



# Evaluating the roles of food matrix, lipid micronutrients and bioactives in controlling postprandial hypertriglyceridaemia and inflammation

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## Abstract

Lipids play an important role in human nutrition. Although adequate lipid consumption is necessary for an optimal functioning of the human body, overconsumption of saturated fatty acids can lead to postprandial hypertriglyceridaemia, which triggers the development of atherosclerosis. Important parameters that impact postprandial lipaemia and inflammation are related to the matrix structure and the fat-soluble micronutrient profile of ingested foods/lipids, but the specific effect of these parameters should be further studied, as most of the available studies evaluate their effect at fasting state. This review specifically explores the effects of food structure and fat-soluble micronutrients, from either micronutrient-rich foods or supplements, on postprandial hypertriglyceridaemia and inflammation. The review also highlights the potential of emerging biomarkers such as miRNAs or circulating microvesicles, as an alternative to the widely used biomarkers (e.g. low-density lipoproteins or blood concentration of pro-inflammatory cytokines), to identify inflammation associated with postprandial hypertriglyceridaemia at early stages.

**Key words:** carotenoids: emulsions: fat-soluble vitamins: inflammation: postprandial hypertriglyceridaemia

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## Introduction

Lipids play an important role in human nutrition. They not only represent a high percentage of our caloric intake but are also a source of essential fatty acids and carriers of fat-soluble micronutrients (FSM) such as liposoluble vitamins and carotenoids. Although adequate lipid consumption is necessary for an optimal functioning of the human body, an overconsumption of saturated fatty acids can lead to postprandial hypertriglyceridaemia (overaccumulation of triacylglycerol-rich lipoproteins (TRL) in blood), which triggers the development of atherosclerosis. Indeed, a high TRL level in blood is the major pattern of lipid abnormality in many patients who are treated for atherosclerotic cardiovascular disease<sup>(1,2)</sup>. Postprandial hypertriglyceridaemia has been associated with increases in different biomarkers of metabolic health associated with atherosclerotic cardiovascular disease, such as oxidation rate of low-density lipoproteins (LDL)<sup>(3–5)</sup> or blood concentration of pro-inflammatory cytokines<sup>(6)</sup>, two groups of biomarkers widely used by the research community. However, emerging biomarkers such as microRNAs (miRNA)<sup>(7)</sup>, circulating microvesicles<sup>(8)</sup> or changes in gene expression in blood cells associated with miRNA expression<sup>(7,9)</sup> have shown promising results.

The food matrices in which lipids are embedded are very diverse and are responsible for the modulation of fatty acid release during digestion, bioavailability and metabolic fate once absorbed<sup>(10)</sup>. However, very little information is available regarding the specific effect of food structure on postprandial lipaemia. The available studies focused mainly on emulsion-based dairy products and have highlighted the impact of lipid emulsion structure on lipid absorption rate and lipid postprandial response<sup>(11,12)</sup>. Food compounds can also modulate postprandial lipaemia. Hydrosoluble micronutrients such as niacin (vitamin B<sub>3</sub>), minerals (zinc, copper, magnesium, calcium) and phytochemicals such as polyphenols have a positive effect on postprandial lipaemia, as previously reviewed by our research group<sup>(13)</sup>. Other reviews have also highlighted the effect of macro- and micronutrients on postprandial lipaemia<sup>(14–16)</sup>, but none of them addressed the effect of fat-soluble vitamins and carotenoids. This may be related to the fact that fat-soluble vitamin- and carotenoid-specific effects on postprandial hypertriglyceridaemia and associated inflammation are still not well understood. The link between nutritional supplementation and fasting hypertriglyceridaemia has been reviewed elsewhere<sup>(17)</sup>, but, to date, no review linking FSM

**Abbreviations:** AD, atherogenic dyslipidaemia; CRP, C-reactive protein; CVD, cardiovascular diseases; FSM, fat-soluble micronutrients (i.e., fat-soluble vitamins and carotenoids); HDL-C, high-density lipoprotein-cholesterol; HDL, high-density lipoproteins; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-17A, interleukin-17A; IL-18, interleukin-18; LDL, low-density lipoproteins; LDL-C, low-density lipoprotein-cholesterol; miRNAs, microRNAs; NEFA, non-esterified fatty acids; TG, triacylglycerol; TNFα, tumour necrosis factor alpha; TRL, triacylglycerol-rich lipoproteins; VCAM-1, vascular cell adhesion molecule 1; VLDL, very low-density lipoproteins.

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supplementation and postprandial hypertriglyceridaemia is available.

This review aims to cover this gap and brings up to date the state of the art regarding the effects of: (i) food structure and (ii) FSM, from either micronutrient-rich foods or supplements, on postprandial hypertriglyceridaemia. We will also discuss the potential of emerging biomarkers (miRNAs, circulating micro-vesicles) to determine the inflammatory state associated with postprandial hypertriglyceridaemia.

### Postprandial hypertriglyceridaemia and inflammation: where are we now?

Cardiovascular diseases (CVD) are the dominant cause of death in the world<sup>(18)</sup>. Residual cardiovascular risk, which is defined as the risk of cardiovascular events that persists despite achievement of treatment goals for low-density lipoprotein-cholesterol (LDL-C), blood pressure and glycaemia is largely associated with atherogenic dyslipidaemia (AD). AD is mainly characterised by fasting and postprandial hypertriglyceridaemia (postprandial hyperlipidaemia), low high-density lipoprotein-cholesterol (HDL-C) and increase of small and dense LDL. AD is often present in individuals at high cardiovascular risk such as persons with overweight or obesity, individuals suffering from type 2 diabetes and subjects suffering from metabolic syndrome who frequently share the same insulin-resistant state<sup>(19,20)</sup>. The pathophysiology of AD is widely explained by the blood accumulation of TRL synthesised by the liver (very low-density lipoproteins, VLDL) and the intestine (chylomicrons). This accumulation has been attributed to the overproduction of both VLDL<sup>(21)</sup> and chylomicrons<sup>(22)</sup> and a defective TRL removal process because of several associated mechanisms: reduction of lipoprotein lipase activity, changes in the apolipoprotein composition of TRL impairing particle clearance, and defect in the hepatic uptake of TRL and their remnants<sup>(23)</sup>. Elevated fasting and postprandial blood TRL concentrations, which are mainly related to the increase in chylomicron and VLDL production, are now considered a causal risk factor for low-grade inflammation, atherosclerotic CVD and all-cause mortality. Indeed, there are extensive epidemiological, genetic and biological data showing that the increase of TRL reflected by the fasting and postprandial blood triacylglycerol (TG) level and/or the measurement of remnant cholesterol (remnant cholesterol = total cholesterol – LDL-C – HDL-C) is a causal risk factor for atherosclerosis through direct and indirect mechanisms<sup>(24)</sup>. TRL and its remnants can promote atherosclerosis via modulating inflammation, oxidative stress and formation of foam cells<sup>(25)</sup>. In a multi-directional Mendelian randomisation human study, it has been shown that elevated non-fasting remnant cholesterol was causally associated with low-grade inflammation. Indeed, a 1-mmol/L-higher level of non-fasting remnant cholesterol was associated observationally with a 37% higher C-reactive protein (CRP) level and causally with a 28% higher level of ischaemic heart disease<sup>(26)</sup>. The potential inflammatory mechanisms for atherogenesis in hypertriglyceridaemia have been described in a recent review<sup>(27)</sup>. In summary, circulating monocytes can take up TRL and their remnants and possibly non-esterified fatty acids

(NEFA) to become foamy monocytes with an inflammatory phenotype (high level expression of tumour necrosis factor alpha (TNF $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) and type I transmembrane protein CD11c). Foamy monocytes adhere firmly to vascular cell adhesion molecule 1 (VCAM-1)/intercellular adhesion molecule 1 (ICAM-1) expressed on activated endothelial cells and infiltrate into plaques, where foamy monocytes differentiate into foam macrophages, thereby contributing to atherosclerosis. Foamy monocytes can also possibly infiltrate other tissues and may therefore play a pivotal role in the development of inflammation in other tissues. TRL remnants and NEFA can also enter arterial walls directly, be engulfed by lesional macrophages and increase macrophage lipid accumulation, promoting foam macrophage formation and contributing to atherogenesis. Macrophages including foam macrophages secrete cytokines, which, along with those derived from foamy monocytes, can further increase inflammation in macrophages and other cells in plaques and promote atherosclerosis progression. TRL, their remnants and NEFA can interact with endothelial cells and induce endothelial cell inflammation and activation, with up-regulation of cytokines and adhesion molecules such as ICAM-1 and VCAM-1, which mediate monocyte adhesion and recruitment into atherosclerotic plaques. Finally, TRL remnants and NEFA also impair the balance of nitric oxide and reactive oxygen species (ROS) in endothelial cells, leading to endothelial dysfunction.

Given the damaging consequences of postprandial hyperlipaemia, mitigating nutritional strategies should be implemented in patients in addition to their usual medical treatment.

### Effect of food structure and composition on postprandial hypertriglyceridaemia and/or inflammation

Postprandial hypertriglyceridaemia can be modulated by many factors, such as structure and composition of the meal/food consumed, lifestyle factors or biological factors<sup>(14)</sup>. The effect of food matrix on postprandial hypertriglyceridaemia, which can be defined as the nutrient and non-nutrient components of foods and their molecular relationships, is still not very well characterised<sup>(13,28)</sup>. More particularly, food structure, that is, the organisation of food constituents, can be innate or built during food manufacturing. Food matrix/structure can impact food destructuring during digestion and, therefore, the release and transformation of macro- and micronutrients<sup>(29,30)</sup>, which affects their *in vivo* absorption<sup>(31)</sup>. This part of the review thus summarises the latest insights on the relationships between food structure built during food manufacturing and postprandial hypertriglyceridaemia.

#### Effect of food structure with a focus on fat distribution

The first study that assessed the impact of food structure on postprandial hypertriglyceridaemia was that of Drouin-Chartier *et al.*<sup>(32)</sup>. The authors showed that dairy fat from a soft cream cheese induced a higher TG response in the early postprandial phase compared with butter or with firm cheddar cheese. However, the measured absolute TG response for the intervention period (6 h) was similar for all products. Although the authors did not measure fat droplet size in their products, they



suggested that TG could increase faster with the soft cream owing to the smaller fat droplet size of this product compared with butter or cheddar. However, this may not be the only reason, as discussed later. Hansson *et al.*<sup>(33)</sup> then reported different TG responses of four different dairy meals (butter, cheese, whipped cream and sour cream) containing the same fat content. The authors reported that the intake of sour cream induced a significantly higher serum TG response than all the other dairy meals. Like Drouin-Chartier *et al.*,<sup>(32)</sup> the authors attributed these differences to fat droplet sizes without reporting the related values. A limiting factor in this second study was that the different products were given with toast, which probably influenced the TG postprandial response. In both studies, the results could partially be influenced by food consistency (liquid, semi-liquid or solid), as it seems that liquid foods trigger higher TG response of foods with similar composition<sup>(11)</sup>. Food structure, which also encompasses food consistency, affects gastric emptying<sup>(34)</sup> and kinetics of lipid digestion, as proven by several *in vitro* studies<sup>(35,36)</sup>. However, these *in vitro* data sometimes conflict with the conclusion of *in vivo* studies. For example, Mulet-Cabero *et al.*<sup>(35)</sup> suggested that lipid digestion occurs faster for semi-solid foods than for liquid foods, because of a predicted faster gastric emptying of lipids. These data disagree with the *in vivo* TG responses to solid and liquid dairy matrices reported by Drouin-Chartier<sup>(32)</sup>, Hansson *et al.*<sup>(33)</sup> and Diaz *et al.*<sup>(11)</sup>. The comparison and validation of gastric behaviour of such *in vitro* and *in vivo* studies is difficult because the *in vivo* studies scarcely address the structural changes of food in the stomach and the composition of each gastric emptying. However, Kjølbaek *et al.*<sup>(37)</sup> showed a higher TG response for a gel-based casein product than for a casein drink, supporting the hypothesis of Mulet-Cabero<sup>(35)</sup>. Kjølbaek *et al.*<sup>(37)</sup> suggested that these results could be due to the structure of each product, as the only difference between the two products was that the gel-based product was the result of the acid gelation of the drink. Differences in TG response could also be linked to the fact that casein loses its micellar structure at acid pH, which could affect the lipid digestion rate. However, in the same study, Kjølbaek *et al.*<sup>(37)</sup> reported a similar TG response of two cheddar cheeses with the same nutritional profile but different structures (one solid, one semi-solid), in disagreement with the hypothesis of Mulet-Cabero<sup>(35)</sup>. It seems that not only macrostructure of foods but also the fine structure of ingredients can affect the postprandial triglyceridaemia response via different digestion rates of lipids. This was illustrated recently in a study that showed a strong influence of the amylose content of starches on lipid digestion of starch-based gels: the higher the amylose content, the higher the lipid digestion per gram of oil<sup>(38)</sup>. Other *in vitro* studies have suggested that food processing can also affect lipid digestion<sup>(39–41)</sup> via structural modification of macro- and micronutrients and, therefore, potential TG response, although validation with *in vivo* models is needed before health/nutrition-related conclusions can be made, as results may differ<sup>(42)</sup>. More recently, Gleize *et al.*<sup>(43)</sup> conducted a study on twelve healthy subjects who received four starchy foods with similar compositions but different structures (custard, pudding, sponge cake and biscuit)<sup>(43)</sup>. Results showed that custard TG

response was significantly higher than pudding and biscuit TG responses. This could be linked to the lipid droplet size/structure of the products: biscuits displayed big fat “flakes” (18 000 µm) while custard was composed of very small droplets (30 µm)<sup>(43)</sup>. Overall, the available studies suggest that solid food structure limits the TG response, perhaps because solid food structure may modify the accessibility of the lipid droplets to enzymes. Results of Salt *et al.*<sup>(36)</sup>, who addressed both *in vitro* lipid digestion of muffins and free oil, support this conclusion. Gleize *et al.*<sup>(43)</sup> also showed that, despite TG postprandial concentrations being different for the four tested products, plasma TG peaked at 3 h for all products. This suggests that, although the food matrix could impact the accessibility of lipids to enzymes, it neither delayed fatty acid absorption by enterocytes nor their secretion into chylomicrons.

As mentioned above, it is widely accepted that the TG postprandial response is influenced not only by the type/amount of fat but also by droplet size distribution<sup>(28)</sup>, which is known to change during the digestion process<sup>(44)</sup> and impact lipid digestion, as reviewed elsewhere<sup>(30,45)</sup>. However, information regarding the specific effect of droplet size on postprandial hypertriglyceridaemia is still scarce. Vors *et al.*<sup>(46)</sup> evaluated the effect of droplet size of milk and reported higher postprandial chylomicrons, apolipoprotein B-48 and TG concentrations with smaller droplet sizes. However, emulsions were administered together with other food matrices, entangling the extrapolation of the results to droplet size effect only. Similar observations with the same limitations were reported by Tan *et al.*<sup>(12)</sup>, Laugerette *et al.*<sup>(47)</sup> and Garaiova *et al.*<sup>(48)</sup>. In a recent study, Howard *et al.*<sup>(49)</sup> tried to overcome this gap by evaluating the effect of two standardised emulsified high-fat meals only differing in fat droplet size on postprandial hypertriglyceridaemia. No other food was given together with the emulsions. They reported a droplet-size-dependent increase of TG concentrations over time, with the increase being more important with fine emulsions than with coarse emulsions. This was in agreement with the observations of the above-mentioned studies that administered emulsions with other foods<sup>(12,32,46–48)</sup>. Howard *et al.*<sup>(49)</sup> showed that a high-fat meal with a smaller lipid droplet size induces a sustained pro-vascular inflammatory and pro-thrombotic milieu, whereas a large lipid droplet size attenuates the rise in vascular inflammatory and thrombotic parameters similarly to a meal with negligible fat content. As this is the first human study evaluating the isolated effect of fat droplet size on vascular inflammation, the results should be considered carefully. Another study showed that emulsion droplet size affected gastrointestinal hormone release and that evenly dispersed, stable, small-emulsion droplets within the stomach lead to prolonged gastric distension and accelerated fat sensing. This prolonged feelings of satiation, which can be seen as something beneficial<sup>(50)</sup>.

There may be situations where having a small lipid droplet size to provide a fast delivery of lipids/FSM to the body may be beneficial to health, in case of specific supplementations for subgroups of the population such as elderly. Based on the protective effect of FSM, and considering that emulsions with small droplet sizes enhance FSM bioaccessibility/bioavailability<sup>(43,51)</sup>, FSM may help to tackle the potential negative effect of

fine emulsions on postprandial hypertriglyceridaemia (see below).

### Effects of emulsifiers

Polysorbates and carboxymethylcelluloses, two emulsifiers commonly used by the food industry and research community, were shown to have a detrimental effect on health<sup>(52–54)</sup>, although their effect on postprandial hypertriglyceridaemia has not yet been deeply considered. In an *in vivo* study in rats, Nassara *et al.*<sup>(55)</sup> compared the effect of water-in-oil emulsions on postprandial hypertriglyceridaemia. The different emulsions presented similar droplet sizes (9–10 µm) but were stabilised either with synthetic emulsifiers (polyoxyethylene sorbitan monooleate, also known as Tween80, or sodium stearyl-2-lactylate) or protein-based emulsifiers (sodium caseinate or  $\beta$ -lactoglobulin). The authors concluded that the use of proteins to emulsify lipids has the potential to decrease lipid postprandial response compared with synthetic emulsifiers. The effect of casein and whey proteins – two protein-based emulsifiers – on postprandial hypertriglyceridaemia has also been evaluated by Mariotti *et al.*<sup>(56)</sup>. The authors concluded that the type of milk protein did not affect postprandial plasma glucose, amino acids, insulin or NEFA, but reported that caseins markedly reduced postprandial TG and plasma chylomicrons. No significant differences between the meals regarding postprandial oxidative stress, endothelial function or low-grade inflammation were found. In a different study, Keogh *et al.*<sup>(57)</sup> evaluated the effect of emulsions stabilised with egg lecithin, sodium sterol lactylate, sodium caseinate/monoglyceride and Tween80 on postprandial hypertriglyceridaemia. The interpretation of their results is difficult, as the authors did not report emulsion droplet size and, therefore, it is unclear if reported differences between emulsions are related to droplet size or to the used emulsifier. Authors reported *in vitro* fatty acid release rate, and emulsions with the highest digestibility rate were not always the emulsions with the greatest impact on TG postprandial concentrations<sup>(57)</sup>. This suggests that both droplet size and emulsifiers are important parameters to take into consideration when evaluating the impact of food emulsions on postprandial hypertriglyceridaemia.

### Effects of FSM on postprandial hypertriglyceridaemia and/or inflammation

The specific effects of each FSM on postprandial hypertriglyceridaemia are challenging to address, as FSM are generally not consumed individually. Moreover, the use of individual FSM is somehow controversial and not common in research, because it ignores the potential interactions between nutrients within the food matrix. This matrix effect is widely acknowledged for FSM bioavailability, something out of the scope of this review but reviewed elsewhere (e.g. Chungchunlam and Moughan<sup>(58)</sup> and Dima *et al.*<sup>(59)</sup>). In this section, we cover the effects that different FSM can have on postprandial hypertriglyceridaemia and inflammation when ingested in food matrices or supplements, acknowledging that the food matrix itself and its effect on lipid

digestion can affect postprandial hypertriglyceridaemia. The available literature is focused on foods rich in FSM from plant-based sources. In the future, the research community should also address the impact of foods rich in FSM from animal sources on postprandial hypertriglyceridaemia.

### Effects of FSM-rich foods

A meta-analysis encompassing the effect of a wide range of foods/food components (sugars, fibre-rich foods, alcohol, fats, proteins, alcohol and more), some of them containing FSM, on postprandial TG response can be found in the literature<sup>(60)</sup>, although the specific effect of FSM was not assessed. Some studies indicate a relationship between FSM and TG postprandial response. Available information is summarised in Table 1. For instance, Gomez-Marín *et al.*<sup>(65)</sup> showed that long-term consumption of a Mediterranean diet, known to be rich in FSM, improves to a greater extent the postprandial TG levels in individuals with type 2 diabetes than just following a low-fat diet. Here, we addressed the linkage between FSM-rich foods, notably tomato meals<sup>(66,67)</sup>, legumes<sup>(68–72)</sup>, nuts<sup>(73–79)</sup>, orange juice<sup>(74,80–83)</sup> or certain diets<sup>(65,84)</sup> (Table 2) and postprandial hypertriglyceridaemia.

**Effects of tomato products.** Tomatoes are particularly rich in carotenoids (mainly lycopene, but also  $\beta$ -carotene and lutein) and contain a significant amount of vitamin E<sup>(85,86)</sup>.

A study by Burton-Freeman *et al.*<sup>(67)</sup> reported that a high-fat meal containing tomato paste significantly attenuated LDL oxidation and interleukin 6 (IL-6), showing a decrease in inflammation, although total postprandial TG concentrations were increased compared with a high-fat meal with equivalent calories and macronutrient content. Arranz *et al.*<sup>(66)</sup>, who assessed the effect of tomato juice on postprandial hypertriglyceridaemia, reported a beneficial effect of tomato on postprandial hypertriglyceridaemia. These authors showed that consumption of tomato juice together with olive oil increased the carotenoid levels in blood (mainly  $\beta$ -carotene and lycopene) and reduced the concentration of commonly used postprandial hypertriglyceridaemia biomarkers, such as TG, total cholesterol and LDL- or HDL-cholesterol concentrations. In fact, two meta-analyses<sup>(87,88)</sup> have reported that tomato supplementation has significant beneficial effects on IL-6, blood lipids, blood pressure, endothelial function and short-term changes in CRP levels, although it is not clear when the authors of these two meta-analyses refer to values at fasting or postprandial state.

**Effects of legumes.** The results of Nilsson *et al.*<sup>(69)</sup> suggested that consumption of 101 g (weight before cooking) of legumes (beans) as a starter for dinner can regulate the inflammation response of the first meal during the following day in comparison with the consumption of 89 g of white bread. Indeed, they reported a significant decrease in IL-6 and interleukin 18 (IL-18), as well as in blood glucose and insulin at postprandial state (between 30 and 180 or 30 and 120 min for glucose and insulin, respectively). Although the FSM content of the legumes used in this study was not addressed, it is known that beans do contain



**Table 1.** Summary of relevant studies regarding the effect of fat-soluble micronutrients from supplements on postprandial hypertriglyceridaemia and/or inflammation

Supplement	Study design	Micronutrient content	Effects	Reference
Mix of phytonutrients	Effect of consumption of a <b>mix of phytonutrients</b> for a period of 2 weeks (in a randomised, double-blind, parallel-group, placebo-controlled study, with 146 healthy normal-weight subjects).	15 mg lycopene, 15 mg phytonutrients, 4 mg phytoene and phytofluene, 0.5 mg $\beta$ -carotene	Increase plasma levels of lycopene, phytofluene and phytoene after a high-fat meal (postprandial state, 8 h after food intake) increased and decreased oxidised LDL concentration in comparison with the control group.	(61)
Vitamin E supplementation	Effect of the type of meal ingested (high-fat meal, low-fat meal or high-fat meal with <b>vitamin E supplementation</b> ) on postprandial hypertriglyceridaemia (2–4 h) in 10 healthy normocholesterolaemic volunteers.	536 mg vitamin E ( $\alpha$ -tocopherol)	Vitamin E supplementation of a high-fat meal did not reduce serum triacylglycerol concentration, although it had a protective effect on endothelial function when measuring brachial artery vasodilation in the postprandial state.	(62)
Vitamin E and C supplementation	Effect in the oxidation–reduction balance and endothelial function before and after a meal (2–8 h) with or without antioxidant supplementation treatment (8 d) in patients with type 2 diabetes or impaired glucose tolerance. 60 subjects participated in the study (20 healthy, 20 with type 2 diabetes and 20 with impaired glucose tolerance; in every group there were 10 males and 10 females).	600 mg/d of N-acetyl-cysteine, 50 mg/d of vitamins and 500 mg/d of vitamin C.	No effect on lipid profile at the postprandial state was reported, but vitamin E treatment, in healthy subjects and subjects with impaired glucose tolerance, induced a significant improvement at the postprandial state in redox balance parameters, serum C-reactive protein and serum vascular cell adhesion molecule-1 levels VCAM-1.	(63)
Vitamin E supplementation	Effect of <b>vitamin E</b> or placebo supplementation for 6 weeks on fasting and postprandial hypertriglyceridaemia (after a fatty meal) before and after supplementation in a single-blind placebo-controlled trial with 30 patients with type 2 diabetes; randomly divided into two groups of study to receive vitamin E or identical placebo capsules daily for 6 weeks.	268 mg vitamin E	No effect on lipid profile was found, but a decrease in malondialdehyde levels in the postprandial state (2 h after food intake) was reported.	(64)

FSM (e.g.  $\alpha$ -,  $\beta$ - and  $\gamma$ -tocopherols: 4–17 mg/100 g<sup>(89,90)</sup>). We hypothesise that not only fibre but also FSM could play a role in regulating this inflammation response. Other studies did not report a significant decrease in commonly used biomarkers, such as interleukins or TG<sup>(68,71,72)</sup>, or reported a decrease only for certain bean varieties<sup>(70)</sup>. However, studies with a lack of decrease in hypertriglyceridaemia biomarkers did show a protective effect against postprandial metabolic stress (decrease of postprandial insulin/enhanced cholecystokinin response associated with reductions of plasma glucose and insulin concentrations in diabetic patients) (see Table 2 for detailed information)<sup>(68,70–72)</sup>. As previously stated, legume effects can largely be attributed to their high content in fibre, and the beneficial effect of FSM from legumes is a hypothesis that should be validated. However, Reverri *et al.*<sup>(71)</sup> showed that, compared with fibre-matched or micronutrient-matched meals, the bean meals were more efficient in modulating insulin response, likely highlighting a synergic effect between fibre and micronutrients, supporting our hypothesis.

**Effects of nuts.** Beneficial effects of walnuts at postprandial state have been reported by several authors<sup>(74,75,77,78)</sup>. This may be partly due to the presence of vitamin E in nuts. Ros *et al.*<sup>(78)</sup> reported that replacing monounsaturated fat with walnuts in a Mediterranean diet improves endothelium-dependent vasodilation in subjects with hypercholesterolaemia. In agreement with these results, Cortés *et al.*<sup>(75)</sup> showed that walnuts reversed the impairment of endothelial function associated with the consumption of a high-fat meal. In a later study, Berryman *et al.*<sup>(74)</sup> evaluated the isolated effect of walnuts and walnuts components (meat, skin and oil) on postprandial lipaemia. They observed lower postprandial triglyceridaemia for walnut meat and skin than for whole walnut or oil. Since authors did not use a control (e.g. control oil), they could only conclude that certain parts of walnuts have a positive effect on postprandial lipaemia, but when comparing the results of Berryman *et al.*<sup>(74)</sup> with those of other studies, it seems that, if they had included a control, they would have also observed an improvement with whole walnut and walnut oil. Haddad *et al.*<sup>(77)</sup> reported a reduction of oxidised LDL at the postprandial state when comparing a walnut meal against a control meal that contained refined oil.

Beneficial effects of other nuts on postprandial hypertriglyceridaemia have also been reported. For example, Berry *et al.*<sup>(73)</sup> reported that the postprandial increase in plasma TG was significantly lower after a meal containing whole almond particles than after a meal containing defatted almond flour + almond oil or sunflower oil. The authors linked their observations to the different bioaccessibility of lipids in their almond samples (regulated by the structure and its digestion). In an *in vitro* study, the effect of almond structure on lipid digestion has been demonstrated: authors showed a higher lipid release for smaller particles than for larger particles of almonds, due to the greater proportion of disrupted cells<sup>(91)</sup>. The differences observed by Berry *et al.*<sup>(73)</sup> among samples may also be influenced by the vitamin E content of the almond meals. We hypothesise this because, although not significant, postprandial increase in plasma TG seems to be mitigated when comparing the meals containing defatted almond flour + almond oil with

**Table 2.** Summary of relevant studies regarding the effect of foods containing fat-soluble micronutrients on postprandial hypertriglyceridaemia and/or inflammation

Foods	Study design	Micronutrient content	Effects	Reference
Tomato paste	Comparison of the effect of a high-fat meal containing <b>tomato paste</b> a high-fat meal with equivalent calories and macronutrient content in a single-centre, randomised, crossover, two-arm, two-sequence, placebo-controlled study with 29 healthy subjects (15 females and 14 males).	Tomato paste meal: 21 mg vitamin C, 270.38 mg lycopene, 7.97 mg vitamin E, 8.48 mg $\beta$ -carotenes. Control meal: 21.4 mg vitamin C, 0 mg lycopene, 4.5 mg vitamin E, 0.05 mg $\beta$ -carotenes	Attenuated LDL oxidation and interleukin 6 (IL-6) while increasing total triacylglycerol concentration at postprandial state (360 min).	(67)
Tomato juice	Effect of <b>tomato juice together with olive oil</b> compared with the effect of tomato juice alone on postprandial hypertriglyceridaemia (0–24 h) in an open, controlled, randomised and crossover feeding study with 11 subjects (6 men and 5 women), with mean body mass index of $23 \pm 2$ kg/m <sup>2</sup>	141 mg carotenoids	Increased the carotenoid levels in blood and reduced the concentration of commonly used postprandial hypertriglyceridaemia biomarkers, such as triacylglycerol, total cholesterol or LDL- or HDL-cholesterol concentrations.	(66)
Legumes	Comparison of <b>high- and low-fibre meals</b> at the postprandial state in 8 healthy men. High-fibre meal contained bean flakes.	Not indicated*	Decrease in plasma concentration of glucose and insulin (during first 2 h after meal ingestion). Increase of plasma cholecystokinin.	(68)
Legumes	Effect of <b>bean dinner</b> on postprandial hypertriglyceridaemia and colonic fermentation after a standardised breakfast (11–14 h post evening meals) in a randomised crossover design with 16 healthy young adults.	Not indicated*	Decreased blood glucose and insulin responses, increased satiety hormones, suppressed hunger hormones and hunger sensations, increased GLP-2 concentrations and suppressed inflammatory markers in the postprandial state. Higher colonic fermentative activity after the brown bean dinner.	(69)
Legumes	Comparison of a <b>black bean meal</b> with fibre-matched or antioxidant-matched meals at the postprandial state (5 h) in 12 adults with metabolic syndrome.	300 mg grape seed extract was used to match the antioxidant content of the black bean meal. No other specifications are given by the authors	Insulin content was lower after the black bean meal.	(71)
Legumes	Comparison of <b>canned bean breakfast</b> with a control breakfast at the postprandial state (over 6 h) in a crossover study with 12 subjects with type 2 diabetes (5 women).	Not indicated*	Glucose and insulin levels were lower after bean consumption compared with the control meal.	(70)
Nuts	Effect of <b>walnuts</b> and walnut components (meat, skin and oil) on postprandial lipaemia in a randomised, controlled, postprandial, four-period crossover study with at least 1 week separation between testing sessions was conducted with 15 subjects (9 women, 6 men).	Not indicated†	Lower postprandial triglyceridaemia for walnut meat and skin than for whole walnut or oil.	(74)
Nuts	Effects of high-fat meals enriched with <b>walnuts or olive oil</b> on postprandial endothelial function (4 h) in a randomised crossover design with 12 healthy subjects and 12 patients with hypercholesterolaemia. Two weeks before intervention, participants were instructed to follow a cholesterol-lowering Mediterranean diet and to abstain from physical exertion.	Olive oil: 30 mg vitamin E ( $\alpha$ -tocopherol)/100 g olive oil. Grams of olive oil in the diet are not indicated Walnuts: 156.8 mg vitamin E (1.8 mg $\alpha$ -tocopherol and 155 mg $\gamma$ -tocopherol)/100 g walnuts. Walnuts partially replaced olive oil. Subjects ate between 40 and 65 g of walnuts per day Test meal before endothelial measurements: sandwich with 100 g white bread, 75 g salami, and 50 g fatty cheese, 125 g fat-rich (10%) yogurt and water <i>ad libitum</i> . Additionally, participants consumed 25 mL olive oil soaked into the bread (olive oil meal) or 40 g shelled walnuts (walnut meal)	In comparison with olive oil, walnuts reverse the impairment of endothelial function associated with eating a fatty meal.	(75)
Nuts	Effect of a <b>walnut</b> meal on postprandial oxidative stress and antioxidants in a randomised, crossover, and controlled-feeding study with 16 healthy individuals.	Control diet: 8.9 mg vitamin E (8.4 mg $\alpha$ -tocopherol and 0.5 mg $\gamma$ -tocopherol) Walnut diet: 13.2 mg vitamin E (0.5 mg $\alpha$ -tocopherol and 18.7 mg $\gamma$ -tocopherol)	Oxidised LDL significantly decreases from baseline following walnut consumption (2–8 h after consumption).	(77)

**Table 2.** (Continued)

Foods	Study design	Micronutrient content	Effects	Reference
Nuts	Effect of a 4-week <b>walnut</b> diet on postprandial endothelial function (4 h) in a randomised, crossover, study with 21 men and women with hypercholesterolaemia. Effects of a cholesterol-lowering Mediterranean diet and a diet of similar energy and fat content in which walnuts replaced 32% of the energy from monounsaturated fat were compared.	Walnuts: 156.8 mg vitamin E (1.8 mg $\alpha$ -tocopherol and 155 mg $\gamma$ -tocopherol)/100 g walnuts. Walnuts partially replaced olive oil. Subjects ate between 40 and 65 g of walnuts per day Test meal before endothelial measurements: 100-g bread sandwich with 50 g lean pork ham, an apple and tap water. For the control diet, the bread was soaked with 15–20 mL olive oil, whereas 20–32.5 g walnuts were incorporated into the test meal during the walnut diet	Compared with the Mediterranean diet, the walnut diet improved endothelium-dependent vasodilation and reduced levels of vascular cell adhesion molecule-1. The walnut diet significantly reduced total cholesterol and LDL-cholesterol.	(78)
Almonds	Comparison of the effects of three meals containing 54 g fat provided as <b>whole almond seed</b> macroparticles (WA), almond oil and defatted <b>almond flour</b> (AO) or a <b>sunflower</b> oil blend (control) on postprandial changes were evaluated to assess the effect of almond oil bioaccessibility in a randomised crossover trial with 20 healthy men.	Not indicated <sup>‡</sup>	Postprandial increase in plasma triacylglycerol was significantly lower after the WA meal containing whole almond seed macroparticles than after the other two meals. Increases in plasma glucose concentrations (0–180 min) were significantly higher after this same meal than after the almond oil meal, but no significant differences from the control meal were observed.	(73)
Hazelnuts	Assessment of the postprandial effects of <b>hazelnut-enriched high-fat McDonalds®</b> meal (3 h after meal consumption) in a randomised and crossover trial with 22 healthy subjects.	Meal was supplemented with 40 g hazelnut Vitamin E ( $\alpha$ -tocopherol) content: 24.1 mg/100 g hazelnuts	Inclusion of hazelnut decreased oxidised LDL levels after a McDonalds® meal. It also affected gene expression; although due to the small number of participants, a conclusive statement regarding this matter cannot be made.	(76)
Orange juice	Assessment of the postprandial effect of <b>blond or red orange juices</b> consumed with a fatty meal (2 h after meal consumption) in a randomised crossover design with 18 healthy subjects.	Both juices had the same nutritional properties and phenolic composition (not specified) except for total anthocyanins (only in red juice 53.1 $\pm$ 5.3 mg/L)	Inclusion of red orange juice decreased postprandial triacylglycerol and total cholesterol levels.	(80)
Orange juice	Assessment of the postprandial effect (2–5 h) of the inclusion of <b>orange juice</b> on two different high-fat meals (meals high in either saturated or monounsaturated fatty acids). Two controlled, randomised crossover parallel interventions were interventions with 33 (meal high in saturated fatty acids) or 22 (meal high in monounsaturated fatty acids) healthy women.	Micronutrient profile of orange juice not specified	Meal high in saturated fatty acids increased cytokine levels in comparison to the meal high in monounsaturated fatty acids. Orange juice intake was able to mitigate the increment in postprandial inflammation, induced by SFA high-fat meal consumption, for only a particular cytokine (IL-17A).	(82)
Mediterranean diet	Assessments of postprandial effect (4 h) of long-term consumption of <b>Mediterranean or low-fat diets</b> with selected patients from the Cordioprev study (241 patients with and 316 patients without type 2 diabetes). Subjects were randomly assigned to receive either a Mediterranean diet rich in olive oil or a low-fat diet.	No specific micronutrient targeted. Effect of Mediterranean diet as a whole was evaluated	Long-term consumption of a Mediterranean diet rich in olive oil (3 years) improves postprandial lipaemia and remnant cholesterol concentration in people with type 2 diabetes. No effect was seen in people with type 2 diabetes who followed the low-fat diet.	(65)

\* Although FSM content was not reported, legumes are known to contain vitamin E ( $\alpha$ -,  $\beta$ - and  $\gamma$ -tocopherols: 4–17 mg/100 g dry weight<sup>(89,90)</sup>).

† Although FSM content was not reported, walnuts are known to contain vitamin E and carotenoids (vitamin E: 43 mg/100 g dry weight, carotene: 0.03 mg/100 g dry weight<sup>(117)</sup>).

‡ Although FSM content was not reported, almonds are known to contain vitamin E (mainly  $\alpha$ -tocopherol: 20–80 mg/100 g dry weight<sup>(92,93)</sup>). All values are for orientation.

It is important to note that observations of these studies cannot be attributed only to the effect of fat-soluble micronutrients, as these foods/meals contain other compounds with a potential beneficial effect on the measured biomarkers (e.g. fibre).



the one containing sunflower oil. This suggests a protective effect of vitamin E, as reported elsewhere<sup>(92,93)</sup>. The protective effect of hazelnuts in combination with a high-fat diet has also been reported by Di Renzo *et al.*<sup>(76)</sup>. These authors observed a decreased low-density lipoprotein oxidation after a high-fat meal when this meal included hazelnuts.

**Effects of orange juice.** The beneficial effects of orange juice on postprandial hypertriglyceridaemia were first suggested by Cerletti *et al.*<sup>(80)</sup>. These authors observed a significant decrease in TG concentration after a test meal just by changing water from control meal for red orange juice, with TG decrease being not significant for blond orange juice. Another study suggested that the consumption of orange juice helps to reduce the increase of the inflammatory cytokine interleukin 17A (IL-17A) after a high-fat meal high in saturated fatty acids, but not for other tested cytokines<sup>(82)</sup>. A recent study compared orange juice with fermented orange juice and concluded that fermented orange juice has also a beneficial effect on postprandial hypertriglyceridaemia<sup>(81)</sup>, although no control was included in the study, limiting the extrapolation of their results.

### Effect of supplements

Extensive evidence has demonstrated that antioxidants such as vitamin E or carotenoids (but also vitamin C and polyphenols) have protective effects in preventing cardiovascular diseases<sup>(94)</sup>. Some authors have reported specific beneficial effects of FSM (Table 1) and foods/meals containing FSM (Table 2) during the postprandial state. For example, a study by Deplanque *et al.*<sup>(61)</sup> in a randomised, double-blind, parallel-group, placebo-controlled study, with 146 healthy normal-weight subjects reported that consumption of a mix of phytonutrients for a period of 2 weeks (a mixture of lycopene and phytosterols: 15 mg of each), phytoene and phytofluene (4 mg total) and  $\beta$ -carotene (0.5 mg)) was enough to increase plasma levels of lycopene, phytofluene and phytoene after a high-fat meal (postprandial state, 8 h after food intake) and decreased oxidised LDL concentration in comparison with the control group. These authors did not observe significant differences in glucose, insulin and TG levels during the postprandial state (8 h after food intake, except for insulin that was measured 2 h after food intake), although values were lower for the supplemented group.

Some information about the effect of vitamin E in postprandial hypertriglyceridaemia can also be found in the literature. Bae *et al.*<sup>(62)</sup> reported that vitamin E supplementation of a high-fat meal did not reduce serum TG concentration, although they observed protective effects of vitamin E on endothelial function when measuring brachial artery vasodilation during the postprandial period (changed from 13.3% to 6.6% ( $p \leq 0.05$ ), 7.1% ( $p \leq 0.05$ ) or 13.2% at 2, 4 or 6 h after eating a high-fat meal). In later studies, Neri *et al.*<sup>(63)</sup> and Hejazi *et al.*<sup>(64)</sup> reported that serum TG profile at postprandial state was not significantly modified after vitamin E supplementation; even though Neri *et al.*<sup>(63)</sup> supplementation also contained vitamin C. However, Hejazi *et al.*<sup>(64)</sup> observed a decrease in malondialdehyde levels (a lipid peroxidation marker) in the postprandial

state (2 h after food intake) in comparison with the placebo group. Neri *et al.*<sup>(63)</sup> also reported that, even though no effect on lipid profile was found, vitamin E treatment in healthy subjects and subjects with impaired glucose tolerance induced a significant postprandial improvement in redox balance parameters, serum CRP and VCAM-1 levels. No other study focusing on the effect of single FSM is available.

Overall, published data suggest that the presence of FSM in foods tends to decrease postprandial hypertriglyceridaemia and/or inflammation. However, available studies are still limited and therefore should be considered carefully. More research is needed to fully understand the mechanisms underlying FSM effects in this context.

### Novel biomarkers to determine the effect of liposoluble vitamins on postprandial hypertriglyceridaemia and inflammation

Postprandial hypertriglyceridaemia and inflammation can be assessed by measuring different biomarkers, the most popular ones being TG and cholesterol levels, oxidised LDL, CRP and cytokines, as shown by the previous studies cited in this literature review. However, it is important to identify and study the potential of novel biomarkers, as the above-mentioned traditional biomarkers have shown limitations in identifying inflammation at early stages<sup>(95,96)</sup>. In this part of the review, we focus on the potential of miRNAs and circulating microvesicles as emerging biomarkers for postprandial hypertriglyceridaemia and inflammation.

#### miRNAs

miRNAs are a class of gene expression regulators<sup>(97)</sup> that can potentially be interesting biomarkers to evaluate postprandial hypertriglyceridaemia after a high-fat meal. Indeed, monocytes can interact with postprandial TRL before they migrate to the endothelium<sup>(27,98)</sup>, affecting the transcription of genes involved in lipid homeostasis and inflammation. Measurement of miRNAs can be used for early detection of asymptomatic and symptomatic diseases<sup>(99,100)</sup>, including cardiovascular ones. Certain miRNAs likely modulate cholesterol efflux and reverse cholesterol transport in mammals, as reviewed by Dávalos and Fernández-Hernando<sup>(101)</sup>. In a study in rainbow trout, Zhu *et al.*<sup>(102)</sup> evaluated the different expression of miRNAs known to be involved in cholesterol metabolism when feeding the animals with either a vegetable- or marine-based diet, to address whether miRNAs can be used as biomarkers to determine postprandial hypertriglyceridaemia. These authors reported that a plant-based diet significantly reduced the expression of miR-223, probably a consequence of the absence of dietary cholesterol, in agreement with data obtained in mice<sup>(103)</sup> or in humans<sup>(104)</sup>. However, authors also observed discrepancies for other miRNAs, suggesting that there is a limitation regarding the extrapolation of results between different species<sup>(102)</sup>.

The potential use of miRNAs as a biomarker to determine hypertriglyceridaemia/inflammation has been suggested by several studies<sup>(7,105)</sup>, with different focuses on how to use





miRNAs as biomarkers. miRNAs can potentially be used to evaluate differences between healthy and metabolically disturbed/intervened individuals at a fasting state (lipaemia)<sup>(105,106)</sup> or to evaluate the differences in the same individuals but at a different state (fasting versus postprandial state)<sup>(7,9,107,108)</sup>. Table 3 summarises the main results of these studies. The circulating miRNA profile of adults with obesity performed by Ortega *et al.*<sup>(106)</sup> suggested that the miRNA profile in plasma was different when comparing obese with non-obese subjects at fasting state. According to these results, patients with morbid obesity showed a significant increase in the levels of the miRNAs miR-140-5p, miR-142-3p and miR-222 and a significant decrease in the levels of miR-532-5p, miR-125b, miR-130b, miR-221, miR-15a, miR-423-5p and miR-520c-3p, compared with healthy individuals at fasting state. In a later study by the same research group<sup>(105)</sup>, a comparison of miRNA levels of sedentary individuals before and after 8 weeks of a normocaloric diet enriched with 30 g of nuts was performed. As in their previous study, authors observed differences between miRNA profiles before and after the diet intervention. Interestingly, they reported a decrease in mi-R221, which is somehow contradictory with the results of their previous study (mi-R221 concentration being lower in obese than in healthy individuals), which highlights the different regulation of this miRNA in plasma in healthy versus obese/metabolically compromised subjects.

Lopez *et al.*<sup>(7)</sup> also evaluated differential miRNA expression between fasting and postprandial states (2 h after food consumption) in peripheral blood mononuclear cells (PBMCs) of healthy humans. Compared with miRNA expression signature at fast (and when following the inclusion criteria of >1.2-fold under- or overexpression and statistical difference ( $p < 0.05$ )), the authors reported nine down-regulated and nine up-regulated miRNAs in the postprandial state (Table 3). miRNAs hsa-miR-223-3p and hsa-miR-223-5p – the above-mentioned miRNAs involved in cholesterol metabolism in different animal models<sup>(102–104)</sup> – were also detected in this study (see Table S1 of Lopez *et al.*<sup>(7)</sup>) but did not meet the criteria to be selected as overexpressed miRNAs. In a later study, Mantilla-Escalante *et al.*<sup>(108)</sup> evaluated the whole mouse miRNome and tried to establish a relationship between the expression of mouse and human miRNAs in the postprandial state. Not all the selected miRNAs from the mouse model (Table 3) showed the same trend in human subjects, but some of these miRNAs (hsa-miR 206, hsa-miR 409-3p and hsa-miR 27b-5p) were up-regulated both in mice and in humans. Interestingly, Lopez *et al.*<sup>(7)</sup> also reported an increase of hsa-miR 206 and hsa-miR 27b-5p in the postprandial state, although the increase was not sufficient to meet their inclusion criteria. Contrary to the results of Mantilla-Escalante *et al.*<sup>(108)</sup>, Lopez *et al.*<sup>(7)</sup> found a lower expression of miRNAs hsa-miR 409-3p in the postprandial state. Regarding the other miRNAs selected by Mantilla-Escalante *et al.*<sup>(108)</sup>, Lopez *et al.*<sup>(7)</sup> reported lower levels of hsa-miR-10a-3p and hsa-miR-340-3p, and higher levels of hsa-miR-543 and hsa-miR-125a-3p when comparing fasting with postprandial state, although, again, the difference remained insufficient to meet their inclusion criteria. More recently, Quintanilha *et al.*<sup>(9)</sup> studied the effect of high-fat high-saturated meal ingestion on plasma miRNA expression during the postprandial period in healthy women (Table 3).

When comparing their results with the results of Lopez *et al.*<sup>(7)</sup>, we observed a shared trend between results (only hsa-miR 200c-3p and hsa-miR 92b-3p showed different tendencies), although in the study of Lopez *et al.* (2018) none of the miRNAs identified by Quintanilha *et al.*<sup>(9)</sup> meet the inclusion criteria, which could be influenced by the sex difference between studies. Finally, Daimiel *et al.*<sup>(107)</sup> evaluated the effect of olive oil consumption on miRNAs during postprandial state, focusing on fifty-three cardiovascular-related miRNAs. They found that, regardless the polyphenol level in the olive oil, hsa-let-7e-5p was down-regulated in the postprandial period (Table 3), in agreement with the trend presented by Lopez *et al.*<sup>(7)</sup>. Conversely, observations for miR-328a-3p were contradictory, as it was decreased in one study<sup>(107)</sup> and increased in another<sup>(7)</sup>. Moreover, Lopez *et al.*<sup>(7)</sup> observed almost no differences between fasting and postprandial state for miR-20a-5p.

These differences between studies highlight the need for more and larger human *in vivo* studies to be able to define a reliable range of miRNA biomarkers suitable to assess human postprandial hypertriglyceridaemia. One of the limitations of the available studies is that they tend to focus (or only show the results) on certain miRNAs instead of reporting the whole miRNA human profile, which restricts the comparison with the results of other studies, unless compared studies evaluate the same miRNAs. Only Lopez *et al.*<sup>(7)</sup> reported all miRNAs. Since the expression pattern of miRNAs regulates gene expression and, in some cases, can be associated with different human pathologies, the identification of problematic miRNAs can be of great use for the research community both to try to regulate their expression and to explore their use as relevant biomarkers.

### Circulating microvesicles

Endothelial microvesicles can be released into the blood stream from the endothelium as a response to activation, injury or apoptosis of endothelial cells<sup>(109)</sup>. Associations between high levels of these microvesicles, endothelial dysfunction and obesity have been reported<sup>(110–112)</sup>. Their potential use as biomarkers to determine the effect of fat consumption in the postprandial state, both in healthy and in non-healthy individuals, has been already evaluated by some studies<sup>(8,113)</sup> that reported a significant increase after fat consumption. However, the levels of microvesicles seem to be also affected by blood flow<sup>(114,115)</sup>. This could affect the interpretation of the results, although Araujo *et al.*<sup>(8)</sup> showed that the circulation of endothelial microvesicles increases in a similar way in individuals with postprandial lipaemia and those with postprandial lipaemia plus disturbed blood flow. According to a recent study by Kumar *et al.*<sup>(116)</sup>, it is not only the blood concentration of endothelial microvesicles that changes after fat consumption, but also their fat composition. High-fat diet dramatically changes the lipid profile of intestinal epithelial exosomes from predominantly phosphatidylethanolamine to phosphatidylcholine, which results in the inhibition of the insulin response and therefore contributes to insulin resistance<sup>(116)</sup>. The use of microvesicles as biomarkers has not been fully validated yet, but the available results support their high potential.

**Table 3.** Relevant human studies regarding the expression of miRNAs related to postprandial hypertriglyceridaemia/inflammation

Experimental design	miRNAs most relevant observations	Reference
Human study. Comparison of miRNAs profile at fasting state of healthy and obese individuals at fasting state. Thirty-two healthy men and six morbidly obese patients with surgery-induced weight loss. The most relevant miRNAs were validated in 80 men and in 22 patients (after surgery-induced weight loss). Effects of diet-induced weight loss in nine obese patients.	Morbidly obese patients showed a: • significant increase of miR-140-5p, miR-142-3p and miR-222 • significant decreased levels of miR-532-5p, miR-125b, miR-130b, miR-221, miR-15a, miR-423-5p and miR-520c-3p.	(106)
Human study. Comparison of miRNAs profile at fasting state of sedentary individuals before and after an intervention diet (8 weeks 30 g nuts-enriched normocaloric diet). Profile of 192 common miRNAs was assessed in 10 healthy women before and after an 8-week trial. The most relevant miRNAs were validated in an extended sample of 30 participants (8 men and 22 women).	miRNAs were modified by treatment; results showed a significant ( $p < 0.05$ ): • decrease in miR-328, miR-330-3p, miR-221 and miR-125a-5p • increase in miR-192, miR-486-5p, miR-19b, miR-106a, miR-769-5p, miR-130b and miR-18a miR-106a variations in plasma correlated with changes in PUFAs, while miR-130b ( $r = 0.58$ , $p = 0.003$ ) and miR-221 ( $r = 0.46$ , $p = 0.03$ ) reflected changes in C-reactive protein.	(105)
Human study. Comparison of miRNAs profile at fasting and postprandial (2 h) states in nine healthy Caucasian non-smoking males, aged 18–23 years.	Down – and up-regulated miRNAs following the criteria of $>1.2$ -fold under-or overexpression and statistical difference ( $p < 0.05$ ) • Down-regulated: miR-613, -629-3p, -24-2-5p, -555, -148a-5p, -621, -875-3p, -513c-5p and -1226 • Up-regulated: miR-653, -19b-1-5p, -363-5p, -885-3p, -339-3p, -938, -148b-5p, -593-5p, -24-2-5p and -200b-5p.	(7)
Mice study. Comparison of miRNAs profile at fasting and postprandial (2 h) states, with human validation in ten healthy subjects (no sex information) of selected miRNAs.	Selected miRNAs down- or up-regulated in mice for human validation: • miR-206-3p, miR-543-3p, miR-466c-5p, miR-27b-5p, miR-409-3p, miR-340-3p, miR-1941-3p, miR-10a-3p, miR-125a-3p and miR-468-3p Human observations: • Significantly up-regulated hsa-miR 206, hsa-miR 409-3p and hsa-miR 27b-5p. • Results of the other miRNAs were inconsistent with mouse model results.	(108)
Human study. Effect of high-fat high-saturated meal ingestion on plasma miRNA expression during the postprandial period (1, 3 and 5 h) in 11 healthy women aged between 20 and 40 years, and with a body mass index between 18.5 and 25 kg/m <sup>2</sup> .	Up- and down-regulated miRNAs that have a differentially significant expression in more than one timepoint: • Up-regulated hsa-miR-200b-3p, hsa-miR-200c-3p, hsa-miR-143-3p, hsa-miR-145-5p, hsa-miR-143-5p and hsa-miR-375 • Down-regulated hsa-miR-1260a, hsa-miR-92b-3p, hsa-miR-136-3p and hsa-miR-205-5p.	(9)
Human study. Effect of virgin olive oil with three different levels of polyphenols (low, medium and high) on plasma miRNAs expression during the postprandial period (1, 2, 4 and 6 h) in 12 healthy subjects (50% men, 50% women).	Fifty-three miRNAs were measured. miRNA expression was affected by polyphenol levels. For all levels, Let-7e-5p was down-regulated. miR-328a-3p and miR-20a-5p were down- and up-regulated, respectively, for low and medium polyphenol levels (without statistical significance for medium level).	(107)

## Future prospects

The role of FSM, food emulsions and food structure in postprandial hypertriglyceridaemia still needs to be better understood. Available studies regarding the impact of liposoluble vitamins on postprandial hypertriglyceridaemia show promising results, although their interpretation can be complex, either because these studies (i) evaluated foods where other components may be playing a role (e.g. polyphenols or macronutrient profile), (ii) were underpowered, (iii) did not assess the effect of food structure or (iv) were constrained to the use of traditional biomarkers (such as interleukins, cholesterol or TG levels). In addition, little attention is given to the influence of digestion on food structure along the gastric tract, as well as lipid digestion and lipid release on postprandial hypertriglyceridaemia, which would certainly help in understanding the mechanism behind the observed *in vivo* postprandial responses. Studies with a global approach addressing both *in vitro* food deconstructing and digestion and *in vivo* biomarkers are thus needed.

From the available literature, it seems clear that dietary approaches that consider food nutrient profile in the postprandial state are needed to properly control postprandial hypertriglyceridaemia. FSM presence in foods appears to have a positive effect in this context. The rise of novel biomarkers such as miRNAs or microvesicles is an opportunity that should also be further explored, as they may bring a better understanding of the metabolic pathways linking foods with hypertriglyceridaemia and inflammation.

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## Authorship

The authors' responsibilities were as follows. A.B.N., E.R.: conceptualisation; A.B.N., E.R.: investigation; A.B.N.: formal analysis, data curation; A.B.N., R.V.: original draft preparation; A.B.N., E.R.: had primary responsibility for final content, reviewing and editing; and all authors: read and approved the final manuscript.

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