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REVIEWS: CURRENT TOPICS

Effects of dietary factors on oxidation of low-density lipoprotein particles

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Abstract

Oxidized low-density lipoproteins (ox-LDLs) appear to play a significant role in atherogenesis. In fact, circulating ox-LDL concentrations have been recognized as a risk factor for cardiovascular disease (CVD). A higher intake of some nutrients and specific food compounds such as monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs) and flavonoids have also been associated with a lower risk of CVD. These dietary factors could be associated to a lower risk of CVD through a reduction of the atherogenicity of LDL particles through limited oxidation. Therefore, the purpose of this article is to review human clinical studies that evaluated effects of dietary antioxidant vitamins, fatty acids (MUFA, PUFA) and specific flavonoid-rich foods on LDL particle oxidation and describe potential mechanisms by which dietary factors may prevent oxidation of LDL particles. Antioxidant vitamin supplements such as α-tocopherol and ascorbic acid as well as β-carotene and fish-oil supplements have not been clearly demonstrated to prevent oxidation of LDL particles. Moreover, inconsistent documented effects of flavonoid-rich food such as olive oil, tea, red wine and soy on LDL particle oxidizability may be explained by difference in variety and quantity of flavonoid compounds used among studies. However, a healthy food pattern such as the Mediterranean diet, which includes a combination of antioxidant compounds and flavonoid-rich foods, appears effective to decrease LDL particle oxidizability, which may give some insight of the cardiovascular benefits associated with the Mediterranean diet.

Keywords: Oxidized low-density lipoprotein; Mediterranean diet; ω-3 Fatty acids; Flavonoids; Ascorbic acid; α-Tocopherol

1. Introduction

Several risk factors for cardiovascular disease (CVD) have been identified. Low-density lipoprotein cholesterol (LDL-C) has long been recognized as the only target to treat for the primary and secondary prevention of CVD [1]. Recently, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III has included as new targets for prevention CVD risk factors triglyceride (TG) concentrations, high-density lipoprotein cholesterol (HDL-C) concentrations and the presence of the metabolic syndrome [2]. Moreover, several new emergent risk factors have been discovered. The presence of small dense low-density lipoprotein (LDL) particles [3] as well as higher C-reactive protein concentrations [4] has been associated to a higher CVD risk. High circulating oxidized low-density lipoprotein (ox-LDL) concentrations have also been linked to an increased CVD risk [5–13].

Concomitantly, effects of some dietary factors on CVD risk factors have been investigated. For example, monounsaturated fatty acids (MUFAs) as well as polyunsaturated fatty acids (PUFAs) have been identified as protective against CVD [14–16]. Moreover, a higher consumption of fruits and vegetables has been associated to a reduced CVD risk [17–19]. Recently, a higher flavonoid intake has also been associated with a lower CVD risk [20,21]. Therefore, considering that circulating ox-LDL concentrations is an emergent risk factor for CVD and that some nutrients and or specific food have been associated to a reduced CVD risk, in the following sections, we will review human clinical studies that evaluated effects of dietary antioxidant vitamins, fatty acids (MUFA, PUFA) and specific flavonoid-rich foods on LDL particles oxidizability. Moreover, we will focus on mechanisms which may explain the beneficial properties of these dietary components on LDL particle oxidation parameters.

2. Role of ox-LDL particles in atherogenesis

Oxidized LDL particles are present in atherosclerotic lesions [5,22] and have been suggested to play a significant

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role in atherogenesis [23]. An elevated plasma LDL concentration leads to an increased rate of entry of LDL particles inside the artery wall [24]. While LDL particles are protected from oxidation in plasma by antioxidant compounds, LDL particles trapped within artery wall are prone to oxidative damage [24]. Molecules such as peroxyl and alkoxyl radicals, nitric oxide and transition-metal ions (iron, copper) contain one or more unpaired electrons which react with other radical or nonradical molecules resulting in a new radical molecule. If lipids get damaged by free radicals, it sets up a chain reaction leading to lipid peroxidation [25]. Before being completely oxidized, LDL particles have to undergo some modifications. At first, native LDL particles contain one intact polypeptide [apolipoprotein B-100 (apoB-100)], no lipid peroxides or aldehydes, and are enriched in PUFA and antioxidants [26]. Minimally modified oxidized low-density lipoprotein (MM-LDL) particles are characterized by oxidation of phospholipids on the surface of LDL particles [26]. At this stage, the apoB moiety of LDL is intact but the particle has lost PUFA and antioxidant compounds. Since the structure of the apoB molecule is unchanged, LDL particles are not yet recognized by scavenger receptors of macrophages, although they are still recognized by LDL receptors [27]. Minimally modified ox-LDL particles can induce the expression of monocyte chemotactic protein-1 (MCP-1) and macrophage colony-stimulating factor (M-CSF) by endothelial cells which, respectively, initiate monocyte recruitment to artery wall [28] and promote differentiation of monocytes into macrophages [29]. Further oxidation of the MM-LDL particle leads to modification of apoB as products generated from the catabolism of lipid peroxides, such as aldehydes, interact with lysine residues of apoB-100, rendering LDL particles more negatively charged, which result in decreased affinity for LDL receptors and an increased affinity for scavenger receptors [30]. These fully ox-LDL particles activate endothelial cells which respond by expression of adhesion molecules such as the vascular cell adhesion molecule-1 and intercellular adhesion molecule 1 at their surface [31,32], which, in addition to MCP-1, will promote adhesion and entry of monocytes into artery wall. These monocytes will later differentiate into macrophages through action of the M-CSF. Fully ox-LDL particles are recognized by scavenger receptors of macrophages and are internalized. However, contrary to the LDL receptor, which is under feedback inhibition, scavenger receptors of macrophages are not down-regulated with the increasing cholesterol content of macrophages. Consequently, macrophages keep taking up ox-LDL particles and accumulate an important amount of intracellular lipids in artery wall [24], which will induce the release of proinflammatory cytokines by macrophages, which further promote recruitment of monocytes and accumulation of lipid-laden macrophages or foam cells, which are the most predominant cell type in the earliest atherosclerotic lesions called fatty streaks [24]. Thus, a vicious circle of oxidation, modification of lipoproteins and further inflammation can be maintained in the artery by the presence of these ox-LDL. Circulating ox-LDL concentrations have been related to intima media thickness and plaque occurrence in the carotid and femoral arteries in men [33,34] as well as with the progress of atherosclerosis in carotid arteries [35].

3. Oxidized LDL as a marker of CVD risk

Several case-control studies have reported high plasma ox-LDL concentrations in patients with a coronary heart disease (CHD) or with an elevated risk of CHD compared to healthy individuals [5–13]. Toshima et al. [9] have demonstrated that plasma ox-LDL concentration was a more specific and more sensitive marker of CHD risk than total cholesterol (TC), TG, apoB and HDL-C concentrations in patients with established CHD. A study from Suzuki et al. [10] also reported that circulating ox-LDL concentrations were a better marker of coronary artery disease in high-risk patients than TC, TG, HDL-C, LDL-C, lipoprotein (a) concentrations and TC:HDL ratio. More recently, Meisinger et al. [6] made concordant observations and identified circulating ox-LDL concentrations as a strong predictor for acute CHD in middle-aged men. Furthermore, the addition of plasma ox-LDL concentrations to establish risk factors may improve cardiovascular risk protection. For instance, plasma ox-LDL concentrations have been proposed to give additive information to Global Risk Assessment Scoring [7], which is based on age, total and HDL-C concentrations, systolic blood pressure, type 2 diabetes and smoking for primary prevention of CHD [36].

4. How to measure ox-LDL

Different methods have been developed to assess LDL particle oxidation. The most widely used technique to evaluate the susceptibility of LDL particles to oxidation is an in vitro method consisting of measuring the lag time for isolated LDL particles to resist to copper (Cu^{2+})-induced oxidation [37]. This technique allows the determination of different parameters of oxidation, such as lag time, propagation rate and maximum rate of oxidation. Lag time is defined as the time between the addition of copper or other oxidants to isolated LDL and the time when the oxidation begins. In this sense, the lag time is a measure of resistance of LDL particles to oxidation, which reflects the antioxidant capacity of LDL particles. As antioxidants present on the surface of LDL particles must be consumed for the particle to undergo oxidation, a longer lag time reflects a higher resistance of LDL particles to oxidation. Propagation rate and maximum rate of oxidation can also be determined through this technique and higher values for both of these parameters indicate a higher oxidizability of LDL particles [38,39]. Another method that is used to assess the susceptibility of LDL is to measure copper-induced

formation of conjugated dienes. However, although widely used, the relevance of the in vitro LDL oxidation assays is under debate due to the unphysiologically high Cu^{2+} concentrations that are used, and it has been suggested that oxidation of LDL particles determined by these methods may not reflect oxidation in vivo because most factors relevant to oxidation of LDL particles in vivo are lacking. Therefore, other methods have been developed in order to evaluate in vivo oxidation of LDL particles.

Although possible to some extent, blood is not a site likely for LDL particle oxidation to occur since it is naturally rich in antioxidants [24]. However, even if oxidation of LDL particles occurs within artery wall, ox-LDL particles are found and can be measured in the plasma [40]. The explanation for this observation has been suggested to be associated to the fact that ox-LDL can accumulate within small atherosclerotic plaques. Rupture of these plaques can therefore lead to release of ox-LDL accumulated within these lesions [41]. Accordingly, high plasma and plaque levels of ox-LDL have been found to be correlated to the vulnerability of atherosclerotic lesions to rupture [22]. In addition, the amount of ox-LDL in coronary plaques correlates with plasma levels of ox-LDL [42]. Different immunochemical methods have been developed to determine circulating ox-LDL concentration in human plasma samples using anti-ox-LDL monoclonal antibodies. The two major anti-ox-LDL monoclonal antibodies that are currently used are the FOH1a/DLH3 [40] and 4E6 [43]. The FOH1a/DLH3 recognizes oxidized phosphatidylcholines (OxPCs) generated during oxidative modification of LDL and is used in combination with an anti-apoB antibody in order to identify apoB-containing particles modified with OxPC [41]. On the other hand, the monoclonal antibody 4E6 is directed against a conformational epitope in the apoB-100 moiety of LDL that is generated as a consequence of substitution of lysine residues of apoB-100 with aldehydes [7]. This antibody developed by Holvoet et al. [43] detects ox-LDL but has also been reported to slightly react with malondialdehyde-modified LDL, which is a lipid peroxidation product. Circulating ox-LDL concentrations assessed with these two antibodies have been associated with cardiovascular risk [5–13]. The present article will review studies that have assessed oxidizability of LDL particles with a peculiar interest to dietary factors thought to affect this susceptibility. To facilitate comprehension, we will refer to *susceptibility of LDL particles to oxidation* for studies that have used in vitro methods and to *circulating ox-LDL concentrations* for those using in vivo methods.

5. Diet and LDL particle oxidizability

Consumption of specific foods and nutrients is likely to influence the LDL particle oxidation process. Several foods have been suggested to have a bioactive role because of their antioxidant properties. However, some nutrients without specific antioxidant activities may also protect LDL particles against oxidation. In this regard, many studies have investigated the dietary effects of antioxidant vitamin supplementation, as well as fatty acids (MUFA, PUFA) and, more recently, flavonoid consumption on LDL particle oxidation parameters. These studies are presented and discussed in the following sections.

5.1. Antioxidant vitamin supplements

Supplementation with antioxidant vitamins such as α-tocopherol, ascorbic acid and β-carotene used alone or in combination had long been considered to be cardioprotective [44]. However, controlled clinical trials using antioxidant vitamin supplements to prevent CVD have yielded conflicting results. While some secondary prevention interventions have shown that α-tocopherol supplementation alone [45–47] or in combination with ascorbic acid [48,49] can reduce CVD risk, other studies have found no effect of α-tocopherol supplementation in either primary and secondary prevention [50–55]. Recently, Miller et al. [56] performed a meta-analysis on the effects of α-tocopherol supplementation on risk of total mortality using data from randomized clinical trials and found that a supplementation of α-tocopherol higher than 400 IU/day may actually increase all-cause mortality. Despite this inconsistence in results, many studies have evaluated the impact of supplementation with antioxidant vitamins on LDL particle oxidizability.

5.1.1. α-Tocopherol supplements

α-Tocopherol is the active form of vitamin E and is contained principally in vegetable oils such as soybean, corn, cottonseed and sunflower oils [57]. Supplementation with α-tocopherol has been found to have beneficial effects on the susceptibility of LDL particles to oxidation in healthy [58–62], diabetic [61–65] and dyslipidemic subjects [66–68] as well as in smokers [69] (Table 1). Moreover, α-tocopherol supplementation in combination with other antioxidant vitamins such as ascorbic acid and β-carotene has been reported effective to decrease susceptibility of LDL particles to oxidation [70–74]. Some studies have even established the minimum dose of α-tocopherol needed to decrease the susceptibility of LDL particles to oxidation at 400 IU/day [59,60].

α-Tocopherol is lipid soluble and has been found to be the most abundant antioxidant in LDL particles. Some mechanisms have been proposed to explain the capacity of α-tocopherol to inhibit oxidation of LDL particles in vitro. For instance, α-tocopherol can inhibit radical chain propagation by scavenging highly reactive lipid peroxyl and alkoxyl radicals, which promote the propagation of the chain reaction of lipid peroxidation [75–77]. Moreover, α-tocopherol may decrease the assembly of active NADPH-oxidase responsible for reactive oxygen species production [75], which are involved in lipid peroxidation of LDL particles. However, under certain circumstances,

Table 1
Studies investigating the effects of α-tocopherol supplementation on LDL oxidation parameters

Authors (date)	Subjects' characteristics	Study design/duration	Dosage (per day)	Outcomes
Reaven et al. (1993) [66]	Mildly hyperlipidemic subjects ($n=16$)	Randomized Free-living Supplement provided 8 weeks	1600 mg, control	↑ Lag phase with AT after 4 and 8 weeks compared to control = Maximum rate of propagation
Jialal et al. (1995) [60]	Healthy subjects ($n=48$)	Randomized Free-living Supplements provided 8 weeks	60, 200, 400, 800 or 1200 IU, placebo (soybean oil)	↑ Lag phase with AT (400, 800 and 1200 IU/day) compared to baseline ↓ Oxidation rate (CD) with AT (800 and 1200 IU/day) compared to baseline
Princen et al. (1995) [59]	Healthy subjects ($n=20$)	Parallel Free-living Supplements provided 2 weeks	25, 50, 100, 200, 400 or 800 IU	↑ Lag phase with AT (25, 100, 200, 400 and 800 IU/day) compared to baseline ↓ Propagation rate with AT (400 and 800 UI/day) compared to previous dose
Reaven et al. (1995) [64]	T2D males ($n=21$)	Randomized Free-living Supplements provided 10 weeks	1600 IU or placebo	↑ Lag phase with AT compared to previous dose
Suzukawa et al. (1995) [58]	Healthy subjects ($n=8$)	Free-living Supplements provided 4 weeks	150 mg (1 week) and 300 mg (3 weeks)	↑ Lag phase with AT compared to baseline ↓ Propagation rate compared to baseline
Fuller et al. (1996) [65]	Diabetic subjects ($n=28$)	Randomized Free-living Supplements provided 8 weeks	1200 IU or placebo	↑ Lag phase with AT compared to baseline and to placebo ↓ Oxidation rate (CD) with AT compared to baseline
Mol et al. (1997) [61]	T2D subjects ($n=11$) Healthy subjects ($n=14$) Smokers ($n=12$)	Free-living Supplements provided 4 weeks	600 IU	↑ Lag phase in three groups compared to baseline ↓ Maximal rate in healthy and T2D subjects compared to baseline
Wen et al. (1999) [67]	Hyperlipidemic subjects ($n=37$)	Free-living Supplements provided 6 weeks	100, 200, 400, 800 and 1600 IU, placebo	↑ Lag phase with AT (100, 200, 400, 800 and 1600 IU/day) compared to baseline
Devaraj and Jialal (2000) [62]	T2D+CCV subjects ($n=25$) T2D subjects ($n=25$) Healthy subjects ($n=25$)	Free-living Supplements provided 3 months	1200 IU	↑ Lag phase in three groups compared to baseline
Upritchard et al. (2000) [63]	T2D ($n=57$)	Randomized Placebo-controlled 4 weeks	Placebo or 500 ml tomato juice or 800 IU AT or 500 mg ascorbic acid	↑ Lag phase with AT and tomato juice compared to baseline
Van Tits et al. (2001) [69]	Male smokers ($n=128$)	Randomized Free-living Supplements provided 2 years	400 IU or placebo	↑ Lag phase with AT compared to baseline
Hodis et al. (2002) [68]	Hypercholesterolemic subjects ($n=353$)	Randomized Free-living Supplements provided 3 years	400 IU, placebo	↑ Lag phase with AT compared to placebo
Carpenter et al. (2003) [148]	Carotid endarterectomy subjects ($n=104$)	Randomized Free-living Supplements provided 3 months	500 IU, placebo	↑ Lag phase with AT compared to placebo

AT, α-tocopherol; CD, conjugated diene; T2D, type 2 diabetes.

α-tocopherol may also act as a pro-oxidant molecule when it reacts with lipid radicals and form the α-tocopheroxyl radical [76], which promotes lipid peroxidation.

α-Tocopherol supplementation has been found to decrease the susceptibility of LDL particles to oxidation, which suggests that α-tocopherol could prevent atherosclerotic lesions through the decrease of LDL oxidation. However, as discussed earlier, results from α-tocopherol supplementation trials and epidemiological studies and CVD risk are inconsistent [45–55]. Hodis et al. [68] have found that a 3-year supplementation with α-tocopherol decreased the susceptibility of LDL particles to oxidation but failed to reduce the progression of common carotid artery intima media thickness. Therefore, the role of

α-tocopherol in atherogenesis and CVD is not well understood and remains to be elucidated. Many hypotheses may explain such conflicting observations. First, in vitro methods measuring susceptibility of LDL particles to oxidation may have limitations as presented earlier. Because in vitro studies remove LDL particles from their natural environment, the biological relevance of in vitro LDL particle oxidation remains uncertain, as the natural milieu in which LDL particles are prone to oxidation is difficult to replicate in laboratory, so methods used to measure susceptibility of LDL particles to oxidation may not represent the natural oxidation conditions in vivo. Moreover, only few studies have investigated the effects of α-tocopherol supplementation on circulating ox-LDL concentrations, which has been shown to reflect in vivo oxidation and which has been identified as a marker for CVD [5–13]. In fact, no change in ox-LDL concentrations was observed with α-tocopherol supplementation alone or in combination with other antioxidant vitamins [78,79]. In light of these results, it seems that the favorable effects of α-tocopherol on in vivo LDL oxidizability remain to be documented more thoroughly.

5.1.2. Ascorbic acid supplements

Ascorbic acid (vitamin C) is found principally in fruits and vegetables such as oranges, grapefruits, red peppers, broccolis and cauliflowers [57]. The effects of ascorbic acid supplementation on LDL particle oxidation seem controversial. While some studies found that ascorbic acid supplementation was associated with a reduction of the susceptibility of LDL particles to oxidation [80,81], another study failed to find an effect of ascorbic acid supplementation (at least 500 mg/day) [63]. Moreover, one study failed to find a significant effect of ascorbic acid supplementation on circulating LDL concentrations [82]. Even if ascorbic acid is water soluble and is not incorporated in LDL particles, it has been proposed that this vitamin may prevent LDL particle oxidation by scavenging free radicals and other reactive species in aqueous milieu [76]. Ascorbate may also inhibit the pro-oxidant activity of α-tocopherol by reducing α-tocopheroxyl radical to α-tocopherol and thus regenerating its antioxidant activity [76]. However, it has been found that ascorbic acid decreased oxidation of LDL particles at the early phase of oxidation, whereas it increased at the late phase of oxidation [83]. Therefore, ascorbic acid may react as an antioxidant as well as an oxidant according to the phase of LDL particle oxidation and this might explain controversial results regarding the effects of ascorbic acid supplements on LDL oxidation reported in humans.

5.1.3. β-Carotene supplements

β-carotene is found in considerable amounts in vegetables such as carrots, sweet potatoes and spinach [57]. As with other antioxidant vitamins, β-carotene supplementation has yielded conflicting results with regards to LDL particle oxidizability. In fact, some studies failed to observe any beneficial effect of β-carotene supplementation on susceptibility of LDL particles to oxidation [71,84], whereas Levy et al. [85] found a significant increased in lag time following 3-week β-carotene supplementation (60 mg/day), suggesting a lower susceptibility of LDL particles to oxidation. Therefore, studies are sparse and have not demonstrated a systematically beneficial effect of β-carotene supplementation on oxidation of LDL particles.

5.2. Fatty acids

5.2.1. Monounsaturated fatty acids

MUFAs are found principally in vegetable oils such as olive, rapeseed and peanut oils as well as in poultry, meat, nuts and avocado [57]. Higher MUFA intake has been associated with a more favorable CVD risk profile [14]. Most of the studies comparing the effects of a MUFA-rich diet with PUFA-rich diet on LDL oxidation parameters have found a higher resistance of LDL particles to oxidation after the consumption of MUFA-rich diet [86–93], and few studies have reported discordant results (Table 2). In this regard, Schwab et al. [94] failed to find a difference between MUFA-rich and PUFA-rich diets, while Carmena et al. [95] demonstrated that a MUFA-rich diet led to a higher LDL susceptibility to oxidation compared to a PUFA-rich diet. On the other hand, MUFA-rich diets have been shown to reduce susceptibility of LDL particles to oxidation compared to NCEP step 1 [96], American [97] and high-carbohydrate/low-fat [98,99] diets in healthy subjects. Overall, it therefore appears that MUFA-rich diets are associated with an inhibition of oxidation of LDL particles, although the mechanism underlying this effect needs to be further investigated.

5.2.2. Polyunsaturated fatty acids

ω-6 PUFAs are found in vegetable oils and walnuts, while ω-3 PUFAs are mainly found in fatty fish [57]. High PUFA intake has been shown to be protective against CVD risk [15,16]. However, due to their peculiar structure, that is, the presence of one or more double bonds, unsaturated fatty acids are more susceptible to free radical damage and thus could increase the susceptibility of LDL particles to oxidation. This could provide some explanation on the higher susceptibility of LDL particles to oxidation of a PUFA-rich diet compared to a MUFA-rich diet noted in some studies. However, studies looking at supplementation in ω-3 PUFA-rich oils have not clearly supported this notion (Table 3). While some studies reported no difference in susceptibility of LDL particles to oxidation with fish-oil supplementation [100–103], others found a decrease [104] or an increase in susceptibility of LDL particles to oxidation [105–107]. Difference in design of studies and supplementation dosage may explain in part these inconsistent results. However, several studies investigating the effects on LDL oxidation following fish-oil supplementation

Table 2
Studies comparing the effects of a MUFA diet vs. a PUFA diet and/or a high-carbohydrate/low-fat diet on LDL oxidation parameters

Authors (date)	Subjects' characteristics	Study design/duration	Diets	Outcomes
Reaven et al. (1991) [89]	Healthy subjects ($n=9$)	Randomized Controlled, food provided 5 weeks	MUFA (high-oleate sunflower oil) PUFA (sunflower oil)	↑ Lag time with MUFA diet compared to PUFA diet ↓ Maximum rate of CD formation with MUFA diet compared to PUFA diet
Abbey et al. (1993) [88]	Healthy men ($n=12$)	Randomized, crossover Free-living Supplements provided 3 weeks	MUFA (high-oleate sunflower oil) PUFA (sunflower oil)	= Lag time between diets ↓ Oxidation rate with MUFA diet compared to PUFA diet
Reaven et al. (1994) [90]	Healthy subjects ($n=18$)	Randomized Controlled, food provided 6 weeks	MUFA (high-oleate sunflower oil) PUFA (sunflower oil) Control	↓ Lag time with PUFA diet compared to baseline ↓ Oxidation rate with MUFA diet compared to PUFA and control diets
Carmena et al. (1996) [95]	Healthy men ($n=18$)	Parallel Controlled, food provided 3 weeks	MUFA (olive oil) PUFA (sunflower oil)	↑ TBARS and dienes (AUC) with MUFA diet compared to PUFA diet
Dimitriadis et al. (1996) [149]	T2D subjects ($n=9$) Healthy subjects ($n=7$)	Free-living, oil provided 4 weeks	MUFA (olive oil)	↑ Lag time with MUFA diet compared to baseline in healthy subjects ↓ CD formation with MUFA diet compared to baseline in healthy and T2D subjects
Mata et al. (1997) [91]	Healthy subjects ($n=24$)	Randomized, crossover Controlled, food provided 5 weeks	SFA (palm oil) MUFA (olive oil) ω-6 PUFA (sunflower oil) ω-3 PUFA (fish)	↑ Lag time with MUFA diet compared to SFA, ω-6 PUFA and ω-3 PUFA diets ↑ CD with ω-6 PUFA and ω-3 PUFA diets compared to SFA and MUFA diets
Nestel et al. (1997) [87]	Overweight subjects ($n=15$)	Supplemental food provided 4 weeks	MUFA (Sunola oil) PUFA (flaxseed oil)	↑ Lag time with MUFA diet compared to PUFA diet = Oxidation rate between diets
Schwab et al. (1998) [94]	Subjects with IGT ($n=29$)	Randomized Free-living, oils provided 8 weeks	MUFA (high-oleic sunflower oil) PUFA (sunflower oil)	= Lag time with MUFA compared to PUFA
Castro et al. (2000) [96]	Healthy men ($n=22$)	Randomized, crossover Controlled, food provided 4 weeks	MUFA (olive oil) MUFA (high-MUFA sunflower oil) NCEP-1	↑ Lag time with sunflower oil diet compared to olive oil and NCEP-1 diets = CD among diets
Ashton et al. (2001) [98]	Healthy subjects ($n=28$)	Randomized, crossover Free-living, oils provided 1 month	MUFA (high-MUFA sunflower oil) HCLF	↑ Lag time with MUFA diet compared to HCLF diet ↓ Oxidation rate with MUFA diet compared to HCLF diet
Hargrove et al. (2001) [97]	Healthy subjects ($n=26$)	Randomized, crossover Controlled, food provided 3.5 weeks	AA NCEP-2 MUFA (peanuts) MUFA (peanut oil) MUFA (olive oil)	↑ Lag time with NCEP-2, olive oil and peanut diets compared to AA diet ↓ Rate of oxidation with olive oil compared to AA, peanut and peanut oil diets
Kratz et al. (2002) [92]	Healthy subjects ($n=58$)	Parallel Controlled, Food provided 4 weeks	MUFA (olive oil) ω-6 PUFA (sunflower oil) ω-3 PUFA (rapeseed oil)	↑ Lag time with MUFA compared to PUFA diets ↑ Lag time with ω-3 PUFA diet compared to ω-6 PUFA diet ↑ Rate of propagation with ω-6 PUFA diet compared to MUFA and ω-3 PUFA diets ↓ Rate of propagation with MUFA compared to PUFA diets

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Table 2 (*continued*)

Authors (date)	Subjects' characteristics	Study design/duration	Diets	Outcomes
Nielsen et al. (2002) [93]	Healthy men ($n=18$)	Randomized, crossover Controlled, food provided 3 weeks	MUFA (olive oil) ω-6 PUFA (sunflower oil) ω-3 PUFA (rapeseed oil)	= Lag time with MUFA diet compared to PUFA diets ↓ Propagation rate with MUFA and ω-3 PUFA diets compared to ω-6 PUFA diet
Puiggros et al. (2002) [150]	Mildly hypercholesterolemic subjects ($n=14$)	Parallel 6 weeks	MUFA (olive oil) MUFA+ω-3 PUFA (olive+fish oils)	= Lag time with MUFA diet compared to MUFA+ω-3 PUFA diet = CD with MUFA diet compared to MUFA+ω-3 PUFA diet
Ahuja et al. (2003) [99]	Healthy men ($n=13$) Healthy women ($n=18$)	Randomized, crossover Controlled Food provided, 14-16 days	MUFA (high-MUFA sunflower oil) HCLF	↑ Lag time with MUFA diet compared to HCLF diet in men and women = Maximum CD formation and oxidation rate in men and women
Rodriguez-Villar et al. (2004) [151]	T2D subjects ($n=22$)	Randomized, crossover Free-living, food provided 6 weeks	MUFA (olive oil) HCLF	= Lag time with MUFA diet compared to HCLF diet = Oxidation rate with MUFA diet compared to CHO diet
Aguilera et al. (2004) [86]	PVD men ($n=20$)	Randomized Free-living Supplements provided 4 months	MUFA (olive oil) PUFA (sunflower oil)	↑ TBARS with PUFA diet compared to MUFA diet

AUC, area under the curve; CHO, high-carbohydrate diet; HCLF, high-carbohydrate/low-fat diet; IGT, impaired glucose tolerance; NCEP-1, National Cholesterol Education Program Step 1; NCEP-2, National Cholesterol Education Program Step 2; PVD, peripheral vascular disease; SFA, saturated fatty acid; TBARS, thiobarbituric acid-reactive substance.

containing ω-3 PUFA compared to supplementation with ω-6 PUFA or MUFA oils have reported a reduction in lag time, an indicator of enhanced oxidizability, and a reduction in oxidation rate, an indicator of decreased oxidizability [38,39,58,108,109]. It could be hypothesized that this paradoxal result suggests that lipids present on LDL surface are initially more readily oxidized in LDL particles from individuals consuming fish oil but that the extent of oxidation is lower. Therefore, ω-6 PUFA have been clearly identified to promote LDL oxidation, while effects of ω-3 PUFA fish-oil supplements on LDL oxidation remain difficult to determine. These results underline the fact that all PUFA do not exert the same effects on LDL oxidation depending upon the position of their double bonds.

5.3. Polyphenol compounds

Fruits such as cranberries and blueberries, vegetables (namely onions and beets), olive oil, soy and beverages such as teas and red wine are rich sources of polyphenolic compounds with a high antioxidant activity, for example, flavonoids [110,111]. These flavonoids include several subclasses of molecules such as flavonols, flavones, flavanones and isoflavones [111]. High intakes of flavonol have been associated with lower CVD risk [20,21] in epidemiological studies. However, evaluation of flavonol content of foods is limited. In fact, many factors may affect flavonol content in foods such as seasonal variation, light, climate, degree of ripeness and food preparation and processing [112]. Also, more than 4000 flavonoid compounds have been identified in plants [111]. Therefore, until new and more complete databases become available, it seems difficult to accurately interpret the importance of the flavonoid content of foods.

Flavonoids contain both lipophilic and hydrophilic moieties [113]. Some mechanisms have been proposed to explain the antioxidant action of flavonoids. Firstly, they may directly scavenge some radical species and consequently break chain reaction of lipid peroxidation [110,113]. Secondly, flavonoids may also chelate pro-oxidant metal ions such as iron and copper, which are known to favor free radical formation [110,111,113]. Thirdly, flavonoids may suppress lipid peroxidation by recycling other antioxidants such as α-tocopherol [110]. Finally, flavonoids may also preserve the HDL-associated paraoxonase activity [113], which has been shown to prevent oxidation of LDL particles. Moreover, flavonoids have been found to inhibit cellular enzymes, which are in part responsible of

Table 3
Studies investigating the effects of a ω-3 PUFA diets on LDL oxidation parameters

Reference (date)	Subject characteristics	Study design/duration	Diets	Outcomes
Suzukawa et al. (1995) [58]	Hypertensive subjects ($n=20$)	Randomized, crossover Free-living Supplements provided 6 weeks	ω-3 PUFA (fish oil) ω-6 PUFA (corn oil)	↓ Lag time with fish oil compared to corn oil ↓ Propagation rate with fish oil compared to corn oil
Brude et al. (1997) [100]	Hyperlipidemic male smokers ($n=41$)	Randomized Free-living Supplements provided 6 weeks	ω-3 PUFA (fish oil) Antioxidant supplement ω-3 PUFA (fish oil+antioxidant) Control oil	= Lag time and rate of formation of CD among fish oil, fish oil+antioxidant and control oil diets
Oostenbrug et al. (1997) [104]	Healthy male cyclists ($n=24$)	Free-living Supplements provided 3 weeks	ω-3 PUFA (fish oil) ω-3 PUFA (fish oil+vitamin E) Placebo	= Lag phase among diets ↓ Maximum rate of oxidation with fish oil and fish oil+vitamin E compared to placebo
Sorensen et al. (1998) [39]	Healthy men ($n=47$)	Randomized Free-living Margarine provided 4 weeks	PUFA (fish+sunflower oils) ω-6 PUFA (sunflower oil)	↓ Lag time with fish oil compared to sunflower oil ↓ Maximum rate of oxidation with fish oil compared to sunflower oil
Wander et al. (1998) [108]	Healthy postmenopausal women ($n=41$)		ω-3 PUFA (fish oil)	↓ Lag time with fish oil compared to baseline ↓ Rate of formation of CD with fish oil compared to baseline
Higgins et al. (2001) [101]	Healthy subjects ($n=62$)	Randomized Free-living Supplements provided 16 weeks	ω-3 PUFA (fish oil) MUFA (olive oil)	= Lag phase, maximum CD production, rate of CD production between diets*
Turini et al. (2001) [109]	Healthy subjects ($n=10$)	Randomized Free-living Supplements provided 30 days	ω-3 PUFA (fish oil) MUFA (high-oleic sunflower oil)	↓ Lag time with fish oil compared to baseline ↓ Oxidation rate with fish oil compared to baseline
Leigh-Firbank et al. (2002) [105]	Mildly hypertriacylglyceroleamic men ($n=55$)	Randomized, crossover Free-living Supplements provided 6 weeks	ω-3 PUFA (fish oil) MUFA (olive oil)	↓ Lag time with fish oil compared to placebo (olive oil)
Finnegan et al. (2003) [106]	Moderately hyperlipidemic subjects ($n=150$)	Parallel Free-living Supplements provided 6 months	ω-6 PUFA (sunflower+safflower oils) EPA+DHA (fish oil) ALA (rapeseed+linseed oils)	↓ Lag time with EPA+DHA (1.7g/day) compared to baseline = Lag time with EPA+DHA (0.8g/day) compared to baseline ↓ Lag time with EPA+DHA (1.7g/day) compared to ω-6 PUFA and ALA (9.5g/day)
Pedersen et al. (2003) [38]	T2D patients ($n=44$)	Randomized Free-living Supplements provided 8 weeks	ω-3 PUFA (fish oil) ω-6 PUFA (corn oil)	↓ Lag time with fish oil compared to corn oil ↓ Propagation rate with fish oil compared to corn oil
Piolot et al. (2003) [102]	Healthy subjects ($n=16$)	Free-living Supplements provided 8 weeks	ω-3 PUFA (fish oil)	= Lag time and diene propagation rate compared to baseline
Mesa et al. (2004) [107]	Healthy subjects ($n=42$)	Randomized Free-living Food provided 4 weeks	EPA-rich oil DHA-rich oil MUFA (olive oil)	↓ Lag time with EPA-rich oil compared to placebo ↓ Lag time with DHA-rich oil compared to placebo = Lag time with EPA and DHA compared to baseline = Oxidation rate and maximum dienes with EPA and DHA compared to placebo
Lee et al. (2005) [103]	Healthy postmenopausal women ($n=30$)	Randomized Free-living Supplements provided 5 weeks	ω-3 PUFA (fish oil) PUFA (fish oil+safflower oil) ω-6 PUFA (safflower oil)	= Maximum formation of CDs

ALA, α-linolenic acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
* $P \leq .01$ was used to assess statistical significance.

cell-mediated oxidation of LDL particles such as phospholipase A_2, cyclooxygenase and lipoxygenase, GSH reductase, xanthine oxidase and NADPH-oxidase [114].

Over the last few years, specific flavonoid-rich foods have been investigated for their cardioprotective potential, with a peculiar interest towards LDL particle oxidation. These include different fruits and vegetables, olive oil, tea, red wine and soy.

5.3.1. Fruits and vegetables

Increased fruit and vegetable consumption has been reported to reduce the risk of developing CVD [17–19]. Among the possible explanations for this beneficial effect, fruits and vegetables have been found to decrease susceptibility of LDL particles to oxidation [115,116]. In these studies, nonsmokers experienced a more important decrease in susceptibility of LDL particles to oxidation than smokers [115,116]. Cranberry juice, which is rich in flavonoids, has been recently found effective to decrease circulating ox-LDL concentrations in overweight males [117].

5.3.2. Olive oil

Several studies have investigated effects of olive oil on LDL particle oxidizability with regard to differentiating the importance of the flavonoid vs. MUFA content of olive oil. Such studies have compared the effect of olive oil rich in phenolic compounds vs. olive oil with a lower content in phenolic compounds [118–122]. Overall, high-phenolic olive oil appeared to have beneficial effects on LDL particle oxidizability. Some studies have observed a decrease in susceptibility of LDL particles to oxidation with extra-virgin olive oil [118,120,121], others found an increase with extra-virgin olive oil rich vs. poor in phenolic compounds [123]. Moreover, some studies have found a decrease in ox-LDL concentrations following a consumption of high-phenolic olive oil [119,121,122] compared to low-phenolic compounds. Variety and quantity of phenolic compounds of olive oil may influence results obtained.

5.3.3. Tea

Some studies have investigated effects of tea consumption on LDL oxidation parameters and reported conflicting results according namely to methodological issues. In fact, black and green tea had no effect on susceptibility of LDL particles to oxidation [124–126] with the exception of one study which reported a significantly increased lag time following 4 weeks of tea consumption but failed to report a decreased propagation rate [127]. Recently, Lee et al. [128] have found that consumption of 600 ml/day of green tea decreased significantly circulating ox-LDL concentrations after 2 weeks and 4 weeks compared to baseline in 20 healthy smokers despite no changes in lipid and lipoprotein profile.

5.3.4. Red wine

Red wine has been identified as a high-antioxidant food [110], and red wine flavonoids have been found to increase the serum paraoxanase concentrations, which hydrolyse LDL-associated lipid peroxides, therefore leading to a reduction of LDL oxidation [129]. Several studies have reported a decrease in the susceptibility of LDL particles to oxidation in healthy subjects following the daily consumption of 375 ml/400 ml of red wine for 2 weeks [130–132]. In contrast, de Rijke et al. [133] found no change in susceptibility of LDL particles to oxidation following 4-week consumption of white wine or red wine in 24 healthy individuals. Inconsistence in the results may be related to the variations in polyphenol composition of the red wine used in different studies.

5.3.5. Soy

Soy is rich in isoflavones [110]. Several studies have reported a decrease in susceptibility of LDL particles to oxidation with soy protein consumption [134–137]. Jenkins et al. [135,136] found that soy protein rich in isoflavones led to a decrease in the susceptibility of LDL particles to oxidation in healthy subjects. Similarly, Ashton et al. [137] observed an increase in lag time with 1-month consumption of tofu meals compared to lean meat meals. Moreover, Wiseman et al. [134] reported an increase in the lag time following 17-day consumption of high-isoflavone soy compared to soy without isoflavones. On the other hand, others have reported no effect of high-isoflavone soy on the susceptibility of LDL particles to oxidation [138,139].

5.4. Mediterranean diet

As most nutrients and specific foods reviewed above (antioxidant vitamins, MUFA, and ω-3 PUFA as well as fruits and vegetables, olive oil and red wine) are major constituents of the Mediterranean dietary pattern, the interest for the effects of Mediterranean diet on LDL particle oxidizability has been increasing over the last year. Mediterranean diet has been associated with a reduced risk of CVD [140] as well as with lower recurrence of coronary events [141] and mortality [142]. The Mediterranean diet is characterized by a high consumption of vegetables, fruits, legumes, grains, nuts and seeds, a moderate to high consumption of fish, a low to moderate consumption of dairy products and ethanol (mainly wine) and a low consumption of red meats [143]. In this dietary pattern, olive oil is the principal source of fat [143,144]. Accordingly, the Mediterranean diet is rich in vitamins such as α-tocopherol and ascorbic acid as well as in MUFA, ω-3 PUFA and flavonoids [145].

Panagiotakos et al. [146] have shown that individual who adopted the Mediterranean food pattern have lower circulating ox-LDL concentrations than individual who adopt a Western diet. Recently, we have shown that a 12-week nutritional intervention promoting the Mediterranean food pattern in healthy women lead to a 11% reduction in circulating ox-LDL concentrations [147] and also found that high fruit and vegetable intake could be important in this association. These results suggest that a combination of

dietary antioxidant compounds has beneficial effects on LDL particle oxidizability.

6. Conclusion

Overall, antioxidant vitamin supplements and fish-oil supplements have not been clearly shown to exert a beneficial effect on circulating ox-LDL concentration, which has been identified as a risk factor for CVD. Moreover, inconsistence in the reported effects of flavonoid-rich food such as olive oil, tea, red wine and soy on LDL particle oxidizability may be explained by difference in variety and quantity of flavonoid compounds among studies. Controversy can be partly explained by the fact that, for a given food item, content in antioxidant compounds may vary according to seasonal variation, light, climate, degree of ripeness, food preparation and processing. The effect of these variables on antioxidant content could be studied further. In addition, it would be interesting to investigate the possible interaction and synergic effects of the combination of flavonoid consumption as well as the combination of nutrient and flavonoid intakes. Dose-response studies are also needed to clarify the role of some specific nutrients and foods on the susceptibility of LDL particles to oxidation as well as on circulating LDL concentrations.

The combination of specific foods such as fruits, vegetables, olive oil and fish which contain flavonoids, α-tocopherol, ascorbic acid, β-carotene and ω-3 PUFA are found in the Mediterranean diet and appears to have beneficial effects on LDL particle oxidation parameters. The beneficial effect of the combination of a variety of food on LDL particle oxidizability may be due to some interactions between bioactive compounds and also by specific compounds that have not been yet discovered. The Mediterranean diet has been associated with a lower risk of CHD [140] without affecting LDL-C, HDL-C and TG concentrations [141,146]. The effect of Mediterranean diet on ox-LDL particles may explain, at least in part, its cardioprotective potential. Further intervention trials are needed to investigate this hypothesis.

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