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Impact of dietary fat on gut microbiota and low-grade systemic inflammation: mechanisms and clinical implications on obesity

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ABSTRACT

Dietary fat strongly affects human health by modulating gut microbiota composition and low-grade systemic inflammation. High-fat diets have been implicated in reduced gut microbiota richness, increased Firmicutes to Bacteroidetes ratio, and several changes at family, genus and species levels. Saturated (SFA), monounsaturated (MUFA), polyunsaturated (PUFA) and conjugated linolenic fatty acids share important pathways of immune system activation/inhibition with gut microbes, modulating obesogenic and proinflammatory profiles. Mechanisms that link dietary fat, gut microbiota and obesity are mediated by increased intestinal permeability, systemic endotoxemia, and the activity of the endocannabinoid system. Although the probiotic therapy could be a complementary strategy to improve gut microbiota composition, it did not show permanent effects to treat fat-induced dysbiosis. Based upon evidence to date, we believe that high-fat diets and SFA consumption should be avoided, and MUFA and omega-3 PUFA intake should be encouraged in order to regulate gut microbiota and inflammation, promoting body weight/fat control.

Introduction

Obesity is the most prevalent noncommunicable disorder worldwide, and a major concern for public health (de Heredia et al. 2012). This concern is partially attributed to its association with hypertension (Dorresteijn et al. 2012), type 2 diabetes (Abdullah et al. 2010), cardiovascular disease (Abbasi et al. 2013) and some types of cancers (Harvey et al. 2011). Obesity, as well as associated disorders, has an inflammatory component that is considered a link between these illnesses. Thus, there is great scientific interest in identifying strategies to control the inflammation (Tabas and Glass 2013).

It has been suggested that gut microbiota plays a role in the pathogenesis of obesity (Ley et al. 2005, 2006; Turnbaugh et al. 2006; Turnbaugh, Hamady, et al. 2009; Turnbaugh, Ridaura, et al. 2009) by mechanisms that involve, in part, its action on systemic inflammation (Blaut and Klaus 2012). Higher number of Gram-negative bacteria and increased intestinal permeability in obese microbiota favour the occurrence of metabolic endotoxemia characterised by a high

concentration of lipopolysaccharides (LPS) in the bloodstream (Brun et al. 2007). Metabolic endotoxemia leads to low-grade inflammation, insulin resistance, adipocyte hyperplasia, and reduction of pancreatic beta-cells function (Brun et al. 2007; Krajmalnik-Brown et al. 2012).

Although the most studied dietary factor associated with gut microbiota changes has been prebiotic soluble fibres and probiotics (Davis 2016; Yoo and Kim 2016), the amount of dietary fat as well as its fatty acid composition can affect gut microbiota. Dietary fatty acids may have a potent antimicrobial activity, but its effect on the relationship between obesity and gut microbiota has been neglected. Antimicrobial activity of fatty acids is more explored as a way to increase the shelf-life of food and not to induce changes in gut microbiota (Desbois and Smith 2010). Furthermore, high-fat diets have been implicated in reduction of gut microbiota richness (Zhang et al. 2010; Devkota et al. 2012), increased LPS translocation (Ghoshal et al. 2009), intestinal permeability (Ji et al. 2011), systemic inflammation (Wall et al. 2010), and disruption of the immune system (Shi et al. 2006; Suganami, Tanimoto-Koyama,

et al. 2007; Suganami, Mieda, et al. 2007; Cani and Delzenne 2011). Therefore, there is a growing interest in assessing the role of fat content and type in obesity induction mediated by gut microbiota (Shi et al. 2006; Suganami, Tanimoto-Koyama, et al. 2007; Suganami, Mieda, et al. 2007; Hildebrandt et al. 2009; Laugerette et al. 2011; Moreira et al. 2012).

Thus, the aim of this review is to critically analyse human and animal studies in which the roles of dietary fat on gut microbiota, obesity and low-grade systemic inflammation were investigated. It is intended, therefore, to clarify important issues on this topic and to provide scientists and clinicians a whole and realistic update about the subject.

Methods

Medline/Pubmed, Science Direct, and Lilacs databases were searched for studies published from 2006 to 2016 about the topic of interest. Studies published before this period were also included when its relevance justified the inclusion. Main terms used alone or in combination for search were: gut microbiota; inflammation; obesity; metabolic endotoxemia; dietary fat; fatty acids; probiotics; high-fat diet. All articles were selected if they were related to obesity, dietary fat and gut microbiota interactions. Each selected article was then studied critically. In order to describe our findings, we presented the following sections in this article: "Gut microbiota in obesity", "Dysbiosis, weight gain, and low-grade systemic inflammation", "Role of dietary fat on obese dysbiosis and inflammation" and "Role of probiotics/synbiotics in reversing high-fat diet induced dysbiosis".

Gut microbiota in obesity

Excessive energy consumption is certainly an environmental factor associated with obesity and metabolic diseases. However, when people from the same population consume excess of energy, some subjects exhibit lower susceptibility to weight gain and metabolic changes (Tappy 2004). This fact suggests involvement of gut microbiome, in addition to human genome, on the onset of obesity (Cani and Delzenne 2007).

Most bacteria that inhabit human and mice gastrointestinal tract (99%) belong to four major phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* (Figure 1). There is still no consensus among researchers regarding the dynamics of bacterial phyla, genera and species in faecal microbiota of obese and overweight subjects compared with those of normal weight subjects (Tagliabue and Elli 2013).
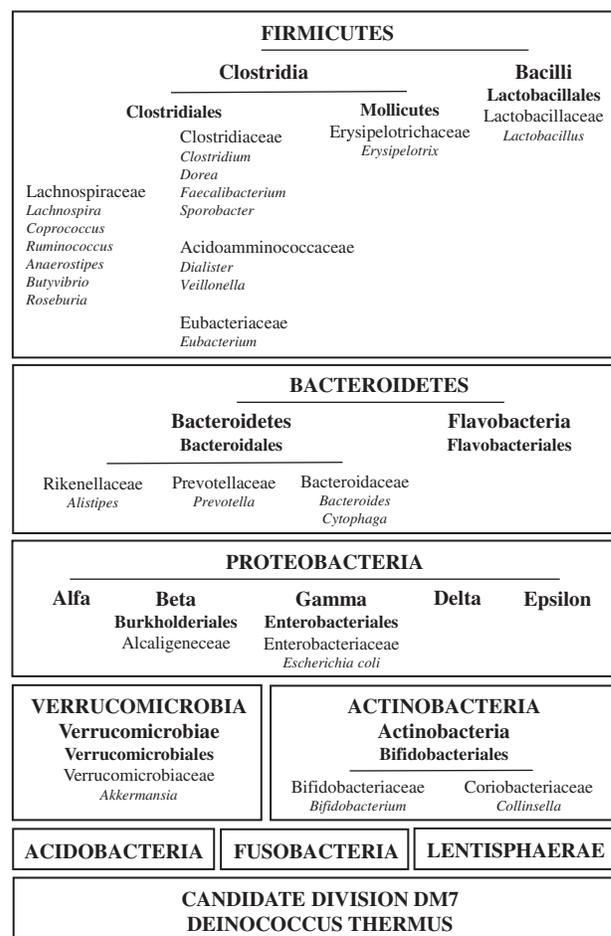
Figure 1. Bacterial hierarchy in gut microbiota. Reprinted from "The role of gut microbiota in human obesity: recent findings and future perspectives" (Tagliabue and Elli 2013), Copyright number: 4092850566123 (2017), with permission from Elsevier.

However, obese dysbiosis have been consistently correlated with an increased ratio of two dominant microbial groups, *Firmicutes* and *Bacteroidetes*, both in rodents (Ley et al. 2005; Turnbaugh et al. 2008) and humans (Ley et al. 2006). In addition, obesity is associated with lower bacterial diversity (Turnbaugh, Hamady, et al. 2009).

Jeffrey Gordon was the first to suggest that changes in gut microbiota may contribute to development of obesity (Bäckhed et al. 2004; Ley et al. 2005, 2006; Turnbaugh et al. 2006). Conventional mice showed an increase of 42% in body fat compared to germ-free mice, although their food intake was lower. Germ-free mice gut colonisation with gut microbiota from conventional mice, in turn, increased to 60% its body fat and, in addition, caused insulin resistance (Bäckhed et al. 2004).

Environmental effects on gut microbiota and our ability to manipulate it in a controlled manner are under increasing study. More recent research has

suggested the use of faecal/gut microbiome transplantation, which involves the transfer of faeces from a healthy donor to a recipient. Until recently, for example, there was no consistently effective treatment for recurrent *C. difficile* infection, which leads to considerable mortality and morbidity, including chronic diarrhoea, colitis, and toxic megacolon. However, faecal/gut microbiome transplantation is being increasingly viewed as the treatment of choice for recurrent *C. difficile* infection (Weingarden et al. 2015; Jayasinghe et al. 2016). As such, faecal/gut microbiome transfer holds significant promise as a treatment for the rapid and concerted modification of an unhealthy microbiota. This practice is now being considered for a wider range of disorders, including obesity and type 2 diabetes (Jayasinghe et al. 2016).

Dysbiosis, weight gain and low-grade systemic inflammation

Reduced bacterial richness seems to play an important role on the onset of excessive weight gain. Le Chatelier et al. (2013) demonstrated that individuals with a low bacterial richness are characterised by more marked adiposity, insulin resistance, dyslipidaemia and low-grade systematic inflammation when compared with high bacterial richness individuals. Dietary changes can restore gut microbial gene richness resulting in clinical phenotypes (Cotillard et al. 2013).

It has been proposed that detrimental changes in gut microbiota could promote weight gain by increasing energy supply to body and lipogenesis (Bäckhed et al. 2004; Ley et al. 2006; Turnbaugh et al. 2006; Bäckhed et al. 2007; El Aidy et al. 2013; Alex et al. 2014). Dysbiosis-induced weight gain could also promote inflammation *per se*, since adipocyte hypertrophy favour macrophages recruitment in adipose tissue (Moreira et al. 2012) and ectopic deposition of triglycerides in liver and muscles promotes proinflammatory factors' secretion by macrophages (Olefsky and Glass 2010). Furthermore, dysbiosis could induce low-grade systemic inflammation by raising intestinal permeability to LPS and endocannabinoid system (ECs) activity (Cani et al. 2007; Muccioli et al. 2010).

Increased energy supply by intestinal microbiome is due to short-chain fatty acids (SCFA) production which can be oxidised by the host providing extra calories (Moreira et al. 2012). It is estimated that more than 10% of total energy requirements can be supplied by dietary fibre fermentation (Bergman 1990). Many biological effects seem to be mediated by these bacterial metabolites. SCFA, especially acetate, propionate and butyrate, can exert indirect effects in gene expression regulation by binding to G-protein-coupled receptors GPR41 and GPR43 (Tremaroli and Bäckhed 2012). Signalling through these receptors is associated with increased expression of glucagon-like peptide 1 (GLP-1, mechanism involving GPR43) and peptide YY (PYY, GPR41 pathway), both in the gut (Zhou et al. 2008). While both peptides are related to reduced hunger and appetite, PYY also decreases intestinal transit and may increase nutrients absorption including SCFA (Blaut and Klaus 2012), favouring weight gain. Bacterial fermentation of carbohydrate and proteins produces SCFA that emerge as mediators in linking nutrition, gut microbiota, physiology and pathology. The amount and relative abundance of SCFA need to be further investigated (Ríos-Covián et al. 2016).

In addition, gut microbiota may favour fat gain by increasing adipocyte lipogenesis (Bäckhed et al. 2007; Alex et al. 2014). Gut microbiota composition could suppress Fasting Induced Adipocyte Factor (FIAF) expression by interacting with entero-endocrine cell surface molecules, such as Toll-like receptors (TLR) (Bogunovic et al. 2007; El Aidy et al. 2013). FIAF is a peptide which is a potent inhibitor of circulating lipoprotein lipase (LPL) (El Aidy et al. 2013). Although FIAF suppression occurs only in intestinal epithelium, and not in liver and adipose tissue where this factor is also produced, it increases LPL activity in adipocytes leading to triglycerides deposition (Bäckhed et al. 2004). Furthermore, it could promote fat gain by changing fat absorption and turnover. FIAF–/– mice exhibited higher intestinal fat uptake and lower fat excretion resulting in obese phenotype (Mattijssen et al. 2014).

The LPS and other compounds from gut microbiota, such as lipoteic acid, peptidoglycan, flagellin and bacterial DNA can stimulate the immune system and induce inflammation. The LPS, however, is considered a main inflammation inducer (Cani et al. 2007) through interaction with TLR4. This inflammation inhibits the appropriate insulin signalling and leads to insulin resistance (Hildebrandt et al. 2009). Under normal conditions, only small concentrations of LPS exceed intestinal epithelium and reach the bloodstream of healthy subjects (Laugerette et al. 2011). In an obesity state, microbial dysbiosis can modulate the distribution of the tight junctions proteins, such as zonula occludens-1 (ZO-1) and occludin, increasing intestinal permeability and the passage of molecules like LPS into the bloodstream, leading to low-grade systemic inflammation (Cani and Delzenne 2011). On the other hand, low-grade systemic

inflammation could increase intestinal permeability by reducing intestinal mucous layer thickness and increasing severity of inflammation (Swidsinski et al. 2007), resulting in a vicious cycle of obesity, increased intestinal permeability, and inflammation.

Obesity is characterised by increased ECs activity. ECs is an important target in the context of obesity and inflammation. It has been demonstrated that ECs was involved in the control of glucose and energy metabolism, and ECs activity can be tuned up or down by specific gut microbes (e.g. *Akkermansia muciniphila*) (Cani et al. 2014). Intestinal microbiome and ECs relationship is crucial for adipogenesis regulation (Muccioli et al. 2010). While gut microbiota modulates ECs, it in turn regulates intestinal permeability and plasma LPS concentrations (Pagotto et al. 2006; Cani and Delzenne 2011). Muccioli et al. (2010) demonstrated that specific changes in gut microbiota after prebiotic ingestion could modify ECs activity in colon and adipose tissue. Blockage of the cannabinoid receptor CB1 reduced intestinal permeability by improving distribution and location of tight junction proteins in obese mice, whereas CB1 activation increased permeability markers *in vivo* and *in vitro* (Muccioli et al. 2010). In addition, changes in gut microbiota and ECs activity regulate expression of adipose tissue hormones (e.g. apelin), which could aggravate low-grade inflammation (Geurts et al. 2011).

Further, diet composition and gut microbiota are closely linked (Daniel et al. 2014), and interaction between gut microbiota and dietary lipids could affect endogenous cholesterol metabolism (Caesar et al. 2016). According to Kübeck et al. (2016), it would be the dietary cholesterol associated with changes in cholesterol-derived metabolites cross-talk between gut microbiota and host metabolism, responsible for obesity development, probably by increasing cholesterol synthesis.

The impact of the proposed mechanisms (Figure 2) for humans still needs further investigations. However, understanding how the composition of the gut microbiota may influence this mechanism may help in the treatment of obesity.

Role of dietary fat on obese dysbiosis and inflammation

Some dietary components, such as fat, have been shown to modulate gut microbiota and, consequently, influence all the mechanisms shown above. Both the amount and quality of dietary fat are related to the induction of obesity mediated by gut microbiota. This discussion is summarised in Figures 2 and 3.

Clinicians and scientific researches have been underestimating the contribution of dietary fat on gut microbiota modulation for years, based on the argument that degradation and absorption of dietary fat mainly take place in the small intestine, thus little, if any, dietary fat could reach the colon in healthy individuals (Salonen and de Vos 2014). The numbers of bacteria generally increase going down the gastrointestinal tract, ranging from $\sim 10^8$ bacteria per g (dry weight) of ileal contents and up to 10^{12} bacteria per g (dry weight) in the colon (Berg 1996). Hence, the gut microbiota was not expected to interact substantially with dietary fat (Salonen and de Vos 2014).

Recent findings, however, lead us to refute this argument. Gabert et al. (2011) showed that about 7% of 13C labelled dietary fatty acids were excreted in healthy subjects, and almost all of them ($\sim 86\%$) were recovered as free fatty acids. This means that fat presence in stool was not due to digestive failure, since digestive lipases were able to hydrolyse triglycerides into free fatty acids.

Free fatty acids, in turn, showed potent antimicrobial effect at very small doses (Huang et al. 2010). It means that fat would significantly interact with gut microbiota, even if only a small portion of the ingested fat reaches the colon. Furthermore, a large volume of *Lactobacillus* and other aerobics and aerotolerant bacteria which also colonise the small intestine (Naidu et al. 1999; Mowat and Agace 2014) are closely related to obesity outcomes (Naidu et al. 1999; Núñez et al. 2014; Raso et al. 2014; Karimi et al. 2015; Song et al. 2015), and thereby likely to substantially interact with dietary fat. Given these findings, we are convinced that dietary fat plays a relevant role in gut microbiota modulation, which could partly explain the deleterious effects of fat imbalance.

High-fat diets

Excessive consumption of high-energy-density foods, especially those derived from fat, has an undoubted role on positive energy balance resulting in weight gain. However, this mechanism is insufficient to explain all metabolic disruptions in obesity. Recognition of the relationship between high-fat diets, gut microbiome and metabolic endotoxemia is recent and can partly explain the manifestation and maintenance of a subclinical inflammatory status that favours the development of insulin resistance and associated diseases (Hildebrandt et al. 2009; Laugerette et al. 2011; Moreira et al. 2012). Table 1 summarises studies that investigated the role of high-fat diets on obesity-induced dysbiosis. Remarkably, changes in the
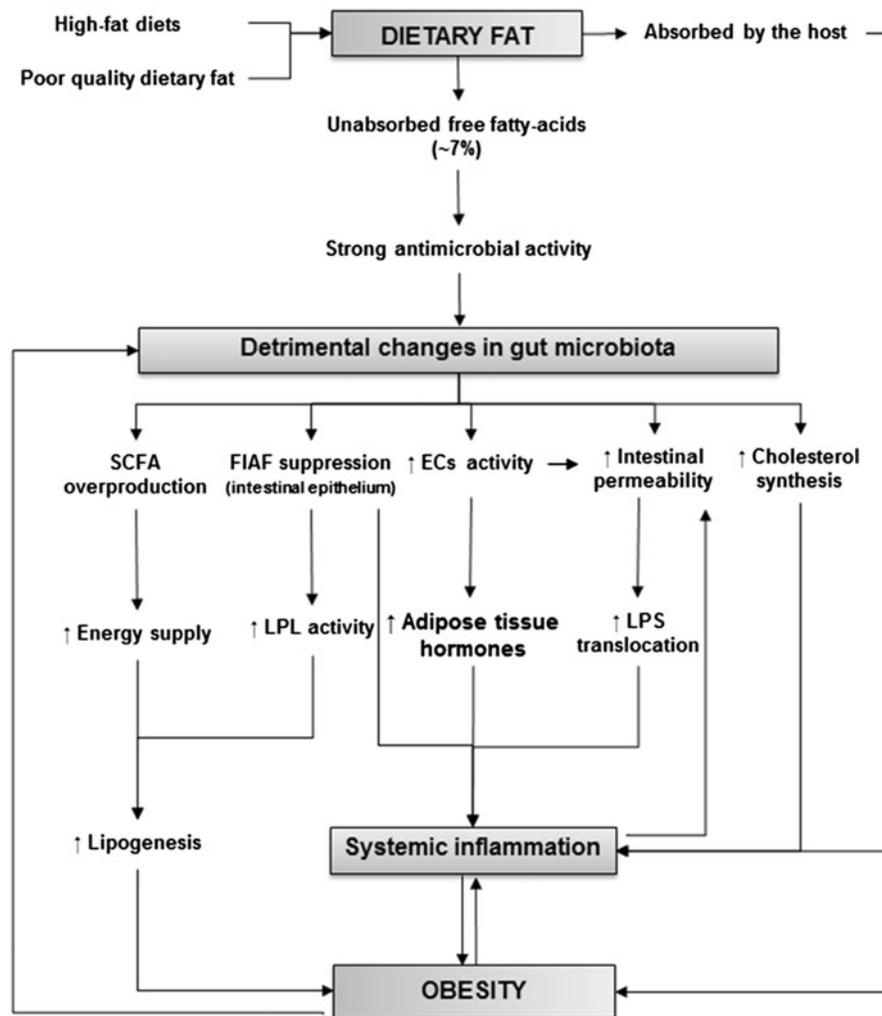
Figure 2. Potential role of high-fat/poor quality dietary fat on gut microbiota, systemic inflammation and obesity. SCFA: short-chain fatty acids; FIAF: fasting induced adipocyte factor; LPL: circulating lipoprotein lipase; LPS: lipopolysaccharide; ECs: endocannabinoid system.

composition of the human microbiome were detectable within 24 hours of initiating controlled feeding (high-fat/low-fibre or low-fat/high-fibre diet) (Wu et al. 2011).

Results from animal studies revealed the supremacy of a high-fat diet in promoting gut microbiota disruption when compared with genetically induced obesity (Turnbaugh et al. 2008; Hildebrandt et al. 2009). Analyses of animal faeces by 16S rRNA gene pyrosequencing showed that high-fat diet changed gut microbiota in both wild-type and knockout RELMβ mice (Hildebrandt et al. 2009). These changes were characterised by increased abundances of *Firmicutes*, *Proteobacteria* and *Actinobacteria*, followed by a reduction in abundance of *Bacteroidetes*. Since wild-type mice became obese and knockout mice remained relatively thin, authors concluded that diet effect was dominant and that high-fat diet, and not obese state, accounted for changes in microbial composition

(Hildebrandt et al. 2009). Similarly, 16S rRNA pyrosequencing of faeces revealed no differences in gut microbiota composition between ob/ob leptin-deficient mice and wild-type mice at the beginning of experiment (Turnbaugh et al. 2008). While low-fat diet did not change microbiota composition over the time in both wild type and genetically obese mice, *Firmicutes* ratio increased significantly from 56% to 71% when wild-type mice were fed with high-fat diet (Turnbaugh et al. 2008). These findings suggest the supremacy of high-fat diet to impair gut microbiota by increasing *Firmicutes/Bacteroidetes* ratio compared with genetically induced obesity. Also, a high-fat diet (60% of fat) compared to a high-carbohydrate diet (66% cho, 23% ptn, 11% fat) exhibits similar results (Daniel et al. 2014).

High-fat diets can increase the proportion of Gram-negative bacteria, induce LPS translocation by incorporation into chylomicrons during fat absorption,
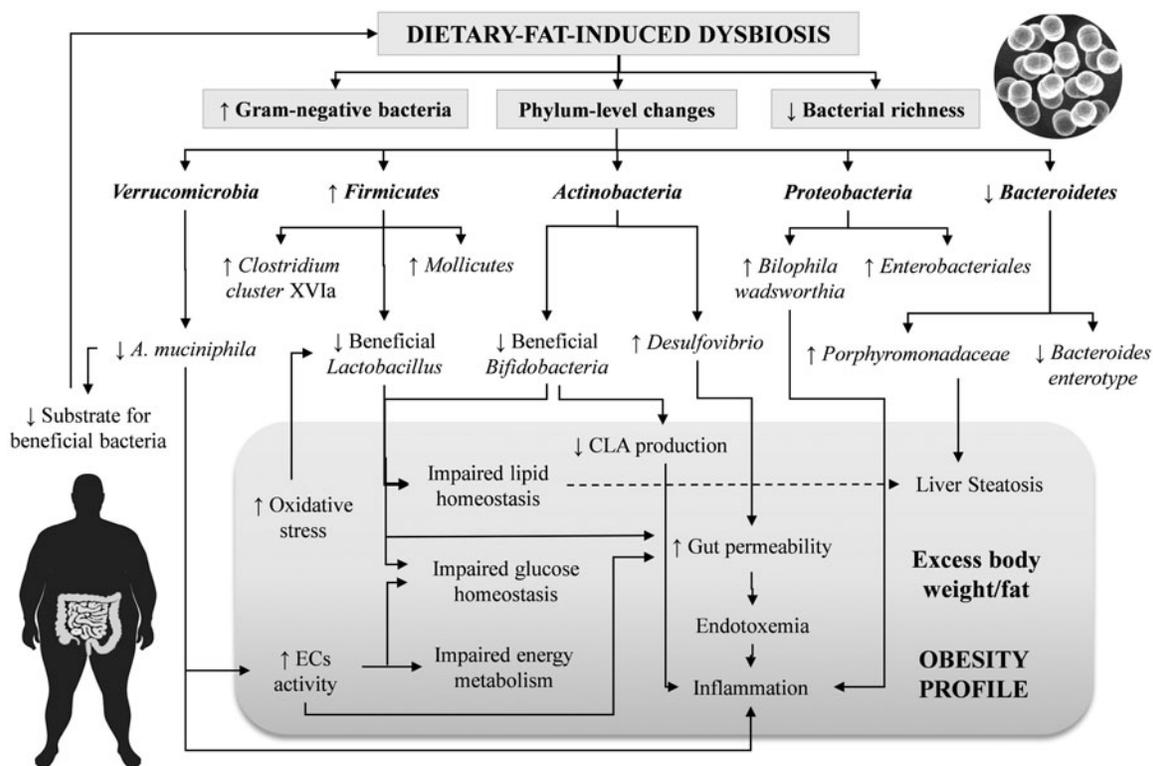
Figure 3. Schematic model regarding dietary fat-induced dysbiosis and metabolic disruptions related to obesity. The effects may vary according to type and amount of fat consumed. All the above-mentioned bacterial changes are related to body weight/fat gain, but these relationships were suppressed in order to improve figure clarity. Arrows indicate pathways of stimulation. CLA: conjugated linoleic acid; ECs: endocannabinoid system.

and reduce intestinal mucosa integrity (Cani et al. 2007; Ghoshal et al. 2009) raising blood concentrations of LPS. Reduction in the expression of tight junction proteins was observed in intestinal mucosa of animals receiving high-fat diets (Cani et al. 2008; de La Serre et al. 2010; Suzuki and Hara 2010).

Increased content of fat in diet can influence the phylum *Actinobacteria*, which plays an essential role on obesity maintenance (Turnbaugh, Hamady, et al. 2009). These diets reduce the number of beneficial Gram-positive *Bifidobacterium* species, increase plasma LPS concentrations, and induce low-grade inflammation (Cani and Delzenne 2011). Likewise, *Desulfovibrio* bacteria growth has been observed during high-fat diet consumption. These bacteria are Gram-negative, opportunistic pathogens, endotoxins producers (Weglarz et al. 2003; Devkota et al. 2012), and are also capable of reducing sulphate to H_2S, damaging gut barrier and promoting inflammation (Zhang et al. 2010; Rey et al. 2013).

The number of the beneficial mucin-degrading bacteria *Akkermansia muciniphila*, a member of *Verrucomicrobia* phylum that colonises mucus layer (Belzer and de Vos 2012), was reduced after consumption of high-fat diet (Everard et al. 2013).

A. muciniphila is found in about 3–5% of microbial community of healthy subjects (Derrien et al. 2004; Belzer and de Vos 2012), and is inversely correlated with body weight in animals (Everard et al. 2011, 2013) and humans (Collado et al. 2008; Karlsson et al. 2012). Close proximity of *A. muciniphila* to human intestinal epithelium has been associated with protective immune system stimulation and anti-inflammatory properties (Zhang et al. 2009; Png et al. 2010; Santacruz et al. 2010). *A. muciniphila* could also contribute to re-establishment of a healthy mucus-associated microbiota after infection by offering oligosaccharides and SCFA from mucus and providing substrates for beneficial bacteria growth (Derrien et al. 2004; Belzer and de Vos 2012). Nevertheless, causal relationship between dietary factors and *A. muciniphila* is not well established and could be influenced by energy restriction (Remely et al. 2015).

It has been emphasised that dietary fat cannot be metabolised under anaerobic conditions. Therefore, it could not serve as an energy source for strict anaerobic bacteria (Blaut and Klaus 2012). Since most bacteria that inhabit our gastrointestinal tract are strict anaerobes (e.g. Clostridia, *Bacteroides*, *Eubacterium*, *Peptostreptococcus* and *Bifidobacterium*)

Table 1. Summary of studies investigating the role of high-fat diets on obesity-induced dysbiosis.

Study	Study population	Diets	Main outcomes
Animal studies			
Cani et al. (2008)	12-wk-old male wild-type C57bl6/J mice	Control diet or carbohydrate-free HFD (72% of fat as corn oil and lard) for 4 wk.	HFD decreased the amount of *Lactobacillus* ssp. and *Bacteroides-Prevotella* spp. and increased *Bifidobacterium* spp Changes in gut microbiota due to HFD consumption induced metabolic endotoxemia, increased the caecal content of LPS, and were correlated with reduced glucose intolerance, body weight gain, fat mass development, lower inflammation, oxidative stress, and macrophage infiltration in visceral adipose tissue
Turnbaugh et al. (2008)	8–9-wk-old male C57BL/6J mice standardised for gut microbiota	Low fat, high polysaccharides diet (16% of fat) or HFD (41% as SFA and PUFA) for 8 wk.	HFD decreased the overall bacterial diversity HFD increased *Firmicutes*, especially *Mollicute* class, and decreased the *Bacteroidetes*
Hildebrandt et al. (2009)	14-wk-old female knockout RELMβ mice and wild-type 129Svev/C57BL/6	1. RELMβ mice on standard chow 2. RELMβ mice on HFD (45% of fat: lard −87.6% and soybean oil −12.3%) 3. Wild-type mice on standard chow 4. Wild-type mice on HFD Experimental period: 21 wk	HFD increased *Firmicutes* class, *Clostridiales* and *Delta-Proteobacteria* and decreased more than 30 different lineages of *Bacteroidetes* on both wide-type and RELMβ mice
Turnbaugh et al. (2009)	8–9-wk-old male C57BL/6J mice standardised for gut microbiota	HFD (data not shown)	HFD ↑*Erysipelotrichi* and bacilli (mainly *Enterococcus*), *Clostridium innocuum*, *Eubacterium dolichum*, and *Catenibacterium mitsuokai*, and ↓*Bacteroidetes*
De La Serre et al. (2010)	Male Sprague-Dawley rats exhibiting either an obesity-prone (DIO-P) or obesity-resistant (DIO-R) phenotype	Low-fat diet (10% of fat: SFA − 5.1%; MUFA − 34.7%; PUFA − 40.2%) or HFD (45%: SFA − 36.3%; MUFA − 45.3%; PUFA − 18.5%) for 12 wk.	HFD decreased total bacterial density and the proportion of *Bacteroidales* and *Clostridiales* orders in both phenotypes HFD increased intestinal permeability, plasma LPS, ileal inflammation associated with TLR4 activation, and decreased intestinal alkaline phosphatase, an enzyme that detoxifies LPS in DIO-P rats
Murphy et al. (2010)	7-wk-old male ob/ob mice and C57BL/6J wild-type mice	Ob/ob mice fed with low-fat diet (10% of fat) vs. wild-type mice fed either a HFD diet (45%) or a low-fat-diet (10%) for 11 and 15 wk	HFD increased *Firmicutes* after 15 wks and decreased *Proteobacteria* after 11 and 15 wk *Bifidobacterium* levels were lower in HFD wild-type mice when compared to lean wild-type after 11 wk
Suzuki and Hara (2010)	4-wk-old Otsuka Long Evans Tokushima Fatty (OLETF) (obese strain), and Long Evans Tokushima Otsuka (LETO) (lean strain) rats	Low-fat diet (19% of fat) or HFD (53%: lard − 76.7%; soybean oil − 23.3%) for 16 wk.	HFD increased intestinal permeability and decreased tight junction proteins (claudin-1, claudin-3, occludin and junctional adhesion molecule- 1) expression in small intestine regardless the strain
Zhang et al. (2010)	10–12-wk-old male wild type C57BL/6J and Apoa-I knockout mice	Low fat diet (5.2% of fat) or HFD (34.9%) for 25 wk.	HFD explained 57% of the total structural variation in gut microbiota HFD increased the *Desulfovibrionaceae* and reduced *Bifidobacterium* spp
Devkota et al. (2012)	Pathogen-free C57Bl/6 mice	Low-fat diet (5% of fat) or HFD (38%) derived from milk, lard, or safflower oil during 3 wk	Both HFD reduced the richness of the microbiota compared with low-fat diet; Low-fat diet increased *Firmicutes* but also decreased the abundance of most of other phyla
Everard et al. (2013)	10-wk-old male C57BL/6 mice	Control diet or HFD (60% of fat: lard − 90.6% soybean − 9.3%)+*A. muciniphila* by oral gavage (2108 CFU/0.2 mL) for 4 wk	*A. muciniphila* treatment reversed HFD induced metabolic endotoxemia, adiposity, body weight, and improved body composition and reversed diet-induced fasting hyperglycaemia *A. muciniphila* administration increased the intestinal levels of endocannabinoids, the gut barrier, and gut peptide secretion

(continued)

Table 1. Continued

Study	Study population	Diets	Main outcomes
Mujico et al. (2013)	8-wk-old female ICR mice	Control diet (4% of fat) or HFD (34.3%: SFA – 16.1%; MUFA – 12.7%; PUFA – 5.5%) for 19 wk	HFD decreased the total DNA content in the faeces but increased *Enterobacteriales*
Daniel et al. (2014)	Male C57BL/6NCrl mice/6 mice	HFD (60% of fat) or high-carbohydrate (11% of fat) for 12 wk	HFD altered the gut microbiota composition, increased *Firmicutes* and decreased *Bacteroidetes* after 12 wk
Human studies			
Wu et al. (2011)	Interventional study with health adults	Low-fat/high-fibre diet (13% of fat) or HFD/low-fibre (38%) for 10 days	HFD caused changes in microbiome composition after 24 hours of intervention and this changes were stable within 10 days of study

Fat amounts are presented as percent of total dietary energy content.
HFD: high-fat diet; ZO-1: zonula occludens-1; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; LPS: lipopolysaccharides; TLR4: toll-like receptor 4; wk: weeks.

(Russell et al. 2011), the use of dietary fat as an energy source for gut microbiota growth should not be a prominent mechanism for explaining high-fat induced dysbiosis. Otherwise, when dietary fat content is increased, there is usually a low content of other dietary compounds such as carbohydrate and fibre (Hildebrandt et al. 2009; Turnbaugh, Ridaura, et al. 2009; Murphy et al. 2010; Wu et al. 2011), which could bias the outcome. Low carbohydrate and fibre diets could reduce energy substrates for beneficial bacteria growth such as bifidobacteria (Cani et al. 2009) and *A. muciniphila*, since administration of prebiotics was able to increase its number by ∼100-fold in obese mice (Everard et al. 2011).

Despite the detrimental changes in gut microbioma due to high fat consumption, dietary manipulations can reverse high-fat-induced dysbiosis and then obesity. While high-fat diet increased *Firmicutes/Bacteroidetes* ratio, marked by bloom in the class *Mollicutes* and a dramatically drop-down in overall class diversity, and promoted body weight/fat gain, reduced-fat diet diminished the bloom in *Mollicutes*, increased relative abundance of *Bacteroidetes*, and reduced fat deposition (Turnbaugh et al. 2008). Probiotic administration is another way to manipulate high-fat-induced dysbiosis and obesity, which will be further discussed.

Dietary fat types

Recent studies showed that different types of dietary fat (saturated fatty acid, monounsaturated fatty acid – MUFA and polyunsaturated fatty acids – PUFA), and not only the excess of fat in diet, could change gut microbiota composition and obesity profile (Wu et al. 2011; de Wit et al. 2012; Mujico et al. 2013; Simões et al. 2013; Patterson et al. 2014). Table 2 summarises studies that investigated the role of dietary fat types on obesity-induced dysbiosis.

Consumption of high-SFA palm oil diet induces higher weight gain compared to high-MUFA olive oil diet, high-PUFA safffower oil or low-SFA palm oil diet in mice (de Wit et al. 2012). This obesogenic effect was followed by a reduction in microbial diversity and an increase in *Firmicutes/Bacteroidetes* ratio. Although the above mentioned results fit typical obesity profile (de Wit et al. 2012), the study clearly indicates that overffow of SFA to distal intestine causes microbiota changes rather than obesity itself.

Habitual intake of MUFA, omega-3 PUFA and omega-6 PUFA differently affects the numbers of certain gut bacterial groups studied (Simões et al. 2013). While MUFA and omega-6 PUFA consumption were

Table 2. Summary of studies investigating the role of dietary fat types on obesity-induced dysbiosis.

Study	Study population	Diets	Main outcomes
Animal studies			
Devkota et al. (2012)	Pathogen-free C57BL/6 mice	1. Low-fat diet (5% of fat) 2. HFD (38%: milk fat – 68,5%) 3. HFD (38%: lard – 50%) 4. HFD (38%: safflower oil – 87%) Experimental period: 3 wk	PUFA (safflower oil) and SFA (milk-derived) increased *Bacteroidetes* and decreased *Firmicutes* abundances in a distinctly way of lard-based SFA diet SFA (milk-derived) showed a significant bloom in *B. wadsworthia*, a member of the *Deltaproteobacteria*
de Wit et al. (2012)	9-wk-old C57Bl/6J mice	Low-fat palm oil diet (10% of fat, soybean oil – 55.5% and palm oil – 44.5%) or HFD (45%) with palm oil, olive oil, or safflower oil for 8 wk	HFD with palm oil induced the highest body weight gain and liver tri-glyceride content HFD with palm oil reduced microbial richness and increased the *Firmicutes/Bacteroidetes* ratio HFD with palm oil elevated lipid metabolism-related genes in the distal small intestine which were previously associated with the metabolic syndrome.
Mujico et al. (2013)	12-wk-old female pathogen-free mice	1. Standard diet for 15 wk 2. HFD (60.3% of fat: 91.2% from lard; 8.82% of soybean oil) for 15 wk 3. HFD for 8 wk and HFD-supplemented with oleic acid for another 7 wk 4. HFD for 8 wk and HFD- supplementation with a combination of n-3 fatty acids (EPA and DHA) for another 7 wk	HFD increased body weight, which was reduced by oleic-acid supplementation. Oleic-acid markedly increased total bacterial density and restored the proportions of bacteria that were altered due to HFA consumption EPA and DHA supplementation increased the amounts of *Firmicutes* (especially the *Lactobacillus*) Oleic-acid, EPA, and DHA supplementation lead to a better gut-microbiota profile, which were associated with lower body weight
Patterson et al. (2014)	8-wk-old wild type C57BL/6J mice	Low-fat diet (12% of fat with equal amounts of the tested fat) or HFD (45%) from palm oil, olive oil, safflower oil, or a combination of flaxseed/fish for 16 wk	Palm oil supplementation reduced the number of *Bacteroidetes* compared to olive oil Olive oil consumption increased *Bacteroidaceae* number compared to palm oil, flaxseed/fish oil and high sucrose Flaxseed/fish oil diet increased tissue concentrations of EPA, docosapentaenoic acid, and DHA, and the intestinal population of *Bifidobacterium* low-fat diet
Marques et al. (2015)	Male 8–9-wk-old C57BL/6 mice	Standard diet supplemented with *t*10c12-CLA (0.5%, w/w) or with no supplementation (control) daily for 8 wk	*t*10c12-CLA supplementation decreased visceral fat mass and affected lipid mass composition, but did not affect body weight *t*10c12-CLA increased caecal content of acetate, propionate and isobutyrate *t*10c12-CLA reduced the *Firmicutes* to *Bacteroidetes* ratio, increased proportions of *Porphyromonadaceae* and decreased abundance of *Lachnospiraceae* and *Desulfovibrionaceae*
Human studies			
Wu et al. (2011)	Cross-sectional study in healthy adults	–	*Bacteroidetes* and *Actinobacteria* phylum were positively associated with fat, whereas *Firmicutes* and *Proteobacteria* showed the opposite association Within each phylum, not all lower-level taxa demonstrated similar correlations with dietary components Taxa correlated with BMI also correlated with fat and percent calories from SFA
Simões et al. (2013)	Cross-sectional data was assessed in monozygotic twin pairs with distinct body weight and body fat classification were assessed for habitual dietary intake and faecal microbiota	–	Co-twins with similar daily energetic intake had more similar numbers of *Bacteroides* spp. when compared with the ones with different energy intakes Higher MUFA intake was associated with lower numbers of *Bifidobacterium* and slightly higher numbers of *Bacteroides* spp. Co-twins who ingested identical levels of SFA had very similar *Bacteroides* spp. n3-PUFA intake resulted in a significant positive association with *Lactobacillus* abundance n6-PUFA intake was associated with decreased numbers of *Bifidobacterium*

Fat amounts are presented as percent of total dietary energy content.
HFD: high-fat diet; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; SFA: saturated fatty-acids; PUFA: polyunsaturated fatty-acids; *t*10c12-CLA: *trans*-10, *cis*-12-conjugated linoleic acid; BMI: body mass index; wk: weeks.

negatively associated with an increase in *Bifidobacterium* numbers, an increased ingestion of omega-3 PUFA was positively associated with a higher number of bacteria from the *Lactobacillus* group. Interestingly, Martín-Peláez et al. (2015) suggested, for the first time, a potential prebiotic activity of an olive oil enriched in virgin olive oil and thyme phenolic compounds since they stimulated specific growth of bifidobacteria in the human gut (Martín-Peláez et al. 2015). Although consumption of omega-3 PUFA could be beneficial because several lactobacilli enhance the function of the intestinal barrier (Anderson et al. 2010), Simões and colleagues found no association between BMI, microbiota composition and fatty acid intake (Simões et al. 2013). However, this study (Simões et al. 2013) does not allow us to establish causal relationship between fatty acid consumption and gut microbiota composition due to its observational data.

In a metagenomic study with healthy volunteers, bacteroides enterotype was found to be highly associated with fat consumption, in particular with MUFA and SFA (Wu et al. 2011). Patterson et al. (2014), studying the impact of dietary fatty acids on gut microbiota composition in mice, showed a reduction in *Bacteroidetes* at phylum level in animals fed with high-fat dietary palm oil diet compared to high-fat olive oil diet. High-fat olive oil diet, in turn, increases populations of *Bacteroidaceae* family compared to high-fat palm oil diet, high-fat flaxseed/fish oil diet and low-fat high-sucrose diet. Omega-3 rich high-fat flaxseed/fish oil diet lead to increase in *Bifidobacterium* spp. compared with low-fat high-maize starch diet. These data indicate that SFA (palm oil) consumption could lead to detrimental changes in gut microbiota, but MUFA (olive oil) and omega-3 (flaxseed/fish oil) consumption could be positive to host microbial ecosystem.

Detrimental impact of SFA on gut microbiota composition and inflammation was proven in a robust study (Devkota et al. 2012). Consumption of diet high in SFA derived from milk promoted the growth of low-abundance, sulphite-reducing pathobiont, *Bilophila wadsworthia* in mice. This observation was associated with proinflammatory T helper type 1 (TH1) immune response. These effects were mediated by milk-derived fat-promoted taurine conjugation of hepatic bile acids, which increases organic sulphur availability used by sulphite-reducing microorganisms like *B. wadsworthia*. Although the above-mentioned study (Devkota et al. 2012) was conducted to verify the impact of SFA on intestinal inflammation, not in low-grade systemic inflammation, these data provide plausible mechanistic basis to explain why diets high in SFA diets might increase prevalence of obesity.

Gut microbiota modulation by different kinds of dietary fat could change body weight (de Wit et al. 2012; Mujico et al. 2013) or visceral fat mass even in very small doses (Marques et al. 2015). Oleic acid-derived compound supplementation reduced body weight, increased total bacterial density and restored proportions of bacteria that were increased (i.e. *Clostridium cluster* XVIa and *Enterobacteriales*) or decreased (i.e. *Bifidobacterium* spp.) due to a high-fat diet feeding in mice (Mujico et al. 2013). In the same experiment (Mujico et al. 2013), supplementation of omega-3 PUFA series (such as eicosapentaenoic – EPA and docosahexaenoic acid – DHA) significantly increased the amount of *Firmicutes* (especially *Lactobacillus* group) without reductions in body weight. This study suggests oleic and omega-3 series fatty acids have the potential to beneficially modulate gut microbiota, with the former benefiting weight control.

Using a very small dose of dietary *trans*-10, *cis*-12-conjugated linoleic acid (CLA) (0.5% w/w) (Marques et al. 2015), showed a significant reduction of visceral fat mass in mice which received the supplementation as compared to the control animals. This reduction was accompanied by a beneficial decrease in *Firmicutes* to *Bacteroidetes* ratio. However, CLA supplementation increased total weight and triglycerides concentrations in liver and promoted possibly harmful changes in gut microbiota at genus and family levels. These changes included increased numbers of *Porphyromonadaceae*, which were previously linked to non-alcoholic fatty liver disease (Henao-Mejia et al. 2012). It is important to note that increased fatty liver content could be transient, and to result from fast fat loss (Praveen Raj et al. 2015), and not be a consequence of detrimental changes in gut microbiota. Bifidobacteria could produce the main biologically active CLA isomers, and this was associated with their ability to reduce body fat and to improve immune and inflammatory responses (Russell et al. 2011). Physiological benefits have stimulated supplementation of CLA in safe doses in humans (Dilzer and Park 2012). However, further studies are now needed to better understand the relationships between CLA consumption/production, gut microbiota and liver diseases.

Several types of fatty acids have a potent antimicrobial activity, and although their effects have been mainly explored to preserve foods from pathogens, they can affect gut microbiota composition. It is important to note that antimicrobial activity of fatty

acids occurs after complete enzymatic hydrolysis of fat, when fatty acids are present in a free way (Desbois and Smith 2010). Thus, the modulation of fatty acids by gut microbiota could be more intense in the lower gastrointestinal tract.

Antimicrobial activity of fatty acids has been well described by Desbois and Smith (2010) and will not be deeply discussed here. In summary, antimicrobial activity of fatty acids is complex and depends on the length of their carbon chain and presence, number, position and orientation of double bonds. Regarding the structure, the presence of hydroxyl in carboxyl group seems to be important for the antimicrobial activity of fatty acids (Zheng et al. 2005). Unsaturated fatty acids (UFAs) tend to have greater activity than SFA with the same length carbon chain (Zheng et al. 2005; Desbois et al. 2008). Often, antimicrobial activity of PUFA increases in the same direction of the number of double bonds in their carbon chains and the naturally occurred *cis* orientation seems to have a greater antimicrobial activity than *trans* orientation (Feldlaufer et al. 1993). Medium- and long-chain UFAs tend to be more active against Gram-positive than Gram-negative bacteria (Galbraith et al. 1971). The most potent MUFA usually have 14 or 16 carbon atoms (Feldlaufer et al. 1993), and in SFA, 10 or 12 carbons. Antibacterial effect of SFA tends to decrease as chain length gets longer or shorter (Sun et al. 2003; Wille and Kydonieus 2003).

Dietary fat and gut microbiota also seem to share key pathways of obesity induction. It has been proposed that some SFA (e.g. palmitic acid and lauric acid) initiate inflammatory response by acting on LPS receptor (TLR-4) in adipocytes and macrophages, which can contribute to inflammation of adipose tissue in obesity (Huang et al. 2012). These mechanisms are also related to metabolic and immune responses related with infection by LPS (Cani and Delzenne 2011). Another mechanism involves the role of fatty acids in intestinal permeability through mucosal mast cells stimulation (Ji et al. 2011). Cytokine secretion by mast cells, such as TNF-α, IL-1β, IL-4 and IL-13 may promote LPS translocation (Moreira et al. 2012), thus favouring metabolic endotoxemia. Moreover, FIAF expression could also mediate inflammatory status inducted by fatty acids.

SFA, but not UFA, induces a severe proinflammatory profile in mice lacking FIAF but not in the control animals (Huang et al. 2012). A previous study indicated a presence of protective autocrine mechanism by which high-fat diets induce FIAF expression. FIAF overexpression inhibits mesenteric lymph node macrophages uptake of proinflammatory fatty acids and consequently reduces inflammatory status (Lichtenstein et al. 2010). Since the presence of microbiota suppresses FIAF expression in entero-endocrine cells as previously mentioned, we believe that dysbiosis could contribute to proinflammatory status by enhancing SFA uptake in mesenteric lymph node macrophages.

On the other hand, omega-3 PUFA series are recognised for their anti-inflammatory properties (Wall et al. 2010). Although the anti-inflammatory properties of omega-3 fatty acids are well described, new mechanisms of action are still being proposed (Calder 2013). Macrophages are one of the major sources of proinflammatory factors, and EPA and DHA could downregulate the proinflammatory cytokines TNFα and IL-6 production by TLR-4 ligand, indicating once again the involvement of TLR-4 pathway (Honda 2014). Thus, increased ratio of omega-3/omega-6 may favour the reduction of systemic inflammation and contribute to a reduced morbidity associated with obesity (Gómez Candela et al. 2011).

Role of probiotics/synbiotics in reversing high-fat diet-induced dysbiosis

Since high-fat diets can induce dysbiosis and obesity, it is not difficult to assume that the administration of probiotics/synbiotics could ameliorate high-fat diet-induced obesity. This approach is sustained by a growing body of scientific evidence from animal (Yin et al. 2010; An et al. 2011; Cano et al. 2013; Everard et al. 2013; Núñez et al. 2014; Raso et al. 2014; Karimi et al. 2015; Qiao et al. 2015; Song et al. 2015; Wang et al. 2015; Wu et al. 2015; Prince et al. 2016) and human (Hulston et al. 2015; Osterberg et al. 2015) studies.

Most available studies (Yin et al. 2010; An et al. 2011; Cano et al. 2013; Núñez et al. 2014; Raso et al. 2014; Hulston et al. 2015; Karimi et al. 2015; Osterberg et al. 2015; Qiao et al. 2015; Song et al. 2015; Wang et al. 2015; Wu et al. 2015; Prince et al. 2016) included bacteria from *Lactobacillus* and/or *Bifidobacterium* groups as probiotics/synbiotics, and only few studies included other probiotic bacteria like *A. muciniphila* (Everard et al. 2013), *Enterococcus faecium* (Prince et al. 2016) and *Streptococcus thermophilus* (Osterberg et al. 2015). Although it is too early for definitive conclusions, results from these studies so far indicated the beneficial role of probiotics in preventing and even reversing body weight/fat gain (Yin et al. 2010; An et al. 2011; Everard et al. 2013; Núñez et al. 2014; Hulston et al. 2015; Karimi et al. 2015; Osterberg et al. 2015; Qiao et al. 2015;

Wang et al. 2015; Wu et al. 2015), dysbioses (An et al. 2011; Cano et al. 2013; Núñez et al. 2014; Raso et al. 2014; Wang et al. 2015; Prince et al. 2016), inflammation (Cano et al. 2013; Everard et al. 2013; Raso et al. 2014; Qiao et al. 2015; Wu et al. 2015), gut barrier dysfunction (Everard et al. 2013; Núñez et al. 2014; Raso et al. 2014), and metabolic disruptions (Yin et al. 2010; An et al. 2011; Cano et al. 2013; Everard et al. 2013; Núñez et al. 2014; Raso et al. 2014; Hulston et al. 2015; Qiao et al. 2015; Song et al. 2015; Wu et al. 2015) due to high-fat diet consumption (Table 3).

It is important to note that the impact of probiotics supplementation depends on the type of bacteria used to reverse high-fat diet-induced obesity (Qiao et al. 2015; Wang et al. 2015). In nonobese healthy subjects, the use of a commercial multispecies probiotic supplement prevents body weight and body fat gain but does not alter insulin sensibility due to high-fat diets (Osterberg et al. 2015). On the other hand, the consumption of fermented milk containing *Lactobacillus casei Shirota* consumption twice a day prevents body fat gain and disruptions in glucose metabolism disruptions in a comparable population (Hulston et al. 2015). Despite their methodological differences (Hulston et al. 2015; Osterberg et al. 2015), *L. casei Shirota* could have a potential in re-establishing glucose metabolism after a high-fat diet consumption which needs to be further explored in clinical studies.

Influence of bacterial types on the above-mentioned relationships occurs also at a strain level (Qiao et al. 2015). While the administration of *Lactobacillus reuteri* L3 was beneficial in reduction of body weight, glucose metabolism, LPS translocation, proinflammatory status, and in increase energy expenditure that were altered due to high-fat diet consumption, *L. reuteri* L10 did not show the same results (Qiao et al. 2015). *L. reuteri* L3 is considered a bacterium with anti-inflammatory properties. It is also sensitive to oxidative stress generated by high-fat diets. During the consumption of a high-fat diet, the number of beneficial bacteria *L. reuteri* L3 was reduced, while the number of other proinflammatory strains such as *L. reuteri* L8 was increased (Sun et al. 2016). Thus, the use of *L. reuteri* L3 could contribute to reestablishment of beneficial gut microbiota and inflammatory status. The bifidobacteria from different strains, in turn, could improve (strain *B.* M13-4), decrease (strain *B.* L66-5), or have no effect (strains *B.* L75-4 and *B.* FS31-12) on body weight gain due to high-fat diet, despite all strains improved serum and liver triglyceride (Yin et al. 2010). The fact that bacterial strains of the same species showed different effects on inflammation and obesity, illustrates the complexity of host-bacterial cross-talk, and the importance of investigating specific bacterial strains.

Certain studies deserve to be described due to the relevance of their findings (Everard et al. 2013; Karimi et al. 2015; Prince et al. 2016). Prince et al. (2016) investigated the effect of *Enterococcus faecium*, *Lactobaccillus acidophilus* and *L. casei* on the treatment of primates exposed to maternal high-fat diet. The authors had previously proved the influence of maternal diet on offspring out to 1 year of age in the same animal model (Ma et al. 2014). While the use of probiotics provided beneficial changes in intestinal microbiome, with increased number of bacilli and *Bacteroidetes*, and reduced prevalence of *Proteobacteria*, the effect was not persistent. Further, prior use of probiotics could not protect individuals from intestinal dysbiosis that is induced by a high-fat diet.

Administration of *A. muciniphila* was able to reverse high-fat diet induced metabolic disorders, metabolic endotoxemia, adipose tissue inflammation and insulin resistance (Everard et al. 2013). In the same study, *A. muciniphila* increased intestinal marker of endocannabinoid activities, gut barrier and gut peptide secretion.

Karimi et al. (2015) compared the effects of probiotic supplementation to drug therapy on the outcomes of obesity. Both *L. casei Shirota* and Orlistat were able to reduce the increase in body weight, body mass index, fat mass, leptin, IL-6 and glucose levels due to high-fat diet consumption. Further, *L. casei Shirota* showed better results in reducing body fat mass than Orlistat. These results, in addition to offering a viable alternative to drug therapy, provide a possible and novel explanation to the mechanism of action of Orlistat.

When administered with high-fat diet, Orlistat partially inhibits hydrolysis of triglycerides, thus reducing subsequent formation of free fatty acids in the gastrointestinal tract. Until now, the weight-reducing effect of Orlistat was attributed to reduced rate in free fatty acids absorption (Guerciolini 1997). However, it is possible that this low amount of free fatty acids in the gastrointestinal tract also reduces the potential of high-fat diet to induce dysbiosis by the reduction of antimicrobial fatty acids, and thus, contribute to the results of Orlistat. Unfortunately, the study (Karimi et al. 2015) did not evaluate changes in microbiota composition after probiotic and Orlistat consumption. Thus, studies, which evaluate changes in gut microbiota composition, are now urgently needed.

Table 3. Effects of probiotics/synbiotics on high-fat diet induced obesity.

Study	Study design	Probiotics/synbiotics	Main outcomes
Animal studies			
Yin et al. (2010)	4-wk-old male rats were fed with standard diet or HFD with or without one of the supplemental bacteria strain for 6 wk	1. *B.* L66-5 2. *B.* L75-4 3. *B.* M13-4 4. *B.* FS31-12	When compared with the control group, *B.* M13-4 improved body weight gains while *B.* L66-5 induced a decrease in BW *B.* L75-4 and *B.* FS31-12 had no effect on body weight All the probiotics reduced serum and liver triglyceride and ameliorated ectopic lipid deposition in liver Probiotic supplementation did not show significant changes in serum insulin and glucose levels
An et al. (2011)	Male rats were fed with standard diet or high-fat diet with or without probiotic for 7-wk	*B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207	Probiotic reduced body and fat weights, blood serum levels (total cholesterol, HDL-c, LDL-c, triglyceride, glucose, leptin, AST, ALT and lipase levels), and harmful enzyme activities (β-glucosidase, β-glucuronidase and tryptophanase) Probiotic significantly increased the supplemented bacteria faecal counts
Cano et al. (2013)	6–8-wk male mice were fed a standard diet or HFD with or without probiotic for 7 wk	*B. pseudocatenulatum* CECT 7765	*B. pseudocatenulatum* reduced serum cholesterol, triglyceride and glucose levels and decreased insulin resistance and improved glucose tolerance in HFD-fed mice Probiotic reduced serum levels of leptin, IL-6 and MCP-1, while increased those of IL-4 in HFD-fed mice Probiotic reduced liver steatosis and improved the function of innate immune system Probiotic increased bifidobacteria and reduced enterobacteria and the inflammatory properties of the gut content in HFD-fed mice
Everard et al. (2013)	10-wk-old male mice were fed with a standard diet or an HFD (60% fat) with placebo gavage, active probiotic gavage, or inactive probiotic gavage for 4 wk	*A. muciniphila*	*A. muciniphila* reversed HFD-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation and insulin resistance *A. muciniphila* increased the intestinal levels of endocannabinoids that control inflammation, the gut barrier and gut peptide secretion These effects were only present in active *A. muciniphila* administration
Núñez et al. (2014)	5-wk-old female mice received a conventional balanced diet or a HFD from bovine lard supplemented with milk, milk fermented by probiotic, probiotic suspension, or water over 60 d	*L. casei* CRL 431	Milk fermented by *L. casei* decreased body weight gain due to HFD Both *L. casei* and fermented milk reduced the increase in glucose, total cholesterol, and LDL-c serum levels due to HFD Fermented milk improved the histology of liver and small intestine *L. casei* increased *Bacteroides* and bifidobacteria in HFD fed animals Both *L. casei* and fermented milk enhanced the phagocytic activity of macrophages
Raso et al. (2014)	Young male rats received standard diet + placebo gavage, HFD + placebo gavage or HFD + symbiotic by gavage for 6 wk	*L. paracasei* B21060, arabinogalactan and FOS	Synbiotic administration down-regulated liver inflammatory markers that were elevated in HFD fed animals Synbiotic improved glucose parameters such as fasting response, hormonal homeostasis, and glycaemic control, and prevented the impairment of hepatic insulin signalling due to HFD consumption

Table 3. Continued

Study	Study design	Probiotics/synbiotics	Main outcomes
Karimi et al. (2015)	6-wk-old male rats were fed with standard diet, HFD from beef tallow, HFD from beef tallow with probiotics, or a HFD from beef tallow with Orlistat for 15 wk	L. casei Shirota	Synbiotic also reduced cytokines synthesis in the liver and restored the HFD-dysregulated TLR 2, 4 and 9 mRNAs toward a physiological level – Synbiotic preserved gut barrier integrity and reduced the relative amount of Gram-negative Enterobacteriales and E. coli in colonic mucosa L. casei Shirota and Orlistat reduced the increase in body weight, body mass index, fat mass, leptin and glucose levels due to HFD consumption HDL and adiponectin levels were higher with L. casei Shirota and Orlistat administration L. casei Shirota was better than Orlistat in reducing body fat mass L. casei Shirota and Orlistat reduced IL-6 when compared to HFD
Qiao et al. (2015)	9-wk-old male mice received standard diet or HFD with or without the addition of a probiotic strain (1 or 2) by gavage	1. L. reuteri L3 2. L. reuteri L10	L. reuteri L3 (but not L. reuteri L10) administration reduced the increase in body weight, glucose, insulin, LPS, and pro-inflammatory cytokine levels due to HFD consumption L. reuteri L3 (but not L. reuteri L10) also increased the energy expenditure and improved mRNA profile related to obesity genotype compared to HFD consumption
Song et al. (2015)	7-wk-old male mice were fed with standard diet, HFD from lard source, or HFD from lard source with probiotics for 10 wk	L. acidophilus NS1	- L. acidophilus NS1 reduced the increase in total cholesterol and LDL-c due to HFD consumption There were no significant changes in HDL-c
Wang et al. (2015)	10-wk-old male mice received standard diet or HFD with or without the addition of a probiotic strain (1, 2 or 3)	1. L. paracasei CNCM I-4270 2. L. rhamnosus I-3690 3. B. animalis ssp. Lactis I-2494	Probiotic strains attenuated weight gain and macrophage infiltration into epididymal adipose tissue and markedly improved glucose–insulin homeostasis and hepatic steatosis Probiotic strains shifted the overall structure of the HFD-disrupted gut microbiota toward that of lean mice fed a standard diet L. paracasei and L. rhamnosus increased caecal acetate but did not affect circulating LPS-binding protein; in contrast, B. animalis did not increase acetate but significantly decreased adipose and hepatic TNF-α
Wu et al. (2015)	8-wk-old male mice received a standard diet, HFD + control gavage or HFD + probiotic by gavage for 8 wk	L. plantarum K21	L. plantarum K21 alleviated body weight gain and epididymal fat mass accumulation, reduced plasma leptin levels, decreased cholesterol and triglyceride levels, and mitigated liver damage due to HFD L. plantarum K21 downregulated the hepatic expression of PPAR-γ, improved intestinal barrier and gut microbiota composition due to HFD
Prince et al. (2016)	Japanese macaque juveniles exposed to a maternal control or high-fat diet were provided with probiotics for 3 months	E. faecium, L. acidophilus, L. casei	Probiotics supplemented primates presented higher abundance of Bacillus and Bacteroidetes while untreated primates had a higher prevalence of Proteobacteria Probiotic pre-treatment did not provide protection from HFD induced dysbiosis
Human studies			
Osterberg et al. (2015)	Twenty non-obese males (18–30 years), after a 2-wk of a normocaloric normofat diet, followed a high-energy HFD (rich in saturated fatty-acids from ice cream and coconut milk) with or without a probiotic for 4-wk	S. thermophiles DSM 24731, L. acidophilus DSM 24735, L. delbrueckii ssp. bulgaricus DSM 24734, L. paracasei DSM 24733, L. plantarum DSM 24730, B. longum 24736, B. infantis DSM 24737, B. breve DSM 24732	Probiotic supplementation attenuated body and fat mass gain due to HFD Probiotic did not altered insulin sensitivity and skeletal muscle pyruvate and fat oxidation
Hulston et al. (2015)	Seventeen normal-weight adults consumed or not (control group) a probiotic twice a day during 4 wk treatment with a normal diet (3 wk) and a high-energy HFD (1 wk)	L. casei Shirota	L. casei Shirota reduced body fat mass gain due to HFD consumption L. casei Shirota prevented the injury on the glucose metabolism parameters like insulin sensitivity and total glucose response after HFD feeding

HFD: high-fat diet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FOS: fructooligosaccharides; LPS: lipopolysaccharide; TNF-α: tumour necrosis factor-α; IL-6: interleukin 6; MCP-1: monocyte chemotactic protein-1; wk: weeks.

Conclusions

The consumption of high-fat diets seems to be more relevant in promoting dysbiosis than genetically induced obesity. Majority of studies show an increased *Firmicutes* to *Bacteroidetes* ratio and several changes at family, genus, and species levels, resulting in obesogenic and proinflammatory profile. More studies are necessary to deepen the understanding of how excessive fat consumption and the fat's fatty acids profile act in this process, since carbohydrates and dietary fibre restrictions could bias the effects of high-fat diet.

Fatty acids and gut microbiota share important pathways of immune system activation/inhibition. SFAs are related to detrimental changes in gut microbiota, weight gain, increased intestinal permeability, and proinflammatory status. On the other hand, omega-3 PUFA positively modulate host microbial ecosystem and have anti-inflammatory properties, which could ameliorate intestinal permeability. Bacteroides enterotype are highly associated with MUFA and SFA consumption. Besides the effects of omega-3, MUFA could also reduce body weight and restore microbiota composition to a profile before the intake of high-fat diet. A very small dose of *trans*-10, *cis*-12-CLA was able to reduce visceral fat mass and increase *Firmicutes/Bacteroidetes* ratio, but with possible negative effects on fatty liver content. Although many fatty acids showed strong antimicrobial properties *in vitro*, their physiological effects on obese microbiota remain obscure. We encourage scientists to conduct research which would be able to link the antimicrobial activity of specific fatty acids to obesity-related dysbiosis.

The role of fat consumption on gut microbiota, low-grade systemic inflammation and obesity is complex, and many questions remain to be answered by the scientific community. Nevertheless, results of published studies suggest that a balanced diet in regard to fat content is critical not only for host health but also for gut microbiota. Probiotic therapy could be a complementary strategy to improve gut microbiota composition, however, it seems to be not enough to prevent or treat fat-induced dysbiosis due to its transient effects. Thus, based upon the evidence to date, high-fat diets and SFA consumption should be avoided, and MUFA and omega-3 PUFA consumption should be encouraged in order to regulate gut microbiota and inflammation, promoting body weight/fat control.

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Disclosure statement

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