Nutrición Hospitalaria

Revisión

Dysbiosis and metabolic endotoxemia induced by high-fat diet
Disbiosis y endotoxemia metabólica inducidas por la dieta rica en grasa

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Abstract

Introduction: diet plays a decisive role in the prevention and treatment of diseases such as obesity, diabetes, allergies and inflammatory diseases. In addition to this, there are numerous investigations about the role of the microbiota in the genesis of metabolic diseases, especially obesity and its comorbidities.

Objective: the aim of this review is to discuss the influence of high-fat diets on dysbiosis and metabolic endotoxemia.

Results and conclusion: the intestinal microbial ecosystem has been shown to be essential in the performance of functions in the host organism, however, several factors can lead to an imbalance in the homeostasis of the microbiota, known as dysbiosis. High-fat diets are associated with a reduction in intestinal bacterial diversity, changes in membrane integrity, inducing increased permeability and increased lipopolysaccharide (LPS) translocation, changes in the immune system, and generation of low-intensity systemic inflammation. The installed endotoxemia can be considered as a causal factor of subclinical inflammation related to several chronic diseases, and as a result of this, it is essential to know the real impact of hyperlipidic diets on the intestinal microbiota. Thus, it becomes essential to identify dietary strategies that can minimize the inflammatory effects generated from changes in the intestinal microbiota.

Resumen

Introducción: la dieta juega un papel determinante en la prevención y el tratamiento de enfermedades como la obesidad, la diabetes, las alergias y las enfermedades inflamatorias. Agregado a ello, son innumerables las investigaciones acerca del papel de la microbiota en la génesis de las enfermedades metabólicas, principalmente la obesidad y sus comorbilidades.

Objetivo: el objetivo de esta revisión es analizar la influencia de las dietas ricas en grasas sobre la disbiosis y la endotoxemia metabólica.

Resultados y conclusión: se ha demostrado que el ecosistema microbiano intestinal es esencial en el desempeño de funciones en el organismo del huésped, sin embargo, varios factores pueden conducir a un desequilibrio en la homeostasis de la microbiota, conocido como disbiosis. Las dietas ricas en grasas están asociadas a una reducción en la diversidad bacteriana intestinal, alteraciones en la integridad de la membrana que inducen un aumento de la permeabilidad y mayor translocación de lipopolisacáridos (LPS), alteraciones en el sistema inmunológico y generación de inflamación sistémica de baja intensidad. La endotoxemia instalada puede ser considerada un factor causal de la inflamación subclínica relacionada con diversas enfermedades crónicas y, en consecuencia, es imprescindible el conocimiento del impacto real de las dietas hiperlipídicas sobre la microbiota intestinal. Así, es esencial la identificación de estrategias dietéticas que puedan minimizar los efectos inflamatorios generados a partir de alteraciones en la microbiota intestinal.

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INTRODUCTION

In recent years, interest in the intestinal microbiota and its interactions as the host has increased (1). In particular, investigations on the role of microbiota in health regulation and onset of diseases such as inflammatory diseases, allergies, diabetes and obesity (2). It is estimated that the human intestinal microbiota is composed of 10 to 100 trillion microorganisms and possesses about 150 times more genes than the human genome (3).

With the advancement of sequencing techniques, metagenomic analyses of 16S rRNA have demonstrated a large number of bacterial genes that inhabit the human gut (4). The predominance of Firmicutes and Bacteroidetes and restricted anaerobic genera such as *Bacteroides, Eubacterium, Clostridium, Ruminococcus, Peptococcus, Bifidobacterium* and *Fusobacterium* were observed in relation to facultative anaerobes such as *Lactobacillus, Escherichia, Enterobacter, Enterococcus, Klebsiella* and *Proteus.* (4,5). However, there is no accuracy in the composition of the microbiota in humans (6), being influenced by the age, genetic and environmental factors, diet and structure of the intestinal wall of the host (7).

The intestinal microbial ecosystem has been shown essential in the performance of functions such as preservation of intestinal mucosal integrity, nutrient absorption and energy homeostasis, as well as being directly linked to the immune and nervous system (8,9). It has recently been suggested that the microbiota may play a significant role in the pathogenesis of obesity and its comorbidities (8,10-13). This is partly due to an imbalance in the homeostasis of the microbiota, known as dysbiosis, which is characterized by changes in diversity, toxin production, increased permeability, and hormonal and immunological changes, culminating in low-*grade inflammatory state* (14).

Lipopolysaccharide (LPS), a constituent of intestinal bacteria, can be an important inducer of the inflammatory response (15). Detected in the intestinal lumen, under normal conditions, it does not represent human health problems. However, when there is an imbalance this can be easily transferred to the circulatory system. This can lead to high plasma levels of LPS, a condition known as metabolic endotoxemia (16). In addition, there is evidence that the type of diet consumed, especially diets rich in fats, may contribute to endotoxemia (17).

Much has been discussed about the role of diet in the regulation and composition of the intestinal microbiota (14,18,19). High-fat diets are associated with a reduction in intestinal bacterial diversity (20), changes in intestinal membrane integrity, inducing increased permeability and increased LPS translocation (21), changes in the immune system and generation of systemic inflammation (22).

Therefore, the purpose of this review is to examine papers from the scientific literature in order to discuss the mechanisms and interactions between diets rich in fats, intestinal microbiota and metabolic endotoxemia.

METHODS

The research was performed in the Medline/PubMed and Scopus databases. The following terms were used in English: endotoxemia; endotoxins; lipopolysaccharides; gut microbiota and dietary fat. The literature search was conducted from January to July 2017. All articles selected and included in this article were published between 2007 and 2017. They were read and critically grouped according to their thematic and scientific relevance. From this, the sections presented in this article were created: "Dysbiosis induced by high-fat diet" and "Diet rich in lipids and metabolic endotoxemia" (Fig. 1).

HIGH-FAT DIET-INDUCED DYSBIOSIS

Well-established scientific evidence reports that excessive intake of fats and refined carbohydrates are strongly associated with obesity and metabolic diseases. However, it is recent discoveries that may also influence the composition of the intestinal microbiota of the host (23). It is known that the human intestine has trillions of microorganisms, containing more genes than the human genome itself. These microorganisms have evolved and are capable of performing specific and unique biochemical and metabolic functions to the microbial species (3).

The role of the intestinal microbiota in the human disease health process has been gaining even more focus and attention, especially on the etiology of obesity and its comorbidities (24). It is suggested that intestinal bacteria are involved in energy homeostasis and body weight control, being able to extract calories from indigestible nutrients and produce short chain fatty acids, amino acids and vitamins (25). In addition, they participate in the regulation and expression of genes that signal metabolic pathways of absorption and storage of nutrients, such as fats, in the host (26).

The interaction microorganisms and host is under a complex interface with the gastrointestinal mucosa. Its outer layer offers conditions for colonization by bacteria and may suffer direct
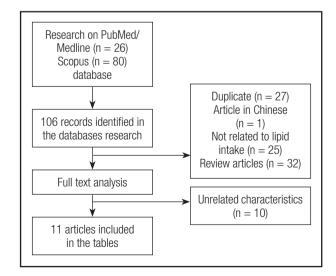

Figure 1.
Study selection process.

influence of the diet (27) since bacteria that degrade mucus are influenced by high-fat diets. Thus, it is evident that diet plays an important role in the modulation of the microbial ecosystem (28).

Studies have reported that the consumption of diets with high-fat contents may alter the composition and functionality of the intestinal microbiota in mice and humans (29-35) (Tables I and II).

Table I. Review of studies investigating high-fat diet-induced dysbiosis in animals

Author/Year	Sample	Treatment/Duration	Main results
Cani et al., 2007	Male C57bl6/J mice CD14 mutant male mice bread in a C57bl6 background 12 weeks old	Control diet High-fat, carbohydrate-free diet 72% fat (oil and lard), 28% PTN and 1% CHO 2 to 4 weeks	Increased plasma LPS led to metabolic endotoxemia in high-fat fed mice diet. Diet rich in fat led to the reduction of *Bacteroides, Eubacterium rectale, Clostridium coccoides* and bifidobacteria. Plasma concentrations of LPS are a sufficient molecular mechanism to trigger metabolic diseases
Hildebrandt et al., 2009	Female RELM_KO mice and 129Svev/C57BL/6 wild-type mice 14 weeks old	Control diet (12% fat, 60% CHO, 28% PTN) High-fat diet (45% fat, 35% CHO, 20% PTN)	High-fat diet decreased Bacteroidetes, increased Firmicutes and Proteobacteria for both genotypes (obese and non-obese)
Murphy et al., 2010	ob/ob mice (leptin deficient) and C57BL/6J wild-type mice 7 weeks old	ob/ob mice: low fat diet Wild-type mice: low-fat diet and high-fat diet (45%) 8 weeks	High-fat diet has increased the Firmicutes phylum ob/ob mice presented reduction of Bacteroidetes. Changes in the microbiota were not associated with markers of energy generated by the microbiota
Daniel et al., 2014	Male C57BL/6NCrl mice	Diet with carbohydrate High-fat diet 12 weeks	High-fat diet caused great impact on the cecal microbiota of mice involving changes in bacterial composition, physiology and metabolites. High-fat diet increased body weight and changes in bacterial diversity. Diet rich in fat led to reduction of Ruminococcaceae (Firmicutes phylum) and increase in Rikenellaceae (Bacteroidetes phylum)
Hamilton et al., 2015	Male Wistar mice, 9 to 10 weeks old	Control diet (13% fat, 23% PTN) High-fat diet (45% fat, 20% PTN) 1, 3 or 6 weeks	High-fat diet increased adiposity and plasma levels of LBP at 3 and 6 weeks. After one week, there was an immediate but reversible increase in paracellular permeability, decreased IL-10 expression, and reduced abundance of genera within the Clostridia class in the ileum in mice fed a high-fat diet. High-fat diet has increased Firmicutes:Bacteroidetes ratio in both the small and large intestine. With a high-fat diet, Deferribacteres increased in the cecum. Control diet increased abundance of Cyanobacteria in the ileum
Kubeck et al., 2016	Germ free male mice and specific pathogen free male C57BL/6N 8 weeks old	Control diet (5% soybean oil, 12% fat) High-fat diet (48% fat, with palm oil and lard)	High-fat diet was associated with increased relative abundance of Bacteroidal *Clostridiales spp* and decrease of Bacteroidal. Dietary cholesterol may affect the binding between microbiota and host metabolism
Shang et al., 2017	Male C57BL/6J mice 6 weeks old	Control diet: low in fat (10%) High-fat diet (60%) for 7 weeks High-fat diet for 5 weeks followed by low fat diet for 2 weeks	Body weight, blood glucose, hepatic triglycerides were higher in the high-fat diet group, regardless of the time. Observed significant difference in diversity and functional properties between group with high-fat diet and control diet. High-fat diet reduced the ratio Bacteroidetes: Firmicutes. High-fat diet followed by diet control restored the diversity and composition of the microbiota in the cecum

Short-term dietary interventions (24 h) have been shown to rapidly change the intestinal microbiota; on the other hand, long-term dietary patterns are able to modulate the composition of the microbiota, despite the detection of resilience after induction of dietary changes (36). Factors such as age, diet time, function, and properties of the different intestinal segments may also influence microbial diversity, and when the cecum and colon mucosa are compared, the latter is more resistant to variations (25).

Theoretically, dietary fat that reaches the colon can be metabolized by bacteria; cholesterol is degraded to form the metabolite coprostanol that is excreted in the feces (37). In addition, high-fat diets can stimulate the production of bile acids, which have antimicrobial activity and eventually select the species capable of metabolizing bile acids in the intestine (1). However, the use of fat as a source of energy for the growth of bacteria remains unclear, since fat metabolization is not performed in anaerobiosis, a condition common to most of the bacteria that inhabit the human intestine (38).

The influence of the diet rich in fat was analyzed in a study with mice fed a hyperlipid diet for three months, which showed a decrease of Bacteroidetes and increase of Firmicutes, Proteobacteria and Actinobacteria (29). Although long-term observations

Table II. Review of studies investigating the dysbiosis induced by a high-fat diet in humans

Author/Year	Sample	Treatment/Duration	Main results
Amar et al., 2008	Healthy men 1,015 people randomly recruited in France	Three-day food record	We found a link between food intake and plasma LPS. Experimental data suggest that fat was more efficient in transporting bacterial LPS from the intestinal lumen into the bloodstream. The results of this study add to the knowledge of mechanisms responsible for the relationships between food intake and metabolic diseases
Wu et al., 2011	Cross-sectional study in healthy adults n = 98	Food frequency questionnaire Food recall	Bacteroidetes and Actinobacteria were positively associated with fat, whereas Firmicutes and Proteobacteria showed a negative association. Enterotypes were strongly associated with long-term diets, particularly proteins and animal fat *(Bacteroides)* versus carbohydrates *(Prevotella)*
Simões et al., 2013	Healthy adult twins	Cross-sectional data were evaluated in pairs of monozygotic twins of different body weight and body fat score was assessed for habitual daily intake and fecal microbiota	Co-twins with similar daily energy intake had similar numbers of *Bacteroides spp* when compared with those with different energy intake. Higher MUFA intake was associated with lower numbers of *Bifidobacterium* and slightly larger numbers of *Bacteroides spp.* Co-twins who ingested identical levels of SFA had very similar *Bacteroides spp.* Intake of n3-PUFA resulted in a significant positive association with abundance of *Lactobacillus.* Ingestion of n6-PUFA was associated with decreased numbers of *Bifidobacterium*
Lyte et al., 2016	Healthy adults (n = 20, mean age 25 ± 3.2 years)	Control diet (olive oil - 20%) High-fat diet with n-3 (fish oil) (35%) High-fat diet with n-6 (grape seed oil) (35%) Diet rich in saturated fat (coconut oil) (35%)	Serum endotoxin concentration was increased during the postprandial period after consumption of a high-saturated fat meal but decreased after the meal with n-3. The n-6 meal did not affect the postprandial endotoxin concentration in relation to the control meal. There was no postprandial effect on inflammatory biomarkers after meals. Postprandial serum triglycerides were significantly elevated after the n-6 meal compared to the n-3 meal. The non-esterified fatty acids were significantly increased after eating the meal with saturated fat compared to the other treatments

LPS: lipopolysaccharide; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids.

concisely present changes in the microbiota, it has been shown that short-term (five weeks) interventions are also capable of modifying the microbial ecosystem of mice (25). In addition, it has been reported that the diversity and composition of the microbiota, after being altered by the high-fat diet, can be reestablished with the intake of low fat diet.

Increased phylum Firmicutes was observed in wild-type mice receiving a high fat diet, and reduction of Bacteroidetes in genetically obese (ob/ob) resistant leptin mice (30). Thus, the authors suggested that a hyperlipid diet rather than the obese *ob/ob* genotype exerted a greater influence on the composition of the microbiota, which was also observed in another study (29). Thus, they emphasize that the microbiota changes observed in mice fed a high fat diet were probably attributable to changes in diet.

Similarly, the provision of a high-fat diet caused a general decrease in microbiota diversity and an increase in the ratio Firmicutes:Bacteroidetes in several studies with mice (25,32,39). Based on these findings, it was suggested that the microbiota of the obese has metabolic pathways that are highly efficient in extracting energy and favoring lipogenesis. This fact was supported by a study that, when transplanting the microbiota from obese mice to germ free mice, presented higher fat gain than animals transplanted with microflora from lean mice (40).

Despite reports of high concentrations of short chain fatty acids in the stools of obese individuals, these changes were not associated with a higher proportion of Firmicutes (41). This result generated research on the characteristics of the obesogenic microbiota, since it seems unlikely that only Firmicutes:Bacteroidetes are the only ones involved in the pathogenesis of obesity (30).

In a study with pairs of monozygotic and dizygotic twins, concordant for thinness or obesity and their mothers, Turnbaugh et al. (42) demonstrated that the microbial ecosystem is shared among family members, but that each individual has a specific bacterial composition. The authors also reported that obesity is associated with changes in phylum level in the microbiota, reduction of bacterial diversity and alteration of genes and metabolic pathways. A greater abundance of Actinobacteria, added to the Firmicutes phylum is reported, suggesting that the action of other phyla in the mechanisms that involve the microbiota and obesity interaction should be investigated.

In addition, mice fed a high-fat diet showed an increase in Clostridia XIV and Enterobacteriales and a decrease in *Bifidobacterium spp* (43). Similar results were also observed in the analysis of the microbiota after ingestion of a hyperlipic diet rich in palm oil and lard (33). Both diets were associated with increased relative abundance of *Clostridiales spp* and decrease of Bacteroidal.

The reduction in gram-positive bacteria such as bifidobacteria directly and negatively affects the integrity of the intestinal membrane, since they are responsible for maintaining and improving the intestinal barrier function, preventing the passage of bacteria and toxins (15). The same function can be attributed to the bacteria *Akkermansia muciniphila,* belonging to the phylum Verrucomicrobia, associated with stimulation of the immune system with anti-inflammatory properties (44). The increase in the abundance of *Clostridiales spp* may be related to mechanisms of metabolic pathways of cholesterol and levels of bile acids (33).

Some studies have reported that the fatty acid profile is also able to modulate the composition of the intestinal microbiota and contribute to the induction of low intensity inflammation (Table III) (23,35,39,43). However, this subject requires more research and more in-depth knowledge (45).

The impact of different types of fats on the host's health, metabolism and microbiota was analyzed (23). Using mice fed a high-fat diet containing palm oil, olive oil, safflower oil and flaxseed oil/fish for 16 weeks compared to mice fed a low fat diet, it was found that mice populations fed palm had relatively lower populations of Bacteroidetes at the phylum level, compared to olive oil diet; this in turn showed an increase in the family *Bacteroidaceae.* However, mice fed flax/fish oil showed a significant increase in the concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and in the intestinal abundance of *Bifidobacterium.* The findings suggest that the impact on the microbiota is due to both changes in the quantity and quality of fat ingested and that fats such as flaxseed oil positively impact the microbial ecosystem of the host.

Similarly, changes in the intestinal microbiota of humans were different according to the intake of different fatty acids, monounsaturated fatty acids (MUFA), omega-3 polyunsaturated fatty acids (PUFA) and omega-6 PUFA. While consumption of MUFA and omega-6 PUFA was inversely associated with an increase in the number of *Bifidobacterium,* an increase in omega-3 PUFA intake was directly associated with a higher number of bacteria in the *Lactobacillus* group (35).

In addition, in a study with middle aged (12 months) mice fed with saturated fat (lard), monounsaturated (soybean oil) and polyunsaturated (fish oil), different responses in the microbiota were observed. The group fed with fish oil showed higher relative abundance of the Proteobacteria phylum and the genus *Desulfovibrio* in the cecal and colonic contents. On the other hand, the diet based on saturated fatty acids conferred a higher Firmicutes:Bacteroidetes and more abundant presence of Verrucomicrobia and Tenericutes (46).

HIGH-FAT DIETS IN LIPIDS AND METABOLIC ENDOTOXEMIA

Obesity, diabetes and insulin resistance are associated with a low intensity systemic inflammation caused by multiple factors and whose triggering agents are not fully elucidated. However, the intestinal microbiota has been largely associated with this scenario (8,24). This evidence was obtained from studies that demonstrated the existence of endotoxemia, the passage of bacterial lipopolysaccharide (LPS) into the bloodstream during consumption of fat-rich diets by mice (47,48). This effect has also been confirmed in human studies (17,49-51).

Naturally the microbiota is a reservoir of LPS, since it is one of the components of the outer cell wall of gram-negative bacteria, and it is possible to detect more than 1 g of LPS in the intestinal lumen. Therefore, under normal conditions LPS is not harmful to the host and appears to be involved in immune regulation, such

Table III. Review of studies investigating the dysbiosis induced by different types of fats in animals

Author/Year	Sample	Treatment/Duration	Main results
De La Serre et al., 2010	Male Sprague-Dawley mice showing obesity-prone (DIO-P) or obesity-resistant phenotype (DIO-R)	Low fat diet 70% CHO, 20% PTN, 10% LIP (25.1% SFA, 34.7% MUFA, 40.2% PUFA) High-fat diet 35% CHO, 20% PTN, 45% LIP (36.3% SFA, 45.3% MUFA, 18.5% PUFA) 8 to 12 weeks	High-fat diet led to reduction of total bacterial density and the proportion of Bacteroidal and Clostridial orders in both phenotypes. High-fat diet increased intestinal permeability, plasma LPS, ileal inflammation associated with TLR4 activation and decreased intestinal alkaline phosphatase, an enzyme that detoxifies LPS in DIO-P mice
De Wint et al., 2012	Male C57BL/6J mice 9 weeks old	Low fat diet made with palm oil (10% LIP) High-fat diet (45%) made with palm oil (SFA), olive oil (MUFA) and safflower oil (PUFA) 8 weeks	Rich saturated fat diet reduced the diversity of the microbiota and raised the ratio Firmicutes:Bacteriodetes. Diets with MUFA and PUFA did not present significant changes in the composition of the microbiota in relation to the low fat diet. High-fat diet with palm oil induced greater body weight gain and triglyceride content in the liver. High-fat diet with palm oil induced elevation of genes related to lipid metabolism in the distal small intestine
Mujico et al., 2013	Female (CD-1) mice 8 weeks old	Control diet High-fat diet (60%) High-fat diet supplemented with oleic acid component High-fat diet supplemented with the combination of n-3 fatty acids EPA and DHA 19 weeks	High-fat diet increased the clostridial cluster XIVa and Enterobacteriales and decreased *Bifidobacterium spp.* High-fat diet induced weight gain, which was reduced by supplementation with oleic acid component and restored the density of the microbiota. Supplementation with combination of n-3 fatty acids EPA and DHA significantly increased the amounts of Firmicutes (especially the *Lactobacillus* group). Body weight positively correlated with the Firmicutes phylum and clostridial cluster XIVa, and negatively with the phylum Bacteroidetes
Hidalgo et al., 2014	Male Webster ICR (CD-1) mice	Standard diet (3% lip) High-fat diet with refined olive oil (20%) High-fat diet with extra virgin olive oil (20%) Fat-rich diet with butter (20%) 0, 6 and 12 weeks	Different diets rich in fats have different effects on intestinal microbiota. After 6 weeks the microbiota from butter fed mice was significantly altered. Differences in diversity in all groups were more evident after 12 weeks
Marques et al., 2015	Male C57BL/6 mice 7 to 8 weeks old	Control diet Diet supplemented with conjugated linoleic acid (t10c12-CLA) (0.5%)	Linoleic acid decreased visceral fat mass, but did not reduce body weight, increased cecal concentrations of acetate, isobutyrate, and propionate. Supplementation revealed lower proportions of Firmicutes and higher proportions of Bacteroidetes, including bacteria *Porphyromonadaceae*
Kaliannan et al., 2015	Fat-1 transgenic and wild-type mice	Standard diet Diet rich in n-6 PUFA (10% corn oil) Diet rich in n-3 PUFA (5% corn oil and 5% fish oil)	Diet with n-6 exhibited elevated levels of metabolic endotoxemia and low grade inflammation. High levels of n-3 fatty acids in the tissue increase the production and secretion of intestinal alkaline phosphatase that induces changes in the microbiota. High levels of n-3 fatty acids in the tissue decrease the production of lipopolysaccharides and intestinal permeability, with reduction of metabolic endotoxemia

(Continue in the next page)

Table III (Cont.). Review of studies investigating the dysbiosis induced by different types of fats in animals

Author/Year	Sample	Treatment/Duration	Main results
Lam et al., 2015	Female C57BL/6J mice 6 weeks old	Control diet High-fat SFA diet (34%) Fat-rich diet n-6 PUFA (31%) Fat-rich diet n-3 PUFA (37%)	Diet rich in saturated fat and n-6 led to similar weight gain. Diet rich in saturated fat increased the HOMA-IR insulin resistance index, permeability and inflammation of the mesenteric mass. Mice supplemented with fish oil and resolvin D1 restored barrier function and reduced inflammation in the colon
Li et al., 2017	Male Sprague-Dawley mice 12 months old	High-fat diet with soybean oil High-fat diet with fish oil High-fat diet with lard 3 months	The structure of the intestinal microbiota in the fish oil group was substantially different from the soybean oil and lard. The group fed with fish oil presented higher relative abundance of the phylum Proteobacteria and the genus *Desulfovibrio* in the cecal and colonic contents. The fish oil-fed group had levels of inflammatory biomarkers in the colon, higher IL-1β, IL-6, IL-17, IL-18 and TNF-α

CHO: carbohydrate; LIP: lipids; PTN: protein; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; LPS: lipopolysaccharide; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; HOMA-IR: insulin resistance index; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-17: interleukin-17; IL-18: interleukin-18; TNF- α: tumor necrosis factor alpha.

as increased phagocytic capacity, lymphocyte proliferation and lymphokine secretion. However, in situations of dysbiosis, which can be caused by the type of diet consumed, the transfer of LPS to the circulatory system can be increased and thus generate what we call metabolic endotoxemia (15).

Diet plays an important role in the regulation of endotoxemia. This evidence is supported by the fact that an increase in plasma LPS occurs in mice fed high-energy diets, whether rich in carbohydrates or fats, for four weeks. However, the high-fat diet proved to be more efficient in favor of LPS transfer from the intestinal lumen to the bloodstream (48).

An increase in postprandial serum endotoxin concentration was observed in healthy adults on high-fat diets, especially those on a saturated fat diet, when compared to subjects who received diets high in polyunsaturated fats (51). Similarly, men who received high-lipid meals also had elevated postprandial LPS levels when compared to fasted individuals (50). A possible explanation for this fact is the ability of LPS to be incorporated into micelles, absorbed and added to chylomicrons, due to the presence of a fraction insoluble in its molecular structure (52).

In addition, there may be an increase in local pressure and loosening of junctional complexes between enterocytes, or even basement membrane rupture, due to excess chylomicrons generated from the hyperlipidic diet. After the lesion caused during fat absorption the intestinal barrier may be compromised, increasing intestinal permeability, mainly to LPS (15).

Thus, consumption of high-fat diets leads to increased intestinal permeability and reduced expression of genes encoding tight or tight junction proteins, such as claudina-1, caludina-3, occludin,

and junctional adhesion molecule 1 (53). This is due to the regulation of permeability by mast cells, through the secretion of mediators such as tumor necrosis factor α (TNF-α), IL-1b, IL-4 and IL-13, receptor-2, favoring LPS translocation (54).

The fatty acid profile of the ingested lipid diet has been shown to be an important modulator of the microbiota, triggering endotoxemia (15). In a study with mice fed omega-6-rich meals, they exhibited conditions that characterized elevated levels of metabolic endotoxemia and low-intensity inflammation (55), while mice fed omega-3 fatty acids had decreased LPS production and permeability, with a significant reduction in metabolic endotoxemia.

In another study, it was observed that diet rich in fats (45% of lipids), when compared to control diet (13% of lipids), increased adiposity and plasma levels of lipopolysaccharide binding protein (LBP) ingestion for three and six weeks. However, with only one week of ingestion, an immediate but reversible increase in paracellular permeability and decreased expression of IL-10 was observed. In addition, a reduction of the abundance of genera within the class Clostridia in the ileum was observed (32).

Increased dietary fat content may influence phylum Actinobacteria, which may reduce the number of gram-positive *Bifidobacterium* species, considered to be beneficial. This may lead to an increase in LPS plasma concentrations, induction of low grade inflammation and maintenance of obesity (56). Likewise, inflammation can also occur with the increase of gram-negative bacteria, for example *Desulfovibrio*, capable of producing endotoxins, reduce sulfate to H2S and impair the intestinal barrier (20).

In addition, habitual intake of saturated fatty acids, derived from diets rich in fats and calories, can directly stimulate TLR4 cells.

Alternatively, there is also a higher concentration of LPS by the increase of gram-negative bacteria, which can stimulate TLR4 and induce the expression of several cytokines, resulting in a state of low intensity inflammation and insulin resistance. In addition, increasing concentrations of circulating fatty acids may further increase nitric oxide production and decrease insulin sensitivity due to impaired lipoprotein lipase (LPL) activity and increased lipolysis (4).

An issue that deserves to be highlighted is the increase in bile production caused by the ingestion of high-fat diets, which acts selectively in relation to colonization of the intestine, being important in the modulation of the microbiota and in the role that it exerts on the permeability and production of endotoxins (57).

CONCLUSION

There is increasing scientific evidence that high-fat diets can modulate intestinal microbiota composition, enhancing LPS uptake and affecting mucosal integrity, resulting in metabolic endotoxemia. Installed endotoxemia is a causal factor of subclinical inflammation related to several chronic diseases and, as a result of this, it is essential to know the real impact of hyperlipidic diets on the microbiota.

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