Influence of minor components of olive oils on the composition and size of TRLs and on macrophage receptors involved in foam cell formation

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Abstract
Metabolic and epidemiologic studies support the idea that the type of dietary fat is more important than the total amount of fat with respect to the development of atherosclerosis and the risk of cardiovascular heart disease. Dietary fat is carried in CMs (chylomicrons), which can be taken up by macrophages without need of further oxidation, leading to the formation of foam cells and initiating or aggravating the atherogenic process. Evidence from different studies has shown that dietary fat can influence the composition and size of TRLs (triacylglycerol-rich lipoproteins), which might modulate their atherogenicity to a certain extent. In particular, experiments in vitro have shown the anti-atherogenic effects of minor components from olive oil when forming part of TRL, as these particles give minor lipid components the opportunity to interact with the cells implicated in endothelial dysfunction and atherogenesis. However, the exact mechanisms mediating CM uptake by macrophages still remain unclear. Thus further studies are needed to understand how the modifications of TRL composition caused by dietary fats could modulate the expression of macrophage receptors and foam cell formation, or even improve the atherogenic risk of these particles.

Atherosclerosis and dietary fat
Metabolic and epidemiologic studies strongly support that the type of dietary fat is more important than the total amount of fat with respect to the development of atherosclerosis and the risk of cardiovascular heart disease [1]. Consumption of MUFAs (mono-unsaturated fatty acids) and PUFAs (polyunsaturated fatty acids) has been associated with lower risk of atherosclerosis development, when compared with SFAs (saturated fatty acids) [2].

Dietary fat is carried in CMs (chylomicrons), which are formed by the enterocytes during the postprandial period. Numerous studies have demonstrated that these TRLs [TAG (triacylglycerol)-rich lipoproteins], and also those of hepatic origin [VLDL (very-low-density lipoprotein)], can cross the endothelial barrier and enter the arterial wall [3]. In addition, CMs can be taken up by macrophages without need of further oxidation, leading to the formation of foam cells, initiating or aggravating the atherogenic process [4].

Influence of minor components of olive oils on atherosclerosis
Olive oils are composed by a major fraction containing glyceridic compounds, such as TAGs, and a fraction of minor components. Apart from phenolics, which are present only in VOO (virgin olive oil), minor components of olive oils include in their composition tocopherols, sterols and terpenic compounds with reported antioxidant and anti-inflammatory properties [5,6]. Experiments in vitro have shown their anti-atherogenic effects even when forming part of TRLs. Incubation of endothelial cells with TRLs derived from a VOO enriched in its unsaponifiable fraction showed a reduction in the production of prostaglandin E2 and thromboxane B2 compared with normal VOO and high-oleic sunflower oil [7]. Therefore these particles give minor lipid components the opportunity to interact with the cells implicated in endothelial dysfunction and atherogenesis.

Influence of the type of dietary fat on TRL composition
The FA (fatty acid) composition of TRLs partially reflects that of the diet and constitutes an important factor that affects their metabolism and could modulate their atherogenicity. Despite dietary FAs being relatively conserved in TRLs, some authors have described significant differences in the absorption of certain FAs [8]. In fact, Hunter et al. [8] found that after the intake of an experimental meal enriched with oleic acid, there was an increase in the percentage of palmitic and linoleic acid in CMs when compared with the FA composition of the meal. In addition, in a study carried out by our group, we found significant differences between the composition of dietary oils and postprandial TRLs when...
molecular species of TAG were studied [9]. Moreover, a recent publication provides evidence that meal FAs result in significant compositional differences in postprandial TRLs of exogenous dietary origin, which could determine differences in their metabolism, as well as their interaction with other potentially atherogenic lipoproteins [10].

It has been shown that the FA composition of this type of particle influences its uptake and lipid accumulation in macrophages, concluding that dietary SFAs carried in CM remnants may enhance their propensity to induce macrophage foam cell formation and demonstrating a link between TRL composition and their atherogenicity [11].

**Influence of the type of dietary fat on TRL size**

It has been suggested that the entry of lipoproteins into the arterial wall is inversely related to the size of the particles; for this reason, it was thought for many years that TRLs were not atherogenic because they are too large to penetrate the tissue [12]. However, TRL remnants formed after the hydrolytic activity of LPL (lipoprotein lipase) can enter the arterial intima and thus be more atherogenic than their nascent precursors [3]. Dietary fat can also affect the atherogenicity of TRLs through its influence on these two aspects, the size of the newly synthesized particles as well as the ability of LPL to hydrolyze TRL particles according to their FA or TAG composition. On the one hand, dietary MUFAs lead to the formation of a reduced number of higher-size CMs, carrying larger amounts of dietary lipids per particle. However, this observation only occurs after long-term MUFA consumption, but not following single meals in subjects with a different background diet, probably due to the adaptation of the enterocyte to long-term MUFA supply [13]. Therefore this reduction in the number of the remnant lipoprotein particles implicated in atherogenesis may have beneficial effects. On the other hand, the quantity, degree of saturation and chain length of the FAs in TRLs are suggested to affect LPL activity. In particular, it has been shown that CMs enriched in n–6 PUFAs were processed by LPL faster than CMs enriched in SFAs, MUFAs or n–3 PUFAs, which may contribute to their increased rate of removal from circulation [14].

**Effects of TRL composition on the expression of macrophage receptors**

CMRs are able to induce macrophages to form foam cells without prior oxidation of the particles, leading to the formation of lipid-laden macrophages in the artery wall and to the development of the fatty streak, the first visible lesion in atherogenesis. Despite numerous studies demonstrating that CMs are taken up by macrophages, the exact mechanisms mediating their uptake still remain unclear.

The proposed receptors that appear to play a role in CM uptake are the LDL (low-density lipoprotein) receptor, the LDL receptor-related protein, the VLDL receptor and various SR (scavenger receptors) such as SR-A and CD36 [15]. Despite a connection between TRL composition and lipid uptake by macrophages being found, nothing is known about its influence of macrophage receptors. Recent studies carried out by our group have demonstrated that incubation of two types of TRL, differing in their lipid composition, with THP-1 macrophages leads to a different mRNA expression of the SR CD36, SR-A2 and SR-B1 (unpublished work).

Unfortunately, to the best of our knowledge, there are no data available on this topic. Thus further studies are needed to explain how the modifications in TRL composition caused by dietary fats could modulate the expression of macrophage receptors and foam cell formation, or even improve the atherogenic risk of these particles.

**References**


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