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Review Article

Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia

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Abstract

Lipopolysaccharide (LPS) may play an important role in chronic diseases through the activation of inflammatory responses. The type of diet consumed is of major concern for the prevention and treatment of these diseases. Evidence from animal and human studies has shown that LPS can diffuse from the gut to the circulatory system in response to the intake of high amounts of fat. The method by which LPS move into the circulatory system is either through direct diffusion due to intestinal paracellular permeability or through absorption by enterocytes during chylomicron secretion. Considering the impact of metabolic diseases on public health and the association between these diseases and the levels of LPS in the circulatory system, this review will mainly discuss the current knowledge about high-fat diets and subclinical inflammation. It will also describe the new evidence that correlates gut microbiota, intestinal permeability and alkaline phosphatase activity with increased blood LPS levels and the biological effects of this increase, such as insulin resistance. Although the majority of the studies published so far have assessed the effects of dietary fat, additional studies are necessary to deepen the understanding of how the amount, the quality and the structure of the fat may affect endotoxaemia. The potential of food combinations to reduce the negative effects of fat intake should also be considered in future studies. In these studies, the effects of flavonoids, prebiotics and probiotics on endotoxaemia should be investigated. Thus, it is essential to identify dietetic strategies capable of minimising endotoxaemia and its postprandial inflammatory effects.

Key words: High-fat diets: Lipopolysaccharides: Gut microbiota: Intestinal permeability

The role of gut microbiota in the development of diseases such as obesity[1], diabetes[2] and atherosclerosis[3] has received increased attention from researchers worldwide. These diseases share a common mechanism because the activation of the immune system leads to greater inflammation[4–9]. Components originating from gut microbiota, such as lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycan, flagellin and bacterial DNA, can cause immune system activation. LPS is thought to be a major inducer of the inflammatory response, suggesting a possible association between intestinal LPS and these metabolic diseases[10–13].

LPS is one of the main components of the external cell wall of Gram-negative bacteria. Therefore, the gut microbiota is a huge reservoir of this endotoxin[14]. There are 10^{12} bacterial cells in each gram of faeces[15]. Consequently, it is possible to detect more than 1 g of LPS in the intestinal lumen[16,17]. Under normal conditions, the presence of LPS in the intestinal lumen does not cause negative health effects[18]. However, some factors can favour the transfer of LPS into the circulatory system. It has been suggested that the type of diet consumed, especially high-fat diets, can contribute to endotoxaemia, which is caused by elevated LPS levels in blood plasma[19].

Thus, considering the impact of metabolic diseases on public health and the association between these diseases and the levels of LPS in the circulatory system, this review will focus on the current understanding of high-fat diets and subclinical inflammation and the new evidence that correlates gut

Abbreviations: JNK, Jun NH_2-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; sCD14, soluble form of CD14; SIBO, small-intestinal bacterial overgrowth; TLR4, Toll-like receptor-4.

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microbiota and intestinal permeability alterations with the increase in blood LPS levels and its biological effects.

Methods

Medline/PubMed, Scielo and Lilacs were searched using the following terms: lipids, high-fat diet, LPS, endotoxins, metabolic endotoxaemia, inflammation, intestinal or gut permeability, gut microbiota, chronic diseases, alkaline phosphatase, pro-inflammatory cytokines, obesity, diabetes, atherosclerosis and inflammatory mediators. For data searches, the terms in English, Spanish and Portuguese were used either alone or in association. Review and original articles were selected according to their titles and abstracts. Each selected manuscript was then studied critically.

The role of diet in the transfer of lipopolysaccharide to the circulatory system

It was once believed that the movement of LPS from the intestinal lumen to the circulatory system would be effectively inhibited by the intestinal epithelia, such that LPS would be present in the circulation only in diseased states. However, LPS has been detected even in the blood of healthy animals[20] and in the plasma of healthy human subjects at low concentrations (between 1 and 200 pg/ml)[19,21,22], suggesting that small amounts of LPS are constantly passing through the intestines. The biological relevance of low circulatory levels of LPS seems to be related to immune modulation. The increase in phagocytic capacity, lymphocyte proliferation and the secretion of lymphokines are some effects of the stimulation of the immune system by LPS. The level of mediators produced by the activated cells determines the beneficial effects, such as resistance to infections, or the negative effects, such as increased inflammation[23,24].

The greater inflammation observed in individuals with metabolic diseases[4–9] could be a consequence of the excessive production of mediators by immune cells stimulated by LPS. Patients with obesity, diabetes, CVD and non-alcoholic steatohepatitis have higher circulating LPS levels than healthy individuals[25–29]. Diet has been shown to play a role in increasing circulatory LPS levels[19,21,30,31]. Excessive fat intake may favour an increase in circulatory LPS, leading to metabolic endotoxaemia[10,22,32–35]. Therefore, excessive fat intake is considered to be one of the triggering factors that increase LPS in the circulatory system.

The oral administration of oil or water to mice confirmed the role of fat intake in LPS movement into the circulatory system; increases in plasma LPS levels were observed only after the ingestion of oil. The higher the fat content of a diet was, the higher the increase in plasma LPS levels[11]. Healthy men presented postprandial increases in LPS levels after consumption of high-fat meals (33 and 50 g) when compared to those who fasted[19,22]. Because LPS contain an insoluble fraction (lipid A) in their molecular structure[36], they can be incorporated into micelles and absorbed and aggregated into the chylomicrons in the postprandial period[20,37].

The transport of LPS by chylomicrons may confer a physiological advantage because it favours hepatic clearance of LPS, reducing LPS toxicity[38,39]. However, excessive chylomicron formation induced by the consumption of high-fat diets can lead to prolonged chylomicronaemia, increasing the chances of extra-hepatic exposure to LPS[20]. Chylomicrons are secreted into the intercellular space and they must reach the lamina propria and lymphatic vessels before entering the systemic circulation. In this process, an accumulation of chylomicrons in the intercellular space due to a high-fat diet may increase the local pressure and cause the loosening of junctional complexes between the enterocytes[40,41] or even basal membrane rupture[42]. It has been demonstrated that during fat absorption, the intestinal epithelium becomes temporarily injured and is repaired approximately 50 min later[43]. After injury, the gut barrier can become compromised, increasing intestinal permeability, especially through the paracellular space, to molecules of higher molecular weight, such as LPS.

Higher fat intake has also been shown to increase intestinal permeability in obese rodents[44]. Dietary fat can indirectly affect intestinal permeability through the activation of mast cells in the intestinal mucosa[45]. Mast cells are directly related to the regulation of transcellular and paracellular intestinal permeability through the secretion of mediators, such as TNF-α, IL-1β, IL-4 and IL-13 as well as tryptase via protease activation receptor-2[46], which in turn favour LPS translocation. TNF-α levels, for example, can increase as a result of myosin light-chain kinase phosphorylation, leading to cytoskeletal contraction and possibly tight junction rupture[47]. Reduced expression of proteins in tight junctions, such as claudin-1, claudin-3, occludin and junctional adhesion molecule-1, has also been observed in the intestinal mucosa of animals fed high-fat diets[48,49].

High-fat diets (49·5 % lipids) also induce changes in the composition of gut microbiota, including the reduction in *Bifidobacterium* spp. and *Eubacterium rectale–Clostridium coccoides* (Gram-positive bacteria) as well as *Bacteroides* (Gram-negative bacteria). A negative correlation between *Bifidobacterium* spp. and plasma LPS levels has been observed, and an increase in bifidobacteria induced by prebiotic intake reduces endotoxaemia[10]. Bifidobacteria can reduce the levels of endotoxins by improving gut barrier function[50–53]. These bacteria do not degrade mucus glycoproteins, as some pathogenic bacteria do; they instead promote a stable environment, inhibiting the translocation of bacteria and toxins[50,54]. In contrast, increasing the proportion of Gram-negative bacteria can decrease the integrity of the intestinal mucosa and lead to higher levels of plasma LPS[11]. The administration of antibiotics to mice fed high-fat diets resulted in changes in gut microbiota composition accompanied by recovery of the integrity of the intestinal epithelia (higher zonulin expression), reduction in metabolic endotoxaemia and reduction in the caecal levels of LPS[44]. These results suggest that changes in the composition of gut microbiota can modulate intestinal permeability and endotoxaemia, even when a high-fat diet is consumed.

High-fat diets can induce changes in gut microbiota without necessarily being associated with obesity. Caecal samples obtained from rats fed high- or low-fat diets for 8 weeks were

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analysed. Not all animals receiving the high-fat diet became obese after 8 weeks, but all the animals eating the high-fat diet showed reductions in the total number of bacteria and increases in the relative proportion of *Bacteroidales* and *Clostridiales* in comparison with the ones that consumed the low-fat diet[48]. These results suggest that excessive fat intake leads to changes in the composition of microbiota without necessarily causing obesity. The differences between obesity-prone and obesity-resistant animals were related to an intestinal enzyme, alkaline phosphatase, which will be discussed later.

Another consequence of the consumption of high-fat diets is the increased production of bile observed in both obese and lean animals[49]. There is evidence to suggest a relationship between bile secretion, microbiota in the small intestine, increased intestinal permeability and endotoxin production. The majority of gut microbiota are mainly located in the caecum or large intestine. The microbiota in the small intestine is less abundant and is usually limited as a source of LPS due to the presence of bile. Bile represents a major challenge to the survival and colonisation of the gastrointestinal tract by micro-organisms. The presence of IgA and mucus, which are secreted into the bile to prevent bacterial growth, and the detergent property of bile acids confer potent antimicrobial properties on bile. However, it is evident that certain bacteria have evolved to resist these antibiotic elements, and pathogens can even use bile to regulate virulence factors[55].

Small-intestinal bacterial overgrowth (SIBO) represents alteration in the local microbiota and is characterised by an increased number of bacteria in the proximal small bowel (10^5 colony-forming units/ml) or the presence of a lower count of bacteria ($>10^3$ colony-forming units/ml), but with a profile of species isolated in the jejunal aspirate that is typical of micro-organisms that normally colonise the large bowel[56]. SIBO has been detected in obese individuals[57], suggesting that the increased circulatory levels of LPS in response to high-fat diet-induced chylomicronaemia might reflect changes in the microbiota of the small intestine.

The chemical structure of bile acid and its concentration might affect the biological effects of bile. Bile acids in the conjugated form are necessary for the absorption of dietary fats and have been suggested to repress bacterial growth in the small intestine through direct antimicrobial effects and up-regulation of host mucosal defences[58]. Bile also reduces the permeation of endotoxin by binding it to micelles *in vitro* [59]. Decreased conjugated bile acid secretion or increased deconjugation reduces the bacteriostatic properties of bile, allowing bacterial growth, which in turn leads to more deconjugation and, ultimately, to bacterial translocation and endotoxaemia[60]. Endotoxaemia can also reflect a direct effect of bile on intestinal permeability. The mechanisms underlying the multifaceted effects of bile acids on the modulation of tight junctions are under investigation[61]. Exposure of Caco-2 cells to bile juice increased permeability through different mechanisms: decreased protein expression in tight junctions[49], occludin dephosphorylation[61] and reduction of transepithelial electrical resistance through the generation of reactive oxygen species (ROS)[62]. The influence of a high-fat diet on the quantity and composition of bile in human or animal models of obesity, and how it affects the composition of microbiota and intestinal permeability, should be further investigated.

Chronic high-fat diets can affect the composition of gut microbiota, increase the incorporation of LPS into chylomicrons and compromise gut mucosal integrity, which can result in the entry of pathogenic agents from the intestinal lumen into the blood stream[10,32,45]. The role of dietary fat in metabolic endotoxaemia is of major concern, and it may partly explain the high prevalence of chronic diseases in Western countries[63,64].

Inflammation and insulin resistance as a result of the biological effects of lipopolysaccharide

Insulin signalling is a very complex process that involves multiple pathways and cascades of phosphorylation events. Interference with these signalling pathways can alter insulin action and lead to the development of insulin resistance[65]. One of the metabolically relevant sites of insulin resistance is white adipose tissue. The hypertrophy of adipocytes and infiltration of macrophages into white adipose tissue can culminate in a higher production of pro-inflammatory cytokines, such as TNF-α and IL-6, through the activation of intracellular signalling pathways involving NF-κB and Jun NH_2-terminal kinase (JNK) systems[66]. Cytokines such as TNF-α can blunt the proper transmission of the insulin signal by altering the pattern of insulin-receptor substrate proteins phosphorylation[65], and LPS can also interfere with the insulin signalling pathways.

The LPS molecule is structurally divided into three parts: lipid A, the oligosaccharide core and the O-antigen[36]. Lipid A is the portion of the LPS molecule that is responsible for endotoxicity. The recognition of an LPS molecule by Toll-like receptor-4 (TLR4) is mediated by the LPS-binding protein, the CD14 co-receptor of TLR4 and the myeloid differentiation protein-2. CD14 is present in soluble form (sCD14), which is derived from both the secretion of CD14 and the enzymatic cleavage of the membrane form of CD14. TLR4 is present on the membrane surface of immune cells (monocytes, macrophages, Kupffer cells) and other cells (adipocytes, hepatocyte, endothelial cells). Upon recognition of LPS, TLR4 undergoes oligomerisation and recruits its downstream adaptor molecules, TIR domain-containing adapter-inducing interferon-β (TRIF) and myeloid differentiation primary response gene 88 (MyD88), into lipid rafts of the membrane, leading to the activation of downstream signalling pathways, such as NF-κB and mitogen-activated protein kinase (MAPK), which can lead to inflammation[38,67,68]. The translocation of NF-κB to the nucleus promotes the activation of genes that codify proteins involved in the inflammatory response, such as TNF-α, IL-6, inducible NO synthase and monocyte chemotactic protein-1[69]. The signalling pathways activated by MAPK include JNK, p38 MAPK and extracellular signal-regulated kinases that can induce insulin resistance via different mechanisms[38,70–72].

Chronic and systemic exposure to slightly increased LPS levels is relevant for the manifestation of many diseases because it induces an immune response and activates signalling pathways that culminate with a subclinical inflammatory status, inhibiting proper insulin signalling and leading to insulin resistance. Insulin resistance is an important component in the pathophysiology

of diseases like obesity, type 2 diabetes mellitus and related co-morbidities, such as hypertension, non-alcoholic fatty liver, cancer, and cardiovascular and renal diseases[38,73–76].

The chronic administration of very low doses of LPS to wild-type mice results in the development of subclinical inflammation, which is followed by increases in body and liver weight, increases in the subcutaneous and visceral adipose tissue and increases in fasting and postprandial blood glucose levels[11]. In human subjects, acute administration of LPS disturbs insulin sensitivity[77–79].

There is a network of factors that, in addition to the action of LPS, contributes to the development of insulin resistance, such as elevated plasma levels of NEFA and mitochondrial dysfunction[80–82] and hormone levels (reduced adiponectin or leptin resistance)[66]. The role of microbiota and molecular patterns associated with microbes may add more complexity to this network, not necessarily as a cause but as a key actor in the relationship between diet and host. The metabolism of phospholipid (phosphatidylcholine) by microbiota results in the production of a metabolite (trimethylamine *N*-oxide), which has been shown to increase the pro-atherogenic phenotype, while the suppression of microbiota by the use of antibiotics inhibits the progression of atherosclerosis and the production of this metabolite[83]. In another animal model of atherosclerosis, the interaction between genetic susceptibility, diet (high-fat diet) and infectious agents illustrates that microbial elements are not the cause of atherosclerotic lesions; instead, they accelerate the progression of the disease in a susceptible host but not necessarily in combination with a high-fat diet[84]. This might also be the case with insulin resistance; LPS may add stronger inflammatory stimuli to a diet and genetic background that are already unfavourable.

Intestinal alkaline phosphatase: a possible therapeutic target

LPS clearance is fundamental to the attenuation of its negative consequences. The liver is the main organ responsible for the removal of LPS from the circulation. The majority of systemic LPS are taken up by the Kupffer cells in the liver and most probably by the endothelial cells as well. The Kupffer cells modify the endocytosed LPS to neutralise its endotoxic activity, passing it to the hepatocytes, which subsequently excrete it into the bile. Some LPS is also removed directly by hepatocytes mediated by lipoproteins[38,85].

Another important mechanism is the dephosphorylation of LPS by the enzyme alkaline phosphatase, which induces a 100-fold reduction in lipid A toxicity[86,87]. In the liver, there is an increase in the expression of this enzyme after LPS injection[85]. The activity of this enzyme is high in enterocyte membranes, where the enzyme also helps to protect against bacterial translocation and regulates duodenal pH and fat absorption[88,89]. A decrease in intestinal alkaline phosphatase activity may decrease LPS degradation and increase circulating LPS levels[90]. Intestinal alkaline phosphatase may also exert a protective effect systemically in addition to that conferred in the intestinal lumen[85,89].

Many food components, including fat, proteins, carbohydrates and some micronutrients, can modulate the expression or activity of the intestinal alkaline phosphatase, depending on the type and quantity of nutrient consumed[88]. A reduction in the activity of this enzyme was observed in the duodenal mucosa of rats with a propensity for obesity receiving high-fat diets[48]. However, intestinal alkaline phosphatase knockout mice gained more weight when fed a high-fat diet than wild-type mice fed the same diet[91].

Sprague–Dawley rats fed high-fat diets presented higher alkaline phosphatase activity in the duodenum and jejunum. They also showed hypertrophy of the jejunal mucosa when compared to the control group, which was fed a control diet (9·5 % of energy from fat). However, rats receiving high-fat diets were subsequently classified as sensitive or resistant to obesity according to weight gain. Mice resistant to obesity were observed to have higher intestinal alkaline phosphatase activity[92]. Some authors suggest that dietary fat content and specific fatty acids can modulate the enzyme activity in different ways[88,93,94]. Thus, more studies are needed to determine the relationship between fat absorption, intestinal alkaline phosphatase activity and LPS clearance.

Recently, the importance of phosphatase in preserving gut microbiota homeostasis and in the protection against pathogenic bacteria was demonstrated in intestinal alkaline phosphatase knockout mice[95]. When high-fat diets affect intestinal alkaline phosphatase activity, it may interfere with the interaction between diet, microbiota and endotoxaemia, suggesting that this enzyme can be a possible therapeutic target in the future. The routes that may favour metabolic endotoxaemia and related diseases in response to the consumption of high-fat diets are represented in Fig. 1.

Future perspectives

The effects of the consumption of two isoenergetic meals (3807 kJ (910 kcal) of either a high-fat or a normal meal) were evaluated in healthy, lean individuals (BMI $< 25\,kg/m^2$). The high-fat meal induced increases in plasma LPS levels and the expression of TLR4, ROS and NF-κB activity[34]. The results of this study emphasise the importance of reducing the amount of fat consumed to a level required to maintain good health.

The chronic and excessive intake of fat has been associated with the development and progression of many non-transmissible chronic diseases. Traditionally, this association is attributed to the biological effects of fats, such as direct activation of the innate immune system through NEFA or through the increase in oxidation of fatty acids[96,97]. Recognition of the relationship between high-fat diets and endotoxaemia 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[33].

Similar macronutrient distributions in two diets differing in fat and carbohydrate sources have shown that the components of the diet rather than the macronutrient composition determine the extent of protection from developing obesity when comparing germ-free and conventional mice, and those components also exert different effects on the composition of microbiota[98].

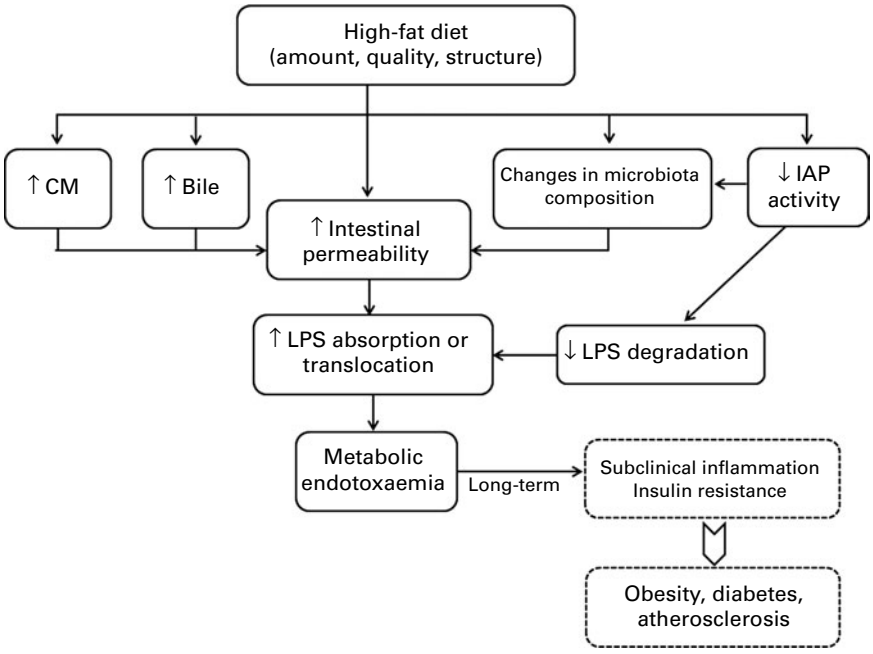

Fig. 1. The possible pathways linking high fat consumption to metabolic endotoxaemia and chronic diseases. CM, chylomicrons; IAP, intestinal alkaline phosphatase; LPS, lipopolysaccharide.

It is important to understand how the fatty acid profile of different lipid sources can affect endotoxaemia. As incorporation into chylomicrons and alteration of intestinal permeability are the main routes contributing to endotoxaemia, how different types of fatty acids can influence postprandial lipaemia and intestinal barrier function should be further explored.

For example, creamy saturated butter has been extensively replaced with vegetable-based 'unsaturated' margarines on supermarket shelves. However, this choice may not be the healthiest. Postprandial lipaemia and chylomicron secretion can be modified by the fatty acid composition and physico-chemical properties of dietary fat, which in turn may have an impact on postprandial endotoxaemia[33]. It has been observed that the consumption of butter in a meal resulted in lower postprandial lipaemia and chylomicron accumulation in the circulation in young men than that in men who consumed olive and sunflower oils[99]. Moreover, oil emulsification has been shown to result in different levels of postprandial lipaemia. Rodents receiving emulsified sunflower oil showed higher postprandial lipaemia than when they were given non-emulsified oil, most probably because emulsification increases the surface area of oil and facilitates fat hydrolysis and absorption. Postprandial endotoxaemia was also higher in the group fed emulsified sunflower oil, showing that the physico-chemical structure of fat can affect the levels of circulating LPS as well[19].

The type of fatty acid can also influence gut barrier function. The influence of oleic, eicosapentaenoic and DHA on intestinal epithelial integrity through the modulation of tight junctions has been demonstrated *in vitro*[100,101], suggesting that the fatty acid profile of different foods might lead to different effects on intestinal permeability and cause differential increases in LPS.

Recently, Laugerette *et al.*[102] investigated the effects of dietary oil composition on markers of endotoxin action. Milk fat, palm oil, rapeseed oil or sunflower oil (22·4 % lipids) was administered to mice for 8 weeks. The palm oil group presented the highest level of IL-6 in plasma; and the highest expression of IL-1β, TLR4 and CD14 was in white adipose tissue[102]. LPS-binding protein is used as a marker of metabolic endotoxaemia because it is a major LPS transporter in plasma, while sCD14 seems to provide protective effects against the LPS response[102], buffering the inflammatory signals by the avoidance of LPS exposure to the cell-anchored membrane form of CD14[103]. The higher inflammatory response observed in the palm oil group was correlated with a greater ratio of LPS-binding protein/sCD14 in plasma. Rapeseed oil intake resulted in higher levels of sCD14 than the intake of palm oil and was associated with less inflammation in plasma and white adipose tissue despite the higher plasma endotoxaemia. This finding reveals that the fatty acid profile can contribute to modulation of the onset of low-grade inflammation by influencing the type of endotoxin receptors and transporters, and it shows that higher endotoxin levels will not necessarily cause a more intense activation of the inflammatory pathways. Thus, components of the diet, such as fatty acids, also trigger inflammation, and LPS, in some situations, might increase the inflammatory burden induced by the diet.

The stimulation of adipocytes with LPS or different types of fatty acids (myristic, palmitic, linoleic or α-linolenic acids) shows that palmitic and linolenic acids are able to trigger inflammation, either alone or synergistically with LPS, inducing a greater increase in IL-6 than that of LPS alone[102]. The activation of immunological cells in the intestine can also be influenced by the type of fatty acids, which in turn can result in different inflammatory response patterns[45,104]. In macrophages, for example, long-chain SFA bind to TLR4 and induce pro-inflammatory cytokine expression[105]. By contrast,

medium-chain TAG were shown to protect rats from LPS-induced injuries of the gut and liver in comparison to maize oil[106].

The possibility that some specific fatty acid types can be incorporated into the cell membrane, changing the composition of the lipid raft domain, indicates that they can shift/displace signalling proteins from the lipid raft and alter the activation of TLR4. LPS and lauric acid (medium-chain SFA) induce dimerisation and activation of TLR4, while DHA, an *n*-3 PUFA, inhibits the recruitment of TLR4 and other signalling proteins (TRIF and MyD88) to the lipid raft. The recruitment of TLR4 to the lipid raft is dependent on NADPH-oxidase, which is mediated by ROS; and LPS and lauric acid increase the cellular levels of ROS, while DHA reduces them[107]. Thus, low-grade inflammation induced by fatty acids is not a common characteristic of all fatty acids[102]. Therefore, although creamy butter may seem to favourably affect lipaemia, its fatty acid profile, which is rich in SFA, may trigger inflammation independently of LPS action. How the fatty acid profile affects bile acid secretion and absorption of the fatty acids and of LPS, as also the increase and duration of postprandial lipaemia and the expression of receptors that bind to LPS and fatty acids, should be examined.

The potential of food combinations to reduce the negative effects of fat intake should also be considered in future studies. Orange juice, for example, when consumed with a high-fat meal, did not induce oxidative stress or inflammation, nor did it increase TLR4 expression or endotoxaemia, compared to when the same type of meal was consumed with water or a glucose solution. The authors attributed this beneficial effect of orange juice to its high levels of bioactive compounds, such as flavonoids, naringenin and hesperidin, because they exert a significant ROS-suppressive effect[21]. In another study, orange juice consumption did not affect the analysed parameters (suppression of cytokines signalling-3, TNF-α, IL-1β, LPS, TLR4) compared to water, cream and a glucose solution[108], suggesting that other phytochemicals may also play an important role in the intestinal environment or systemically[31].

Endotoxaemia induced by dietary fat can also be prevented by the administration of prebiotics and probiotics. A prebiotic is a selectively fermented ingredient that allows specific changes in the composition or activity of the gastrointestinal microbiota that confers benefits upon host well-being and health[109]. Nutrients with prebiotic properties change the gut microbiota, stimulate the secretion of intestinal hormones such as glucagon-like peptide 1 and 2[50] and modulate the activation of the endocannabinoid system in the intestine and in the adipose tissue[110]. All these effects contribute to reduce gut permeability, thereby decreasing endotoxaemia, and systemic inflammation[90]. Probiotics are defined as viable microbial dietary supplements that exert beneficial effects on host health. Some bacterial strains reportedly inhibit TLR4 expression and/or activation in the intestinal epithelial cells[111].

Conclusions

Diet can modify the composition of gut microbiota, increase intestinal permeability and decrease LPS clearance, favouring metabolic endotoxaemia. This endotoxaemia, in turn, can cause subclinical inflammation that has been associated with the manifestation of several metabolic diseases. More studies are necessary to deepen the understanding of how specific nutrients or foods may affect metabolic endotoxaemia to allow the identification of nutritional strategies capable of its modulation. It is essential to identify dietetic strategies capable of minimising the extension and kinetics of postprandial endotoxaemia. From this perspective, two principles of nutrition guidelines seem to be very important: the types of nutrients consumed and the combination of different food types in a meal. This perspective offers new challenges for future studies once current recommendations, especially for foods that are typical sources of fat, have been reviewed. The amount of fat consumed, the fat's fatty acids profile and its physico-chemical properties are important characteristics to consider. In the near future, food will certainly be classified as pro-endotoxaemic or anti-endotoxaemic, which will be useful for future interventional studies.

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