bacterial population can also favor obesity control via vitamin K synthesis and its benefits.

Conclusion and perspectives

In conclusion, the results of these studies suggest that the modulation of specific bacterial populations abundance, such as increasing *Bacteroidetes* and reducing *Firmicutes*, may be beneficial on obesity treatment. The quality of dietary fat directly affects in different ways the integration between FFA, gut microbiota and obesity. Although CLA promotes beneficial changes on gut microbiota composition, further studies are needed to better understand CLA isomers effect on microbiota and host health. Consumption of n-3 PUFA promotes favorable changes in obese gut microbiota, turning it similar to eutrophic people, as

opposed to SFA. Due to the paucity of controlled long-term clinical studies in humans, this complex interaction is not fully understood yet by scientific community. However, the strong antimicrobial activity of FFA, as well as its side effects on gut microbiota (SCFA production, anti-inflammatory effect and vitamin K synthesis) suggest that especially PUFA may be effective on obesity treatment, acting as the link between intestine and host metabolic health.

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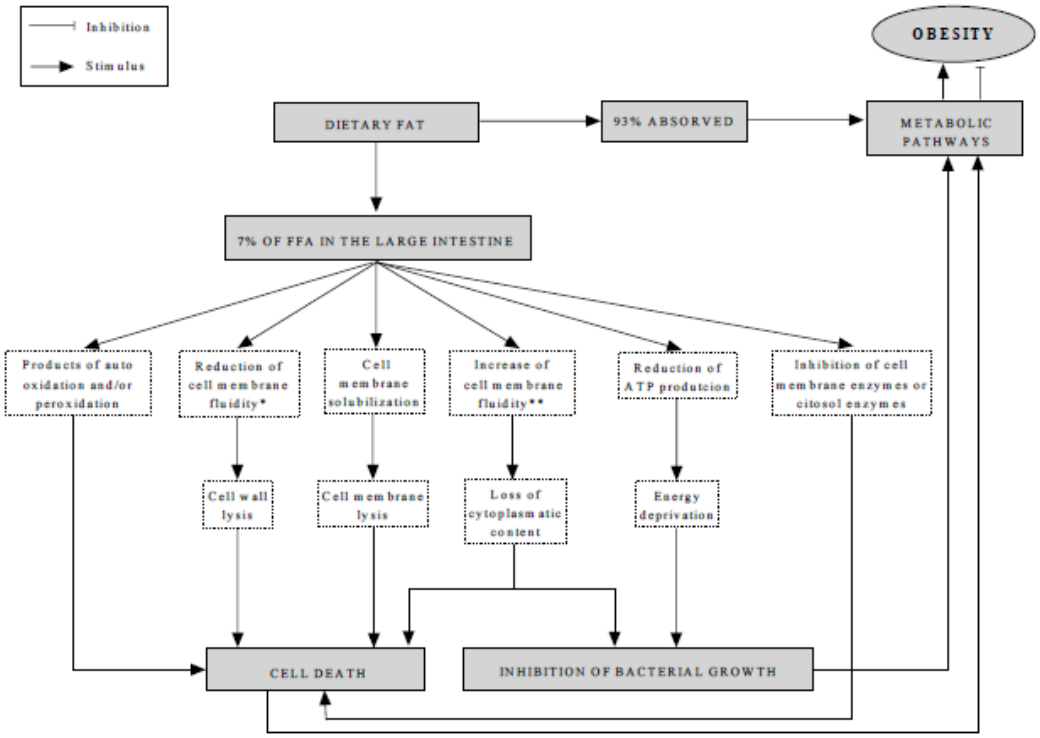

Figure 1. Possible mechanisms involved in bacterial cell death induction or bacterial growth inhibition exerted by free fatty acids, which in turn may change the host metabolism. FFA: free fatty acids. *Mechanism established for saturated fatty acids. ** Mechanism established for unsaturated fatty acids.

Table 1. Studies in which the effects of dietary fat on gut microbiota was assessed.

FA	Intervention	Duration	Effects on microbiota	Ref.
SFA	CD or no carbohydrate HF (72% fat: corn oil and lard)	4 w	HFD ↓ *Bacteroides*, *Prevotella* and *Lactobacillus* ssp.; ↑ *Bifidobacterium* spp.	Cani et al. (2008)
	Polysaccharides rich diet (16% fat), LFD or HFD (41% SFA and PUFA)	8 w	HFD ↓ bacterial diversity and *Bacteroidetes*; ↑ *Firmicutes* (*Molicutes* class).	Turnbaugh et al. (2008)
	LFD or HFD (40,6% fat as beef tallow: 41% SFA, 17% trans, 35% MUFA and 7% PUFA)	8 w	HFD ↑ *Catenibacterium mitsuokai, Clostridium innocuum, Eubacterium dolichum, Erysipelotrichi* and *Enterococcus*; ↓ *Bacteroidetes.*	Turnbaugh et al. (2009b)
	CD or HFD (45% fat: 87,6% lard and 12,3% soy oil)	21 w	HFD ↓ *Bacteroidetes* and ↑ *Firmicutes*, *Clostridiales* and *Delta-Proteobacteria.*	Hildebrandt et al. (2009)
	LFD (10% lip) or HFD (45% fat: lard)	15 w	HFD ↑ *Firmicutes* and ↓ *Proteobacteria e Bifidobacterium.*	Murphy et al. (2010)
	LFD (5,2% lip) or HFD (34,9% fat)	25 w	HFD ↑ *Desulfovibrionaceae* and ↓ *Bifidobacterium spp*.	Zhang et al. (2010)
	LFD (5% lip) or HFD (38% fat: lard, milk or sunflower oil)	3 w	HFD (milk and sunflower oil) ↓ *Firmicutes* and ↑ *Bacteroidetes*. LFD ↑ *Firmicutes* and ↓ other phyla abundance.	Devkota et al. (2012)
	CD (4% lip), HFD (34,3% fat as: 16,1% SFA, 12,6%	19 w	HFD ↑ *Enterobacteriales* and ↓ fecal DNA total contente.	Mujico et al. (2013)

	MUFA and 5,5% PUFA)			
	CD (12% fat: 61,5% soy oil and 38,5% lard) or HFD (43% fat: 35,5% soy oil 64,5% lard)	7 w	HFD ↓ *Bifidobacterium* spp.	Chaplin et al. (2015)
PUFA	CD (9% lip), HFD (40% fat: 20% canola oil, 20% corn oil or 19% corn oil + 1% fish oil)	5 w	HFD with fish oil protected against bacterial overgrowth caused by *n*-6 PUFA.	Gosh et al. (2013)
	CD (4% fat) or HFD + *n* -3 PUFA (3g/kg/day of EPA and DHA)	7 w	*n* -3 PUFA↑ *Firmicutes* and *Lactobacillus* group.	Mujico et al. (2013)
MUFA	CD (4% fat) or HFD + oleic acid-derived compound (1,5g/kg/day)	7 w	Oleic acid-derived compound reestablished total DNA content similar to CD and ↑ *Bifidobacterium* e *Bacteroidetes.*	Mujico et al. (2013)
CLA	CD (12% fat: 61,5% soy oil and 38,5% lard) or 64,5% lard) or HFD + CLA (6 mg)	7 w	HFD ↓ *Bifidobacterium* spp. CLA supplementation ↑ *Bacteroides* and *Prevotella.*	Chaplin et al. (2015)
	CD (6,2% fat) or 0,5% CLA supplementation (6,7% fatt)	8 w	CLA supplementation ↓ *Firmicutes* e ↑ *Bacteroidetes;* ↓ *Desulfovibrionaceae*, *Lachnospiraceae* and *Peptococcaceae* e ↑ *Porphyromonadaceae*	Marques et al. (2015)

↑: increased; ↓: decreased; FA: fatty acid; CD: control diet; HFD: high-fat diet; LFD: low-fat diet; w: weeks; d: days; SFA: saturated fatty acid; PUFA: polyunsaturated fatty acid; MUFA: monounsaturated fatty acid; CLA: conjugated linoleic acid.