

Effects of dietary fat quality on metabolic endotoxaemia: a systematic review

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Abstract

In this systematic review, we critically evaluated human clinical trials that assessed the effects of dietary fat quality on metabolic endotoxaemia. The studies were selected from three databases (PubMed, Scopus and Cochrane Library), and the keywords were defined according to the Medical Subject Headings indexing terminology. Two authors searched independently, according to the pre-defined selection criteria. Quality and risk assessment of bias for each selected study were also evaluated. The results of the included studies demonstrated associations between higher SFA intake and increased postprandial lipopolysaccharide (LPS) concentrations. On the other hand, after the consumption of PUFA, bloodstream LPS concentrations were lower. However, in none of the long-term studies, the consumption of dietary fats did not seem to exert effects on LPS concentration. Hence, SFA seem to act as a risk factor for transient increase in endotoxaemia, while PUFA demonstrated exerting a protective effect. Taken together, the evidence suggests that the dietary fatty acid profile may influence bloodstream endotoxin concentrations through modulation of factors such as LPS clearance, alkaline phosphatase activity, bile acid metabolism, intestinal permeability and intestinal microbiota composition.

Key words: Lipopolysaccharide: Metabolic endotoxaemia: SFA: PUFA

Lipopolysaccharides (LPS) are endotoxins present in the outer membrane of Gram-negative bacteria. Elevated levels of LPS, called metabolic endotoxaemia, can exert detrimental health effects^(1,2). The pathological LPS effects are related to its capacity to activate metabolic cascades and trigger proinflammatory cytokine secretion⁽³⁾. Inflammation as a result of metabolic endotoxaemia has been a topic of intense debate among the scientific community, since it is considered a risk factor for obesity and other chronic diseases, such as insulin resistance, diabetes and CVD^(1,4,5). Moreover, high LPS concentrations were also associated with metabolic syndrome components⁽⁶⁾.

Increased intestinal permeability favours the occurrence of increased LPS translocation to the systemic circulation, due to factors such as high-fat diets consumption and dysbiosis with decreased intestinal bacterial diversity⁽⁷⁾. The incorporation of LPS to chylomicrons may also contribute to plasma LPS concentration increase⁽⁸⁾. Once in the circulation, endotoxin can bind to LBP (lipopolysaccharide binding protein). Due to its longer half-life compared with LPS, LBP is an important marker of plasma endotoxin concentration, as well as CD14 receptor (cluster of differentiation 14). The LPS–LBP complex associated with CD14 can generate an important metabolic

impact, since they can activate inflammation via toll-like receptor 4 (TLR4), leading to the secretion of inflammatory cytokines⁽⁹⁾. Interestingly, the proinflammatory effect of SFA is in part due to the ability to interact with TLR4 receptors⁽¹⁰⁾.

It has been shown that the consumption of high-fat diets is associated with an increase in postprandial LPS concentration^(11–13). However, little is known about the role of different types of fatty acids on endotoxaemia modulation⁽¹⁾. Apparently, postprandial chylomicronaemia may increase the extra-hepatic exposure to LPS⁽⁸⁾, and it may be affected by the quantity and quality of the fat consumed, evidencing a link between lipaemia and endotoxaemia⁽¹⁴⁾.

It has been suggested that a meal fatty acid profile, rather than its fat content, affects postprandial LPS plasma concentrations⁽³⁾. In addition, high LPS concentrations were observed after the consumption of SFA, whereas lower concentrations were observed after the ingestion of *n*-3 PUFA. Apparently, meal fatty acid profile may alter circulating endotoxin concentrations in a different way according to the type of fat consumed⁽¹⁵⁾.

Therefore, the purpose of this systematic review was to critically analyse studies that assessed the relationship between dietary fat quality and metabolic endotoxaemia in humans since

Abbreviations: EU, endotoxaemic units; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharides; TLR4, Toll-like receptor 4.

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the characterisation of the effect of specific nutrients on endotoxaemia can help in the identification of nutritional strategies capable to prevent or treat the damage caused by endotoxaemia and associated co-morbidities.

Methods

Protocol and registration

This systematic review was planned and conducted according to the PRISMA recommendations⁽¹⁶⁾ and registered in the International Prospective Register of Systematic Reviews – PROSPERO (CRD: 42018104349).

Literature search

The search of the original articles included in this review was performed on 10 February 2019, by two authors (T. L. N. C. and L. E. S.) independently in three electronic databases: MEDLINE (PubMed, www.pubmed.com), Cochrane (www.cochrane.org) and Scopus (www.scopus.com).

Keywords were chosen from the Medical Subject Headings, and the following search strategy was used: (*endotoxemia OR endotoxins OR lipopolysaccharides OR lipopolysaccharide-binding protein OR bacterial endotoxin*) AND (*fatty acids OR saturated fatty acids OR monounsaturated fatty acids OR polyunsaturated fatty acids OR high fat diet OR omega-6 fatty acids OR omega-3 fatty acids OR dietary fat OR dietary fat unsaturated*) AND *humans* AND (*epidemiologic studies OR population-based OR survey OR representative OR cross-sectional OR case-control studies OR observational OR clinical trials OR double-blind method OR comparative study*) NOT *reviews*. The search strategy was not restricted by date and included studies published in English, Spanish and Portuguese.

Eligibility criteria and data extraction

The eligibility criteria were applied independently for all included studies, and divergent opinions were settled by consensus. We selected original studies that met the following inclusion criteria: (1) dietary intervention in which a high-fat diet/meal was offered to the study participants; (2) authors described the amount and quality of the dietary fats offered in the diets/meals to the participants (saturated, monounsaturated and/or polyunsaturated fats); (3) LPS and/or LBP concentrations and responses to the dietary interventions were evaluated; (4) metabolic endotoxaemia markers were evaluated by limulus amoebocyte lysate or ELISA methods. We excluded animal and *in vitro* studies, LPS infusion assays, literature reviews, letters, comments, book chapters and abstracts.

For each study included, the following information was extracted: author's name, year of publication, country where the study was performed, study purpose, sample size, participants' sex, age and nutritional status, presence of chronic diseases, study duration, lipid profile of the diet offered to the experimental group, as well as results regarding LPS and/or LBP concentrations and its correlations with lipid-related and inflammation markers.

Quality, representativeness and risk of bias assessment

Quality assessment was conducted according to the Jadad score⁽¹⁷⁾, using a five-point scale focused on evaluating the methodological quality and validity. Each study was selected by the random sequence generation and allocation concealment, blinding of participants and staff, and the participants withdrawal were evaluated. Studies with scores between 0 and 1 were considered of low quality, scores between 2 and 3 were considered of moderate quality and a score of 4 or higher were considered of high quality.

The representativeness was evaluated according to external validity. Thus, a study was considered representative if information such as eligibility criteria, sample size calculation, probability of error and power of the sample were presented.

The risk of bias was also assessed in each study included in this review, using the 'Methods Guide for Effectiveness and Comparative Effectiveness Reviews' criteria from the Agency for Healthcare Research and Quality⁽¹⁸⁾. Selection, performance, attrition, detection and reporting bias were evaluated. The studies were classified as: (1) low risk of bias, when more than 70% of the questions were answered as 'yes (low risk)'; (2) moderate risk of bias, when 40–69% of the questions were answered as 'yes (low risk)' and (3) high risk of bias, when <40% of the answers were 'yes (low risk)'.

Data analysis

Due to the heterogeneity among the included studies, it was not possible to conduct a statistical meta-analysis. Thus, in accordance with the Cochrane handbook⁽¹⁹⁾, the authors opted to perform a systematic narrative review for the analysis of the compiled data. In order to present the results in a more comprehensive manner, the main characteristics and results of each study were described in tables and organised chronologically by year of publication.

Results

Study selection

We identified a total of 735 studies in the three searched databases, of which 112 were duplicates. From the 623 remaining studies, 590 were excluded after analysing the titles and abstracts. After reading the full text of the remaining thirty-three studies, eleven met all criteria of the systematic review. The main reasons for exclusion were: *in vitro* studies (*n* 298), animal studies (*n* 84), studies that administered LPS infusion (*n* 32), studies which did not evaluate LPS and/or LBP concentrations and responses to dietary interventions (*n* 53), lack of dietary intervention with offer of high-fat diet/meal to the subjects (*n* 83) and studies that did not report the amount and/or quality of the dietary fats in the diets/meals offered to the subjects (*n* 16). The reasons for studies exclusion are detailed in Fig. 1.

Description of included studies

All studies included in this review are randomised controlled trials, which evaluated the effect of SFA-, MUFA- and/or PUFA-rich diets on metabolic endotoxaemia markers. Eight out of the

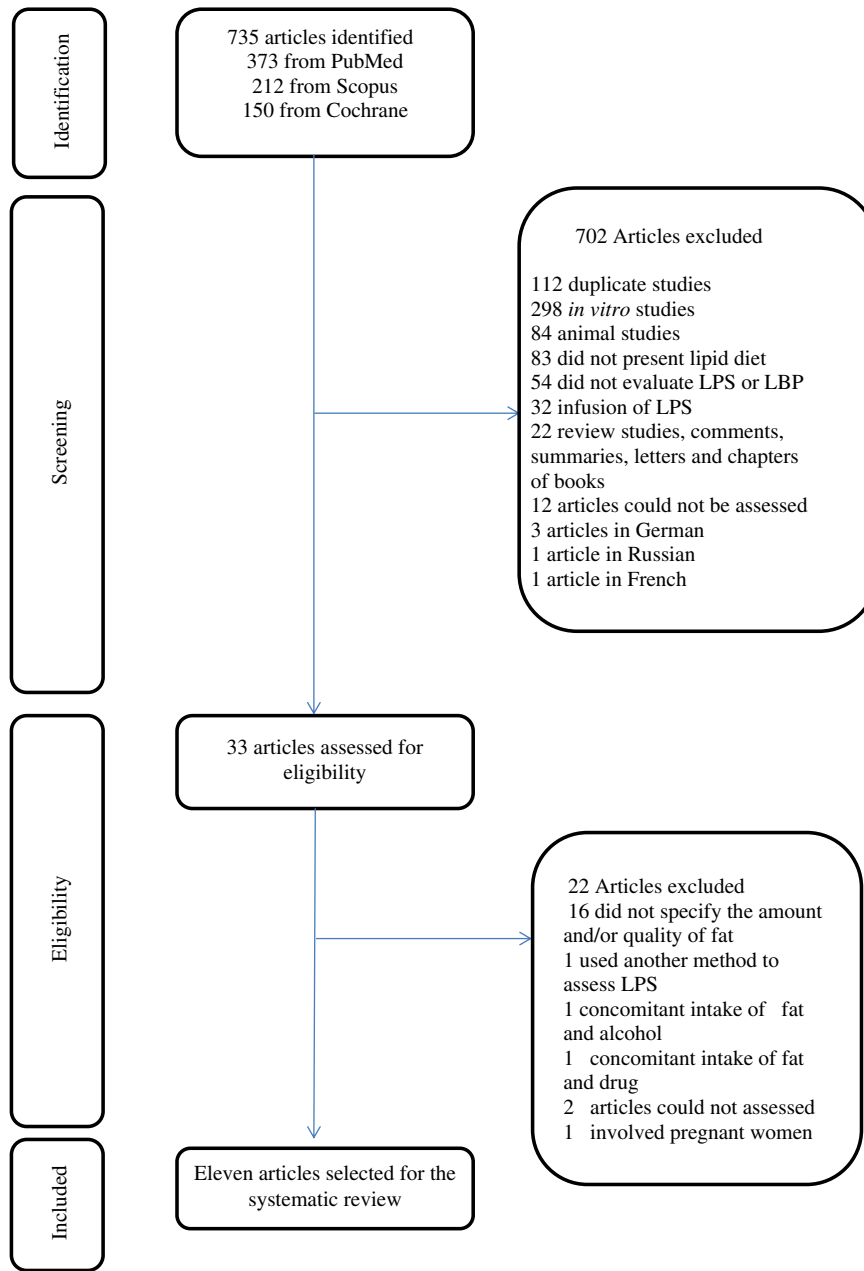


Fig. 1. Flow chart of the study-selection process. LPS, lipopolysaccharide; LBP, lipopolysaccharide binding protein.

eleven included studies evaluated the postprandial LPS response exclusively, only two studies were long-term intervention studies (4 and 12 weeks) and one study evaluated the ratio of LBP:sCD14 during 8 weeks. It is noteworthy to emphasise that studies addressing this research subject are relatively recent and that the oldest article included in this review was published in 2010. The studies contained data on a total of 387 participants, 76% male and 24% female (Table 1). Three studies did not present information regarding the subject's sex^(20–22).

Nine studies included overweight and obese adults. The other two included obese children/adolescents⁽²⁷⁾ and elderly participants⁽²⁵⁾. Furthermore, one trial included subjects with

the metabolic syndrome⁽²⁴⁾ and one trial included subjects with type 2 diabetes, hypertension or hyperlipidaemia⁽²⁵⁾.

In most of the dietary interventions, the researchers offered the subjects high-fat diets containing the three types of fatty acids of interest for this review^(12,14,21–27). Meanwhile, two studies tested diets containing only SFA and PUFA^(15,20).

In the acute studies (1–6 h postprandial response), the fat content of the meals ranged from 35 to 69% of the total energy^(14,15,22–27), therefore above the 20–35% range recommendation⁽²⁸⁾. Moreover, among the long-term studies, the duration varied from 4 to 12 weeks, with the diet fat content of the prescribed diets ranging between 30 and 38% of the total energy

Table 1. Characteristics and main results of lipopolysaccharides (LPS) and lipopolysaccharide binding protein (LBP) concentrations in subjects who received diets containing different types of fats

Reference	Purpose	Sample; sex; age (years)	Nutritional status; mean BMI (kg/m ²)	Duration (h)	Dietetic intervention; total fatty (%)*	Dietary fat composition (%)†	Results of endotoxaemia
Deopurkar <i>et al.</i> ⁽²⁰⁾	Evaluate the effect of saturated fat and CHO on increasing LPS, TLR-4 and SCOS3	<i>n</i> 48; –; 25–47	Healthy; 21.50–24.40	5 h Postprandial	Glucose	–	- Plasma concentration of LPS increased significantly 3 h after cream intake. But it did not increase after glucose, orange juice and water intakes
					Cream	70.0 SFA 28.0 PUFA	- Plasma LPS concentrations remained significantly higher 5 h after cream consumption compared with baseline concentrations
					Orange juice	–	- LBP concentration increased significantly 5 h after glucose ingestion, which did not occur after the ingestion of cream or orange juice
					Water	–	
Clemente-Postigo <i>et al.</i> ⁽²¹⁾	Analyse endotoxaemia after fat ingestion and to associate with insulin resistance and hypertriacylglycerolaemia	<i>n</i> 40; –; 41.41	Morbid obesity; 53.70	3 h Postprandial	Preparation containing 50 g of fat	20.0 SFA 58.92 MUFA 21.25 PUFA	- Subjects in group 3: HOMA ≤ 5 and ΔTAG > 80 mg and group 4: HOMA > 8 and ΔTAG > 80 mg, with higher postprandial hypertriacylglycerolaemia had a significant increase in serum LPS concentrations compared with baseline, and in the chylomicron fraction (there is no difference between groups)
Perez-Herrera <i>et al.</i> ⁽²²⁾	Investigate the effect of the heating process of different oils on the chemical properties and the postprandial inflammatory response	<i>n</i> 20; –; 56	Obese; 37.32	4 h Postprandial	Breakfast containing skimmed milk and muffins, prepared with four different types of oils		- 2 h postprandial, plasma LPS concentrations reduced, with a return to fasting values 4 h after the consumption of olive oil and mix of oils enriched with phenolic compounds
					Virgin olive oil	18.4 SFA 70.5 MUFA 11.1 PUFA	- After consumption of sunflower oil, an increase in LPS concentrations was observed after 4 h postprandial
					Sunflower oil	7.3 SFA 34.3 MUFA 58.3 PUFA	- Olive oil and mix of oils enriched with phenolic compounds led to lower LPS plasma values than the sunflower oil-rich meal, in the 2 and 4 h postprandial period
					Mix of oils (sunflower 30 % and rapeseed 70 %) enriched with antioxidant dimethylpolysiloxane	10.2 SFA 71.8 MUFA 18.0 PUFA	
					Mix of oils (sunflower 30 % and rapeseed 70 %) enriched with phenolic compounds 56 %	5.8 SFA 76.7 MUFA 17.6 PUFA	

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Table 1. (Continued)

Reference	Purpose	Sample; sex; age (years)	Nutritional status; mean BMI (kg/m ²)	Duration (h)	Dietetic intervention; total fatty (%)*	Dietary fat composition (%)†	Results of endotoxaemia
Moreira <i>et al.</i> ^{(14)‡}	Investigate the effect of the consumption of high-fat meal with conventional nuts or containing high oleic content, on LPS and its relation with lipaemia and insulinaemia	n 65; 65 men; (a) 27-20, (b) 27-70, (c) 26-10	Overweight and obese; (a) 29-50, (b) 30-20, (c) 29-90	3 h Postprandial	Test meal composed of strawberry shake and peanuts or biscuit	Conventional peanut 16-25 SFA 51-78 MUFA 32-21 PUFA	- No significant differences were observed in LPS concentrations compared with fasting and postprandial concentrations within each experimental group - After 3 h postprandial, the conventional peanut group and peanut with high oleic content had lower LPS concentrations compared with the control group (biscuit) - Peanut consumption was associated with lower LPS concentration at 3 h postprandial
Laugerette <i>et al.</i> ⁽¹²⁾	Investigate the hypothesis, that subjects differing in LBP:sCD14 ratio changes induced by overfeeding (OF) would develop low-grade inflammation differently	n 18; 18 men; 30.6 ± 2.1	Healthy young; 25.8 ± 0.8	8 weeks; 3 h postprandial	49 % Test meal composed of 100 g of cheese, 20 g of butter and 40 g of almonds (unsalted)	44 SFA 42 MUFA 8 PUFA	- The LBP:sCD14 ratio increased significantly in the cohort after overfeeding (OF) - The postprandial accumulation of LPS increased significantly after OF in the eight subjects of the cohort submitted to this test
Schmid <i>et al.</i> ⁽²³⁾	Compare the effect of a high-fat dairy meal, from the non-dairy meal rich in fat and supplemented with milk, from a high-fat meal without dairy products to the inflammatory and metabolic responses	n 19; 19 men; 41.80	Overweight; 27.10	6 h Postprandial	High-fat dairy meal (bread, cheese, butter, mozzarella cheese and still mineral water) High-fat non-dairy meal supplemented with milk (bread, salami, palm fat, hard-boiled egg and whole-fat milk) High-fat non-dairy control meal (bread, salami, palm fat, hard-boiled egg and still mineral water)	35-55 SFA 14-42 MUFA 3-22 PUFA 26-50 SFA 23-21 MUFA 6-0 PUFA 24-13 SFA 26-04 MUFA 6-9 PUFA	- LPS concentration increased significantly between baseline and 6 h after the ingestion of all three test meals
					61 %		

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Table 1. (Continued)

Reference	Purpose	Sample; sex; age (years)	Nutritional status; mean BMI (kg/m ²)	Duration (h)	Dietetic intervention; total fatty (%)*	Dietary fat composition (%)†	Results of endotoxaemia
Lyte <i>et al.</i> ⁽¹⁵⁾	Study the effect of meal composed of different fatty acids on the postprandial serum concentration of endotoxin	<i>n</i> 20; 12 men; 8 women	Healthy; men = 22-70, women = 22-30	5 h Postprandial	Test meal was a porridge oatmeal with four different oil types and hard-boiled egg, fat-free skimmed milk and orange juice		- Serum LPS concentrations were lower after the consumption of meal rich in fish oil (<i>n</i> -3) compared with meal rich in SFA
					Coconut oil	15.0 SFA 2.0 PUFA (<i>n</i> -6)	- LPS concentration increased during the postprandial period after the consumption of SFA-rich diet
					Olive oil	5.0 SFA 2.0 PUFA (<i>n</i> -6)	- Comparing the mean LPS values between the high-fat and low-fat diets, no statistical difference was verified
					Grape seed oil (<i>n</i> -6)	10.0 SFA 7.0 PUFA (<i>n</i> -6)	
					Fish oil (<i>n</i> -3)	10.0 SFA 2.0 PUFA (<i>n</i> -6) 0.5 EPA + DHA (<i>n</i> -3)	
López-Moreno <i>et al.</i> ^{(24)§}	Evaluate the effect of fat consumption in quantity and quality on the plasma levels of LPS	<i>n</i> 75; 28 men, 47 women; (a) 58-06, (b) 54-60, (c) 56-40, (d) 55-30	Obese with metabolic syndrome; (a) 35-30, (b) 34-50, (c) 35-40, (d) 35-00	12 weeks	35 % High-SFA diet	16.0 SFA 12.0 MUFA 6.0 PUFA	- LPS and LBP concentrations did not change significantly 12 weeks after dietary intake
					High-MUFA diet	8.0 SFA 20.0 MUFA 6.0 PUFA	
					Low-fat diet and rich in CHO complexes	8.0 SFA 11.0 MUFA 6.0 PUFA	
					Low-fat diet and rich in CHO complexes, supplemented with <i>n</i> -3	8.0 SFA 11.0 MUFA 6.0 PUFA 1.24 g EPA + DHA	
					38 % High-SFA diet	38.0 SFA 21.0 MUFA 6.0 PUFA	
				4 h Postprandial	High-MUFA diet	12.0 SFA 43.0 MUFA 10.0 PUFA	- The high-SFA diet increased the postprandial LPS concentrations compared with the other diets - There was no significant change in the postprandial LBP concentrations for all diets
					Low-fat diet and rich in CHO complexes	21.0 SFA 28.0 MUFA 16.0 PUFA	
					Low-fat diet and rich in CHO complexes, supplemented with <i>n</i> -3	21.0 SFA 28.0 MUFA 16.0 PUFA 1.24 g EPA + DHA	
					65 %		

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Table 1. (Continued)

Reference	Purpose	Sample; sex; age (years)	Nutritional status; mean BMI (kg/m ²)	Duration (h)	Dietetic intervention; total fatty (%)*	Dietary fat composition (%)†	Results of endotoxaemia
López-Moreno <i>et al.</i> ⁽²⁵⁾	Evaluate the effect of a high-fat diet on endotoxaemia of the elderly	n 20; 10 men, 10 women; 67-10	Obese, hypertension (n 6), diabetes (n 3), hyperlipidaemia (n 2); 31-90	4 weeks; 4 h Postprandial	Mediterranean diet	<10.0 SFA 24.0 MUFA 4.0 PUFA 0.4 ALA	- A lower plasma fasting LPS concentrations was observed after the long-term intervention of a low-fat, CHO-rich and n-3-enriched diet when compared with the other diets
					SFA-rich diet	22.0 SFA 12.0 MUFA 4.0 PUFA 4.0 ALA	- No differences were observed between diets in fasting and after long-term dietary intervention LBP values
					Low-fat, high-CHO, n-3-enriched diet	10.0 SFA 12.0 MUFA 8.0 PUFA 2.0 ALA	- There was a statistically significant postprandial increase in LPS concentrations and a decrease in LBP concentrations after a low-fat, high-CHO and n-3-enriched diet when compared with fasting concentrations
					60 %		- No significant changes were observed in the postprandial LPS concentrations after intake of SFA-rich diet and Mediterranean diet
Morandi <i>et al.</i> ⁽²⁶⁾	Assess the effect of a high-fat meal on LPS translocation and relationships between IL-6 and glucose homoeostasis in obese children/adolescents	n 20; 11 boys, 9 girls; 9-17	Obese; BMI ≥ the 95 ^o percentile	5 h Postprandial	Ice cream with olive oil and sunflower oil	31.5 SFA 35 MUFA 33.5 PUFA	- LBP and sCD14 decreased significantly after 1 h the meal
					69 %		- LBP, sCD14 and its iAUC did not correlate with IL-6 or glucose homoeostasis
Alayón <i>et al.</i> ^{(27)II}	To evaluate the effect of the intake of a high-fat saturated meal on the metabolic and inflammatory profile and relationship to abdominal obesity	n 42; 42 men; (a) 38.7 ± 10.1, (b) 41.4 ± 7.6	Abdominal obesity and healthy; (a) 23.0 ± 2.2, (b) 30.1 ± 4.1	4 h Postprandial	Breakfast with bread, butter and coffee	32.0 SFA 23.0 MUFA 4.0 PUFA	- Increase in LPS concentrations was observed in both groups - Positive correlation was observed at 4 h prandial post between TAG and LPS concentrations in the obese group

CHO, carbohydrate; TLR4, Toll-like receptor; SOCS3, cytokine-3 signalling suppressor; HOMA, homeostatic model assessment; ΔTAG, change in TAG; ALA, α-linolenic acid.

* Data referring to the percentage of energy from lipids.

† Data referring to the percentage of energy from lipids in the intervention diet. Except for: Deopurkar *et al.*⁽²⁰⁾; Clemente-Postigo *et al.*⁽²¹⁾; Perez-Herrera *et al.*⁽²²⁾; Moreira *et al.*⁽¹⁰⁾, which refer to the centesimal composition of the fatty acids of the intervention diet.

‡ Age and mean BMI presented for each group: (a) conventional peanut; (b) peanuts with high oleic content and (c) biscuit.

§ Age and mean BMI presented for each group: (a) fat-rich diet SFA; (b) diet rich in MUFA; (c) low fat and rich in CHO complexes; (d) low-fat and complex CHO-rich diet, supplemented with n-3.

II Age and mean BMI presented for each group: (a) not obese and (b) obese.

intake^(24,25). Although in two studies, the percentage of dietary fat offered to the subjects was not disclosed, the researchers provided the centesimal composition of the test meals^(20,21).

Quality, representativeness and risk of bias assessment

According to the Jadad score⁽¹⁷⁾, only one study included in this review presented high methodological quality⁽²⁵⁾, five presented moderate quality^(14,15,22–24) and five presented low quality^(12,20,21,26,27).

Only two studies were classified as representative of the target population. Regarding the risk of bias assessment, six studies were considered as having a low risk of bias and three were classified as having a moderate risk of bias. The major limitations were related to the selection bias^(14,15,20–25,27), performance bias^(21,22) and detection bias^(14,15,20–25,27) (Table 2).

Results of individual studies

The mean plasma LPS activity ranged from 0.23 to 1.40 endotoxin units (EU)/ml at the baseline and from 0.28 to 1.70 EU/ml after the ingestion of SFA-rich test meals, demonstrating an increase in LPS postprandial concentrations in response to SFA intake when compared with the fasting state^(12,20,23,27). In the study reported by Laugerette *et al.*⁽¹²⁾, the AUC values for LPS concentrations, during 8 weeks, were higher after the overfeeding period compared with the response to the same SFA-rich meal provided before the overfeeding period. Also, the intake of SFA-rich meals led to an increase in LPS concentrations compared with MUFA- and PUFA-rich meals^(14,15,24).

There was considerable variability in the acute LPS concentration responses to MUFA-rich diets. In two studies, the researchers verified an increase on LPS concentrations after the consumption of a MUFA-rich meal^(21,25). On the other hand, two clinical trials demonstrated a decrease on LPS concentrations after the ingestion of similar MUFA content meals^(14,22). Regarding the effects of long-term MUFA-rich diet, López-Moreno *et al.*⁽²⁵⁾ showed a decrease on LPS concentrations after a 4-week intervention. However, the test diet in this study contained *n*-3 PUFA supplementation. It also presented lower fat (30%) and higher carbohydrate (55%) contents than the other diets tested by the researchers⁽²⁵⁾. Thus, drawing conclusions about the effects of MUFA on LPS concentrations is not possible yet.

Regarding the consumption of PUFA-rich diets, the mean plasma LPS activity among the studies varied from 0.43 to 1.10 EU/ml at the baseline and from 0.26 to 0.70 EU/ml after the test meal ingestion. The assessment of the LPS response to PUFA-rich diets in two clinical trials demonstrated lower concentrations of that marker when compared with SFA^(14,15). According to the results of the two studies mentioned above, both *n*-6 PUFA (conventional peanuts⁽¹⁴⁾) and *n*-3 PUFA (fish oil⁽¹⁵⁾) can reduce LPS concentrations in the bloodstream. Conversely, the ingestion of sunflower oil (PUFA) was associated with higher LPS concentrations⁽²²⁾. However, in that study, the oil was heated before being ingested. Therefore, changes in its chemical properties cannot be discarded, which may have compromised the results and influenced the LPS concentrations⁽²²⁾ (Table 3).

Regarding the LBP concentrations, López-Moreno *et al.*⁽²⁵⁾ demonstrated a postprandial (4 h) decrease in this marker after the consumption of a MUFA-rich meal. Similarly, another clinical trial reported lower LBP concentrations 1 h after ingestion of a fatty acid-balanced meal (31.5% energy SFA, 35.0% energy MUFA and 33.5% energy PUFA) in comparison with the baseline values⁽²⁶⁾. However, the AUC values for LBP concentrations, during a 5 h postprandial period, remained unchanged⁽²⁶⁾. On the other hand, Laugerette *et al.*⁽¹²⁾ demonstrated increased LBP:sCD14 ratio after the test meal, suggesting that variations related to LBP and sCD14 may be linked to pro-inflammatory LPS activity and low-grade inflammation.

Higher LPS concentrations showed a consistent correlation with increased plasma TAG among studies^(14,21,23) (Table 3). Furthermore, postprandial LPS concentrations presented positive associations with adipose tissue inflammation markers, such as, PPARγ and IL-6, while presenting inverse correlations with adiponectin C1Q and collagen domain containing (ADIPOQ), perilipin (PLIN), calnexin (CANX), nuclear factor erythrocytes derived from type 2 (NRF2), X box binding protein (XBP1), uncoupling protein mitochondrial type 2 (UCP2) and NAD-dependent malic enzyme (ME2)⁽²⁴⁾. Moreover, LBP concentrations demonstrated a direct association with caveolin protein coding type 1 (CAV1), nuclear protein complex (ADIR2), protein coding phosphoinositide 3 kinase (PIK3CA) and antigen human prostate specific (APS); in spite of being negatively associated with XBP1, calreticulin (CARL), CANX and protein disulfideisomerase family A, member 3 (PDIA3)⁽²⁴⁾. With regard to peripheral mononuclear cells' inflammation markers, the

Table 2. Type of study, geographic distribution, quality assessment and risk of bias of the selected studies

Reference	Type of study	Country	Jadad score	Quality	Representativeness	Overall risk of bias
Deopurkar <i>et al.</i> ⁽²⁰⁾	Randomised controlled trial	USA	0	Low	No	Moderate (8/12)
Clemente-Postigo <i>et al.</i> ⁽²¹⁾	Randomised controlled trial	Spain	0	Low	No	Moderate (8/12)
Perez-Herrera <i>et al.</i> ⁽²²⁾	Randomised controlled trial, crossover	Spain	2	Moderate	No	Low (10/12)
Moreira <i>et al.</i> ⁽¹⁴⁾	Randomised controlled trial	Brazil	2	Moderate	No	Low (9/12)
Laugerette <i>et al.</i> ⁽¹²⁾	Randomised controlled trial	France	0	Low	Yes	Moderate (7/12)
Schmid <i>et al.</i> ⁽²³⁾	Randomised controlled trial, crossover	Switzerland	2	Moderate	No	Low (9/12)
Lyte <i>et al.</i> ⁽¹⁵⁾	Randomised controlled trial, crossover	USA	3	Moderate	No	Low (9/12)
López-Moreno <i>et al.</i> ⁽²⁴⁾	Randomised controlled trial	Spain	3	Moderate	No	Low (11/12)
López-Moreno <i>et al.</i> ⁽²⁵⁾	Randomised controlled trial, crossover	Spain	4	High	No	Low (9/12)
Morandi <i>et al.</i> ⁽²⁶⁾	Randomised controlled trial	Italy	0	Low	Yes	Moderate (7/12)
Alayón <i>et al.</i> ⁽²⁷⁾	Randomised controlled trial	Colombia	1	Low	No	Moderate (7/12)

Table 3. Effect of fat profile on endotoxaemia and main variables correlated with lipopolysaccharides (LPS) or lipopolysaccharide binding protein (LBP)

Reference	Type of fat*	Effect on endotoxaemia	Endotoxaemia†				Variables correlated with LPS or LBP		
			Baseline (EU/ml)		Postprandial (EU/ml)		Positive correlation	Negative correlation	Method used
			Mean	SD	Mean	SD			
Deopurkar <i>et al.</i> ⁽²⁰⁾	↑ SFA	↑ LPS	0.29 ^a	0.03	0.41 ^b	0.07	–	–	–
Clemente-Postigo <i>et al.</i> ⁽²¹⁾	↑ MUFA	↑ LPS ↑ LPS chylomicrons	–	–	–	–	TAG (<i>r</i> 0.48; <i>r</i> 0.40)	–	Spearman
Perez-Herrera <i>et al.</i> ⁽²²⁾	↑ MUFA ↑ PUFA	↓ LPS ↑ LPS	–	–	–	–	–	–	–
Moreira <i>et al.</i> ⁽¹⁴⁾	↑ SFA ↑ MUFA	↑ LPS ↓ LPS	1.40 1.40	0.30 0.20	1.6 ^a 1.0 ^b	1.20 0.90	TAG (<i>r</i> 0.27)	–	Spearman
Laugerette <i>et al.</i> ⁽¹²⁾	↑ PUFA ↑ SFA	↓ LPS ↑ LBP/sCD14	1.10 10.5	0.20 0.70	0.7 ^{b,c} 14.6	0.50 2.00	–	–	–
Schmid <i>et al.</i> ⁽²³⁾	↑ SFA ↑ MUFA	↑ LPS ↑ LPS	2.30 2.40	0.70 0.80	–	–	TAG (<i>r</i> 0.62)	–	Not mentioned
Lyte <i>et al.</i> ⁽¹⁵⁾	↑ SFA ↑ PUFA (<i>n</i> -3)	↑ LPS ↓ LPS	0.27 0.43	0.03 0.15	0.38 ^a 0.26 ^b	0.20 0.02	–	–	–
López-Moreno <i>et al.</i> ⁽²⁴⁾	↑ SFA	↑ LPS	–	–	–	–	Postprandial LPS: P-selectin (<i>r</i> 0.342) sVCAM (<i>r</i> 0.282) IkBa (<i>r</i> 0.326) MIF1 (<i>r</i> 0.399) PPARG (<i>r</i> 0.437) IL-6 (<i>r</i> 0.534)	Postprandial LPS: LBP (<i>r</i> –0.391) NRF2 (<i>r</i> –0.396) XBP1 (<i>r</i> –0.434) UCP2 (<i>r</i> –0.445) ME2 (<i>r</i> –0.402) ADIPOQ (<i>r</i> –0.368) PLIN (<i>r</i> –0.375) CANX (<i>r</i> –0.342)	Pearson
López-Moreno <i>et al.</i> ⁽²⁵⁾	4 weeks: ↑ MUFA 4 h postprandial: ↑ MUFA ↑ MUFA	↓ LPS ↑ LPS ↓ LBP	0.24	0.01	–	–	Fasting LPS: IkB (<i>r</i> 0.274) Postprandial LPS: MCP-1 (<i>r</i> 0.377) Fasting LBP: MCP-1 (<i>r</i> 0.255) TNF (<i>r</i> 0.419) iAUC LBP and iAUC CD14 (<i>r</i> 0.41)	–	–
Morandi <i>et al.</i> ⁽²⁶⁾	balanced content of SFA/MUFA/PUFA	↓ LBP	–	–	–	–	iAUC LBP and iAUC CD14 (<i>r</i> 0.41)	IL-6 (<i>r</i> < 0.3)	Pearson
Alayón <i>et al.</i> ⁽²⁷⁾	↑ SFA	↑ LPS	Obese: 0.92 Not obese: 0.49	–	1.70 1.33	–	Obese group (<i>r</i> 0.635)	–	Pearson

Effects of dietary fat quality on metabolic endotoxaemia

†, Higher concentration; ↓, lower concentration; ADIPOQ, adiponectin, C1Q and collagen domain containing; ADIR2, nuclear protein complex; APS, antigen human prostate specific; CANX, calnexin; CARL, calreticulin; CAV1, caveolin protein coding type 1; EU, endotoxin units; iAUC, incremental AUC; IkBa, factor κB inhibitor; MCP-1, monocyte chemoattractant protein-1; ME2, NAD-dependent malic enzyme; MIF1, migration inhibitory factor macrophage; NRF2, nuclear factor erythrocytes derived from type 2; PDIA3, protein disulfideisomerase family A, member 3; PIK3C, protein coding phosphoinositide 3 kinase; PLIN, perilipin; sCD14, soluble cluster of differentiation 14; sVCAM, soluble vascular cell adhesion molecule-1; UCP2, uncoupling protein mitochondrial type 2; XBP1, X box binding protein.

^{a,b,c} Unlike letters in the same column indicate significant differences between groups in the same study. Unlike letters on the same line indicate statistical difference between baseline and postprandial values.

* Regarding lipid in the highest amount in the intervention diet.

† Data are means and standard deviations, except for Moreira *et al.*⁽¹⁴⁾; the data are medians and interquartile ranges.

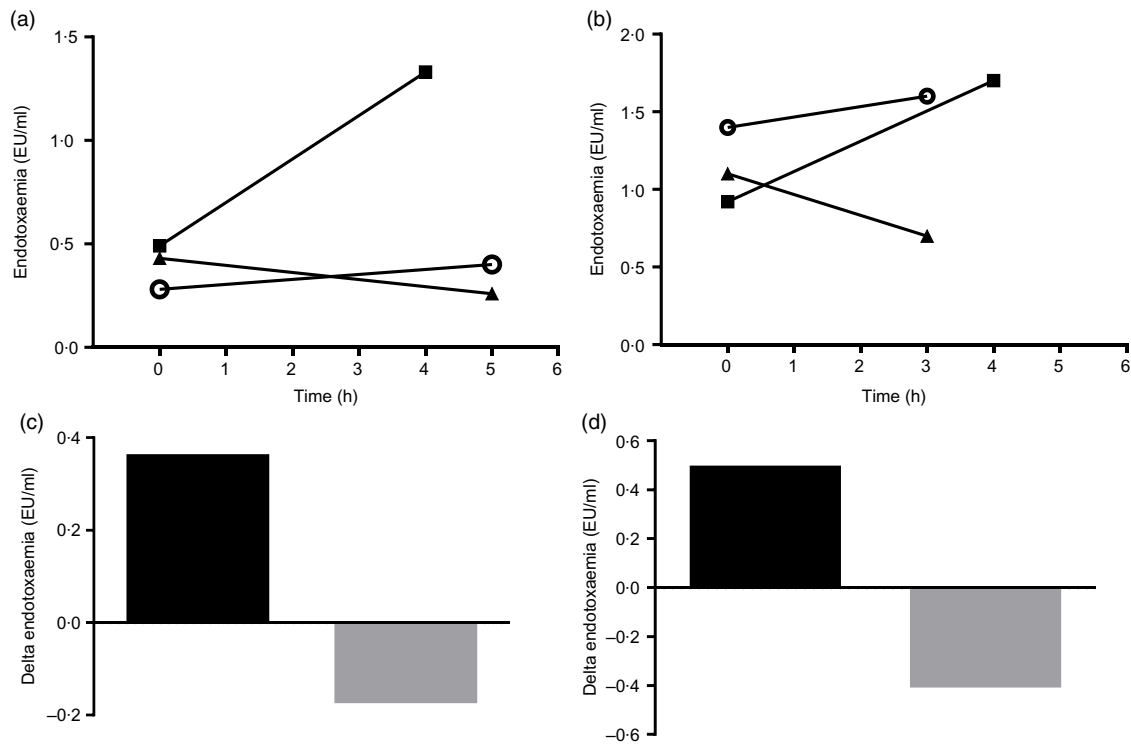


Fig. 2. Postprandial effect of the intake of different fatty acid types (SFA and PUFA) on lipopolysaccharide (LPS) concentrations in eutrophic and overweight subjects. SFA response was obtained by mean values assessed at baseline, 4 h and 5 h postprandial. Delta values (Δ = final – baseline value) were obtained by the mean results obtained in all studies. (a) LPS concentrations in eutrophic subjects. (b) LPS concentrations in overweight subjects. (c) LPS concentrations delta (Δ = LPS final – LPS baseline) in eutrophic subjects after SFA and PUFA intake. (d) LPS concentrations delta (Δ = LPS final – LPS baseline) in overweight subjects after SFA and PUFA intake. (a and b) ○, MUFA; ■, SFA; ▲, PUFA. (c and d) ■, SFA; ■, PUFA. EU, endotoxaemic units.

authors verified positive correlations between LPS and IKBA and MIF1 and negative correlations between LBP and NFκB. In addition, LPS-P-selectin and SVCAM were positively correlated with plasma inflammation markers⁽²⁴⁾.

According to some authors⁽¹³⁾, postprandial IL-6 is correlated with fasting LBP in lean and obese volunteers, and others⁽⁹⁾ observed IL-6 response after overfeeding with butter, cheese and almonds due to the ratio between LBP and sCD14 in plasma. Finally, López-Moreno *et al.*⁽²⁵⁾ verified positive correlations between fasting LPS concentrations and the κ B gene expression, in addition to correlations between LBP and monocyte chemoattractant protein-1 (MCP-1). Moreover, the authors demonstrated correlations between LPS and MCP-1 expression in peripheral mononuclear cells in the postprandial period⁽²⁵⁾.

Discussion

The results from the studies included in this systematic review indicate that the dietary fat profile seems to modulate the LPS concentrations in the bloodstream. While the consumption of SFA-rich meals was associated with an increase postprandial in LPS concentrations^(12,14,15,20,23–25,27), PUFA-rich meals were associated with lower LPS concentrations^(14,15), both in eutrophic and overweight individuals (Fig. 2). In a 4-week high-fat diet study involving animals, increased plasma LPS concentration was verified two to three times during the meal⁽²⁾. However, the mechanisms involved between dietary fat profile and

metabolic endotoxaemia in humans are not fully understood. Thus, here we aim to discuss the possible implications of dietary fatty acids on metabolic endotoxaemia (Fig. 3).

High-fat meal intake stimulates liver production of bile acids, which aid in the digestion and absorption of fats through micelles formation⁽²⁹⁾. Due to its lipid A fraction, LPS is incorporated into the micelles in the intestinal lumen and, thus, the endotoxin is carried out to the enterocytes and incorporated into the chylomicrons^(4,8). After a single exposure to a high-fat load, obese subjects, who had subtle impairment in barrier function, had a greater increase in the permeability of the small intestine compared with non-obese patients. That result suggests that fat themselves are capable of altering paracellular permeability, by directly damaging the tight junctions⁽³⁰⁾.

Dietary fatty acid profile seems to influence the chylomicron–LPS complex transport into the bloodstream. Therefore, considering that chylomicrons are formed after food intake, variations on postprandial LPS concentrations may be linked to lipaemia⁽²⁵⁾.

Some authors observed that the ingestion of long-chain fatty acids, such as *n*-3 PUFA, resulted in lower postprandial TAG concentrations and, consequently, lower lipaemia^(25,31,32). These results can be attributed to the DHA and EPA ability to increase chylomicron clearance and reduce VLDL serum concentration⁽³²⁾. Similarly, the ingestion of fish oil, rich in *n*-3 PUFA resulted in lower postprandial lipaemia, when compared with a SFA-rich oil mix⁽³³⁾ and rapeseed oil, rich in MUFA⁽³⁴⁾. On

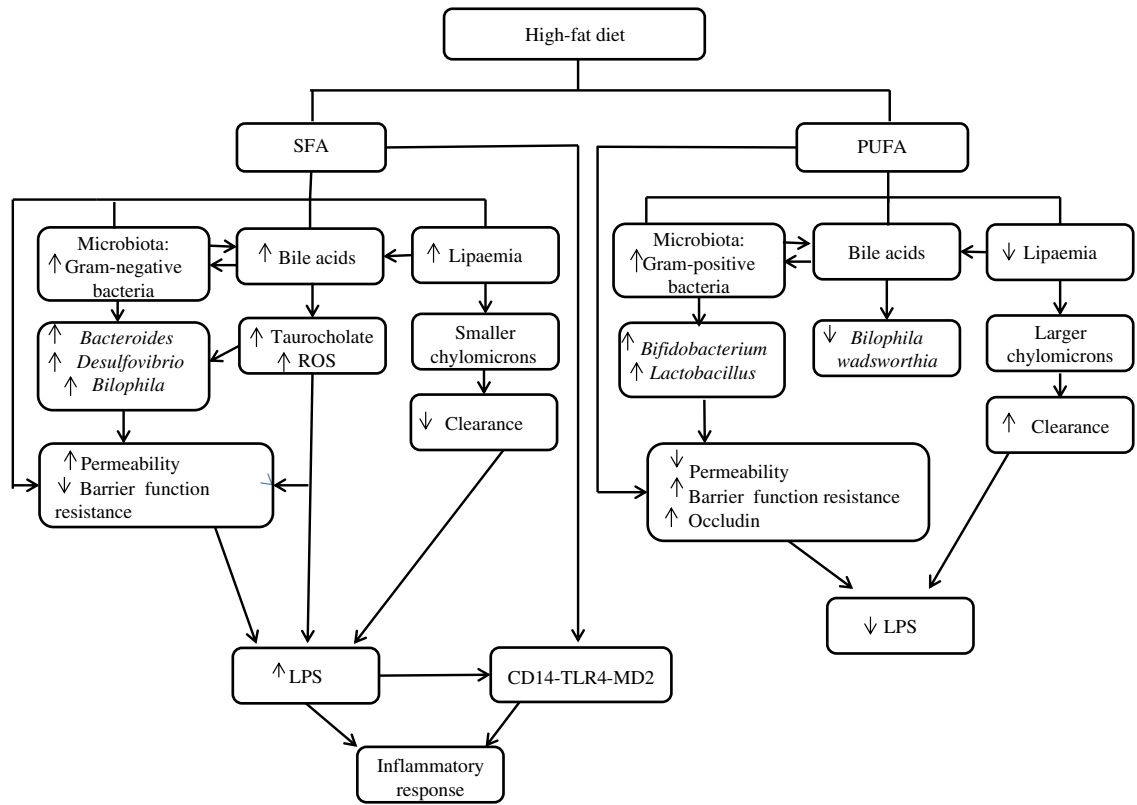


Fig. 3. Possible mechanisms explaining changes in lipopolysaccharide (LPS) concentrations. ↑, Higher concentration; ↓, lower concentration; ROS, reactive oxygen species; CD14, cluster of differentiation 14; TLR4, Toll-like receptor; MD2, myeloid differential protein-2.

the other hand, the ingestion of SFA lead to a higher lipaemia in comparison with both MUFA and PUFA intake^(31,35). It is noteworthy that SCFA and medium-chain fatty acid are not incorporated into chylomicrons and therefore have a limited effect on postprandial lipaemia⁽³⁶⁾. However, more research must be carried out to clarify the effects of different fatty acids with different chemical structures on endotoxaemia.

According to a body of literature^(14,20), other dietary factors may influence the lipidaemic response and LPS concentrations. Deopurkar *et al.*⁽²⁰⁾ demonstrated that the intake of orange juice, associated with a high-fat and high-carbohydrate diet, did not change the LPS concentrations in the bloodstream, neither oxidative stress and inflammation markers concentrations. These results can be attributed to the orange juice flavonoid content, since it can have antioxidant and anti-inflammatory effects⁽²⁰⁾, as well as to the resveratrol and fibres, which may promote a hypolipidaemic effect, through bile acid reduction and sterol reabsorption⁽¹⁴⁾. In this regard, it is important to consider that fatty acids are inserted in a food matrix and the composition of a food and/or a meal as a whole can influence fat digestion and absorption, and consequently their effects on metabolic endotoxaemia⁽³⁷⁾. In addition, the fat structure can also impact postprandial absorption and endotoxaemia. Vors *et al.*⁽³⁸⁾ demonstrated that the consumption of emulsified fat by obese men increased the transport of LPS by kilomicros and led to a more efficient clearance when compared with fat spread. That effect if probably due to the formation of larger chylomicrons from emulsification.

The dietary fatty acid profile also seems to influence the apo composition, as well as the number and size of TAG-rich lipoproteins, such as the chylomicrons⁽³⁵⁾. According to Sakr *et al.*⁽³⁹⁾, PUFA can form larger chylomicrons particles than SFA and these particles are hydrolysed more rapidly by lipoprotein lipase. In addition, the remaining PUFA and MUFA chylomicrons are absorbed faster by the liver than the SFA-enriched particles, in which the clearance is impaired due to the Apo C-III accumulation^(40,41). Therefore, larger PUFA-rich chylomicrons are purified more efficiently than small ones, rich in SFA, and may contribute to decrease LPS concentrations in the circulation and favour metabolic endotoxaemia control⁽⁴²⁾.

Another mechanism that seems to be involved in LPS modulation in response to dietary fat profile refers to bile acid metabolism. Evidence suggests a dynamic and robust interaction between diet, bile acids and intestinal microbiota. Intestinal bacteria participate in the conversion of primary bile acids into secondary ones. In turn, secondary bile acids can modify the bacterial community, by promoting the growth of bacteria capable to metabolise bile acids or exerting bactericide effects^(43,44). In this context, an experimental study in mice demonstrated that the consumption of an isoenergetic diet associated with high-SFA intake modified the composition of bile acids through taurine conjugation. The researchers were unable to show similar results when the consumption of the same diet was associated with PUFA intake. Higher concentrations of taurocholate, besides favouring *Bilophila wadsworthia* growth, a Gram-negative and sulphidogenic bacteria, which

compromised intestinal barrier function, were observed with the consumption of a high SFA diet⁽⁴⁵⁾. On the other hand, fish oil, rich in *n*-3 PUFA, supplementation inhibited the growth of *B. wadsworthia*, suggesting that the type of fatty acid ingested may play a role in the modulation of bile acid composition⁽⁴⁶⁾.

Increased luminal bile concentrations can lead to higher intestinal permeability by suppressing tight junction proteins expression, and thus favouring paracellular transport of LPS⁽⁴⁷⁾. According to Willemsen *et al.*⁽⁴⁸⁾, PUFA intake increases the intestinal epithelial barrier integrity, while the intake of saturated palmitic acid (C16:0) showed detrimental results. These results were associated with increased occludin expression, a tight junction protein, responsible for paracellular intestinal permeability regulation. Moreover, PUFA may influence lipid transportation through the intestinal barrier cells phospholipid membranes, by altering its structure, and therefore preventing the passage of endotoxins into the bloodstream^(48,49).

Although the studies included in this review showed a reduction in LPS concentrations after the ingestion of *n*-3 and *n*-6 PUFA^(14,15) in humans, that same effect was not observed in animal studies⁽⁴⁴⁾. Kaliannan *et al.*⁽⁵⁰⁾ demonstrated that the consumption of *n*-3 PUFA increases the endogenous activity of intestinal alkaline phosphatase and decreases LPS production and intestinal permeability improvement, which resulted in decreased metabolic endotoxaemia⁽⁵⁰⁾. On the other hand, rats fed with *n*-6 PUFA-rich diets presented high concentrations of LPS and LBP⁽⁵⁰⁾. Similarly, the authors observed a reduction in metabolic endotoxaemia and inflammation markers concentration after fish oil supplementation for 2 months (*n*-3 PUFA)⁽⁵⁰⁾. Regarding the different SFA types, we observed that the studies included in this review predominantly used palmitic and lauric acids, found in palm oil, coconut oil, milk and derivatives and that the consumption of both increased LPS concentrations. However, different impacts on endotoxaemia can be observed due to the addition of other dietary components (as for example, emulsifiers) to oils rich in SFA⁽⁵¹⁾. In a study in which rats were fed diets rich in palm oil, the addition of soya lecithin had no impact on endotoxaemia. On the other hand, the addition of milk phospholipids led to a reduction in endotoxaemia⁽⁵¹⁾.

Dysbiosis is another factor that can contribute to increased passage of LPS to the circulatory system, since changes in the intestinal microbiota can change the diversity and abundance of bacteria, increasing Gram-negative bacteria and generating large amounts of endotoxin after bacterial lysis, in addition to affecting the integrity of the barrier⁽⁵²⁾. In an experimental study with rats, the intake of a SFA-rich diet, reduced the intestinal barrier resistance and increased the abundance of H₂S (sulphide acid) producing bacteria, such as *Bilophila* and *Desulfovibrio*⁽⁵³⁾. On the other hand, Patterson and colleagues⁽⁵⁴⁾ observed an increase in the number of bifidobacteria after ingestion of *n*-3 PUFA. Increase in bifidobacteria may have a protective effect against endotoxaemia induced by a high-fat diet, since in rats fed a prebiotic-enriched high-fat diet (oligofructose), an increase in the amount of bifidobacteria was observed, which was negatively correlated with endotoxaemia⁽⁵⁵⁾. The bifidogenic effect may be related to lower endotoxin concentrations in the bloodstream, since these bacteria cannot degrade glycoproteins mucus and preserve the barrier function⁽⁵⁶⁾.

At high concentrations in the bloodstream, LPS can activate inflammatory pathways signalling cascade, therefore favouring the development of chronic diseases⁽⁵⁷⁾. With the aid of proteins, such as LBP (LPS binding protein), CD14 and differentiating myeloid protein 2⁽⁵⁸⁾, LPS binds to the TLR4⁽⁵⁹⁾ and induces cytokine and pro-inflammatory factors secretion, like NFκBp65 and IL-6⁽⁶⁰⁾.

Likewise the LPS, SFA, such as lauric acid (C12:0), can promote the expression of pro-inflammatory factors via TLR4. These fatty acids can bind to CD14 and differentiating myeloid protein 2 and activate the TLR4 through the formation of CD14-TLR4-MD2, an inflammatory signalling complex⁽⁶¹⁾. On the other hand, *n*-3 PUFA appears to exert an anti-inflammatory effect, mediated by the G protein-coupled receptor 120, due to its ability to inhibit the TLR4-induced signalling pathway^(10,61). Therefore, SFA seem to modulate the TLR4-induced inflammatory response, and this effect can be accentuated in the presence of LPS⁽¹⁰⁾.

Furthermore, López-Moreno *et al.*⁽²⁴⁾ also observed a greater inflammatory response after the ingestion of SFA, and the researchers suggested that such outcome could be related to the postprandial increase in LPS concentrations. These findings are supported by positive correlations between LPS and postprandial gene expression of *IkBa* and *MIF1* in peripheral mononuclear cells, both involved in inflammatory response regulation. In addition, a positive relationship was observed between LPS and the adhesion molecules P-selectin and VCAM, which could favour atherosclerosis development⁽²⁴⁾.

Limitations

Relatively few studies have evaluated the effect of the dietary fat profile on humans' metabolic endotoxaemia. Although the acute LPS response studies have previously been explored, only Morandi *et al.*⁽²⁶⁾ evaluated the behaviour of LBP concentrations after dietary fat intake and used the AUC to analyse their data. Since the baseline values of LPS and LBP have not yet been established, we believe that the AUC is a more accurate method to identify and measure changes in these markers concentrations in response to dietary interventions.

It should be noted that the studies included in this review did not consider the different types of SFA and PUFA of the test meals/diets. Due to the heterogeneity of the studies in terms of the test diet, our comments were limited to the type of fatty acid present in greater quantity in the test meals. Another point to be considered is that the number of studies available at the moment is still very small for us to establish a strong conclusion.

Conclusions

Experimental studies and human clinical trials, evaluating the impact of specific nutrients on LPS concentrations, indicated that the dietary fatty acid profile might play a role in metabolic endotoxaemia modulation. According to the studies included in the present review, the intake of SFA-rich meals increased plasma LPS concentrations, while PUFA-rich meals reduce LPS concentrations. It is worth highlighting that such effects were

observed only in studies evaluating the LPS postprandial response. On the other hand, these same results were not verified in long-term intervention studies included in our review. Therefore, SFA intake can be considered as a dietary risk factor for the development of metabolic endotoxaemia. In contrast, the intake of PUFA appears to exert a protective effect.

Finally, in order to decrease LPS concentrations in the bloodstream and consequently prevent chronic diseases associated with metabolic endotoxaemia development, like diabetes, obesity and arteriosclerosis, we believe that changes in the dietary fatty acid profile, such as lowering the intake of SFA-rich meals and increasing PUFA-rich meals ingestion may be a simple but effective strategy and it should therefore be recommended. However, the results need to be confirmed, given the small number of studies involving human subjects. Therefore, future studies on dietary fat quality and endotoxaemia are needed.

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