Review

Olive oil and oxidative stress

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Oxidative stress is defined as an imbalance between the oxidant and antioxidant systems of the body, in favor of the oxidants. Oxidative stress produced by free radicals has been linked to the development of several diseases such as cardiovascular, cancer, and neurodegenerative diseases Olive oil is the main source of fat of the Mediterranean diet which has been shown to be effective against oxidative stress associated diseases and also with ageing. Besides its richness in monounsaturated fatty acids, the oleic acid, olive oil contains minor components with antioxidant properties. In this review, we summarize the state of the art, and degree of evidence, of the body of knowledge concerning the protective role of the major and minor components of olive oil on oxidative stress.

Keywords: DNA oxidation / LDL oxidation / Olive oil / Oxidative stress / Phenolic compounds

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1 Introduction

Oxidative stress is defined as an imbalance between the oxidant and antioxidant systems of the body, in favor of the oxidants [1]. The oxidant systems are free radicals, molecules or molecular fragments containing one or more unpaired electron [2]. Radicals derived from oxygen, included in the so called reactive oxygen species because they are produced through partial oxygen reduction, such as the superoxide anion or the hydroxyl radical, represent the most important class of radical species [1, 2]. Reactive oxygen species are produced in the normal aerobic metabolism [3]. Several situations such as infection, inflammation, ultraviolet radiation, and tobacco smoke can increase free radical production. Free radicals can interact with fatty acids, thus forming peroxyl and alkoxyl radicals, and also with nitric oxide, proteins, and transition metals, such as iron and copper, resulting in new radical molecules [3]. Oxidative stress produced by free radicals has been linked to the development of several diseases such as cardiovascular, cancer, and neurodegenerative diseases and also with ageing [4, 5]. Targets for free radicals are lipids, deoxyribonucleic acid (DNA), and proteins [1 – 3]. If a fatty acid is damaged by free radicals it becomes a free radical itself setting up a chain reaction of lipid peroxidation [2, 3]. Oxidation of the lipid part [6], or directly of the apolipoprotein (apo) B [7], of the LDL leads to a change in the lipoprotein conformation by which the LDL is better able to enter into the monocyte/macrophage system of the arterial wall, and develop the atherosclerotic process [5]. The modified apo B has immunogenic properties prompting the generation of auto-antibodies against oxidized LDL [6]. In addition, 3-cloro- and nitro-tyrosine generation, via myeloperoxidase activity, in HDL, converts the lipoprotein in a pro-inflammatory HDL, and reduces its capacity to remove cholesterol from cells [8]. Nucleic acids are also targets of free radicals. Oxidative stress leads to a plethora of mutagenic DNA lesions in purines, pyrimidines, deoxyribose, and DNA single- and double-strand breaks [9, 10]. Accumulation of mutations from oxidative DNA damage is considered to be a crucial step in human carcinogenesis [9, 11].

The biological oxidative effects of free radicals on lipids, DNA, and proteins are controlled by a wide spectrum of enzymatic antioxidants, such as the scavenger enzymes superoxide dismutase and glutathione peroxidase (GSH-Px), and non-enzymatic antioxidants, such as vitamin E and glutathione [2, 3]. Some non-enzymatic antioxidants, such as vitamins C and E, carotenoids, and phenolic compounds, may be key factors in the pathogenesis of oxidative stress related disorders [2 – 4]. They are essential components for the body and should be present in a correct and healthy diet. A healthy dietary pattern, rich in antioxidants is the so-called Mediterranean diet, which refers to traditional diet-

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Abbreviations: apo, apolipoprotein; **CHD,** coronary heart disease; **DNA**, deoxyribonucleic acid; **εAde**, 1, N^6-ethenoadenine; **εdA**, 1, N^6-etheno-2′-deoxyadenosine; **εdC**, 1, N^4-etheno-2′-deoxycytidine; **GSH-Px**, glutathione peroxidase; **8oxodG,** 8-position to 8-oxo-deoxyguanosine; **VOO,** virgin olive oil

ary patterns found in areas of the Mediterranean countries around fifty years ago [12]. Adherence to the Mediterranean diet has been associated with a low overall, cardiovascular, and cancer mortality in several large cohort studies [13, 14], and has been shown to be effective in the secondary prevention of coronary heart disease (CHD) in intervention studies [15].

Olive oil is the primary source of fat in the Mediterranean diet. Olive oil is a functional food which besides having a high level of MUFA, the oleic acid, contains multiple minor components with biological properties. The content of the minor components of an olive oil varies, depending on the cultivar, climate, ripeness of the olives at harvesting, and the processing system employed to produce the types of olive oil currently present on the market: extra-virgin, virgin, olive oil (UE, 1991), or pomace [16]. Virgin olive oils (VOOs) are those obtained from the fruit of the olive tree solely by mechanical or other physical means under conditions that do not lead to alteration in the oil. They have not undergone any treatment other than washing, decantation, centrifugation or filtration. Oils obtained using solvents, adjuvant, having a chemical or biochemical action, re-esterification process, or any mixture with oils of other kinds are excluded from this category [17]. Extra-VOOs are VOOs with a free acidity, expressed as g of oleic acid/100 g of olive oil, less than 0.8 g.VOOs with an acidity greater than or equal to 3.3 (International Olive Oil Council Regulation/ T.15/NC.n3.Rev2.Nov24, 2006) ($\geq$2 in Europe, European Regulation N. 1513/0) are submitted to a refining process in which some components, mainly phenolic compounds, and to a lesser degree squalene, are lost [18]. By mixing virgin and refined olive oil an ordinary olive oil (olive oil, UE 1991) is produced and marketed. After VOO production, the rest of the olive drupe and seed is processed and submitted to a refining process, resulting in pomace olive oil, to which a certain quantity of VOO is added before marketing. The minor components of VOO are classified into two types: the unsaponifiable fraction, defined as the fraction extracted with solvents after the saponification of the oil, and the soluble fraction which includes the phenolic compounds [19 – 21]. In fact, hydrophilic phenols are components of the unsaponifiable fraction, but being present as droplets in micro emulsion in the lipidic matrix they are easily extracted by a simple liquid-liquid procedure with n-hexane and methanol:water 60:40 without a saponification step. In this review, we summarize the state of the art, and degree of evidence, of the body of knowledge concerning the protective role of both major and minor components of olive oil on oxidative stress.

2 Lipid oxidative damage

The oxidative modification of LDL plays a key role in atherosclerosis and CHD development. It is currently thought that oxidized LDL is more damaging to the arterial wall than native LDL [22]. Elevated concentrations of *in vivo* circulating oxidized LDL show a positive relationship with the severity of acute coronary events [23] and are independently associated with carotid intima-media thickness [24]. In several studies, but not in all [25], circulating oxidized LDL plasma concentrations were predictors for CHD both in CHD patients [26] and in the general population [27]. The type of fat ingested is a key factor concerning LDL oxidation because it can modulate the susceptibility of LDL to undergo oxidative modification. PUFA, rich in double bonds, are more prone to form conjugated dienes than MUFA [28]. Linoleic acid accounts for 90% of the PUFA present in LDL and is the major substrate for its oxidation [28]. In a recently published cross-sectional study, neither dietary fat nor PUFA intake was a major factor related with the susceptibility of LDL to undergo oxidative modification [29]. However, the degree of scientific evidence provided by cross-sectional studies is low [30]. Differences between MUFA- and ω-6 PUFA-rich diets on the susceptibility of LDL to oxidation have been reported in various intervention studies, including several randomized, controlled ones which are those capable of providing first level scientific evidence [30]. In most studies, oleate-rich LDL have been shown to be less susceptible to oxidation than linoleate rich LDL [31 – 37]. Some of the studies performed from 1991 to 2004 on this topic are referred to in a recently reported review [38]. Of the 14 studies referred to [38], only in two of them did MUFA – rich diets not promote a higher resistance of LDL to oxidation than PUFA-rich ones. Compared with high carbohydrate/low fat diets, the MUFA ones had a better effect [39, 40], or a comparable one [41], on the susceptibility of the LDL to oxidation. We must point out that in most studies, the measured parameter was the susceptibility of isolated LDL to oxidation, an *in vitro* test, in which the characteristics of diene formation in LDL after oxidation with copper of the lipoprotein are measured [42]. Also, in many of these studies, instead of natural olive oil, prepared liquid-formula or solid diets highly enriched in MUFA were used. In spite of this, the consistency of the results among the studies supports the idea that MUFA-rich diets are more protective for LDL in front of oxidation than ω6- PUFA-rich diets.

Results of the effects of ω3-PUFA-rich diets on LDL oxidability are, however, still controversial [38]. In several randomized intervention studies, but not in all [43, 44], ω3-PUFA from fish oil increased the susceptibility of LDL to oxidation in front of MUFA-rich [45, 46] diets. One study reported differences among omega-3 fatty acids on the susceptibility of LDL to oxidation, with an increase after eicosapentanoate, but not with docosahexanoate-rich oil, when compared with an olive oil rich diet [47]. The differential effect between ω3-PUFA and MUFA-rich diets also merits being examined by using *in vivo* markers of LDL oxidation, and particularly markers which have been shown to be pre-

dictors for CHD development, such as circulating oxidized LDL and F_2-isoprostanes [48, 49].

One factor which influences LDL oxidability is the LDL particle size. In healthy individuals, circulating oxidized LDL was directly associated with risk factors for the metabolic syndrome and inversely associated with the LDL size [50]. Small, dense LDL particles are more prone to oxidation, they enter the arterial wall more readily than larger buoyant LDL particles [51]. The particle size of the LDL lipoprotein is influenced by the dietary fat. Low-fat diets lead to a decrease of the mean LDL size compared to high-fat diets [52]. In a cross-sectional survey, PUFA intake, but not that of MUFA, was negatively associated with the LDL size in diabetic type 2 patients and subjects with impaired glucose metabolism [29]. Data from intervention studies, however, show that changing the quality of dietary fat from saturated to unsaturated fat does not modify, or only slightly reduces, the LDL peak particle diameter, with no significant difference between diets rich in MUFA, ω6-PUFA, and ω3-PUFA [53].The influence of dietary fat on the LDL particle size is modulated by apo genotypes. Olive oil-rich diets increase the LDL particle size more than carbohydrate-rich diets, this effect being influenced by the apo E genotypes [54]. Higher ω6 (but not ω-3) PUFA intake decreased LDL size in Apo A5 – 1131C carriers, suggesting that ω6 PUFA-rich diets are related to a more atherogenic lipid profile in these subjects [55].

3 Olive oil minor compounds and lipid oxidative damage

Olive oil minor components have also been involved in the antioxidant activity of olive oil. Some components of the unsaponifiable fraction, such as squalene, β-sitosterol, or triterpenes, have been shown to display antioxidant activity in experimental models [19, 56, 57]. Further studies are required to test their beneficial effect from olive oil consumption in humans. Among olive oil minor components, phenolic compounds are those most extensively studied, particularly their antioxidant properties. In experimental studies, olive oil phenolic compounds, like other plant-derived polyphenols [58], counteracted the metal-, radical-, and macrophage-mediated oxidation of lipids and LDL [59 – 61]. In animal models, olive oil phenolics retained their antioxidant properties *in vivo* [62] and delayed the progression of atherosclerosis [63]. The administration of high doses of hydroxytyrosol (10 mg/kg/day) to apo E deficient mice, however, enhanced the atherosclerotic lesion development [64]. This fact points out the importance of the matrix and that of the combination of all antioxidants present in natural foods such as in olive oil. Phenolic compounds from olive oil are bioavailable in humans [65], even from doses (25 mL (22 g)/day) [66] lower than those reported as usual in the Mediterranean diet (30 – 50 g/day) [67]. Tyrosol and hydroxytyrosol are the most characteristic olive oil phenolic compounds [21]. Free forms of tyrosol and hydroxytyrosol and their secoiridoid derivatives represent around 30%, and other conjugated forms such as oleuropeine and ligstroside aglycones, represent almost half, of the total phenolic content of a VOO [18]. Tyrosol and hydroxytyrosol have been shown to be dose-dependently absorbed from olive oil, and despite their short half-life in plasma they can accumulate in the body after sustained consumption [65, 68, 69]. Around 98% of them are present in plasma and urine in conjugated forms suggesting an extensive first pass intestinal/hepatic metabolism of the ingested primary forms [69, 70].

Several studies have been performed on the *in vivo* antioxidant effect of olive oil phenolic compounds in humans, both at postprandial state and after sustained olive oil consumption. Postprandial oxidative stress is linked with postprandial lipemia and hyperglicemia [71]. Data comparing the magnitude of postprandial oxidative stress after olive oil ingestion in comparison with other oils or fats are scarce. Recent data in mice reported the ingestion of fish oil, or its major fatty acid docosahexaenoic acid, to induce a greater postprandial oxidative stress than that promoted by olive oil [72]. Bellido *et al.* [73] reported that butter and walnuts, but not olive oil, elicit postprandial activation of nuclear transcription factor κB, a redox-transcription sensitive factor involved in the inflammatory and proliferative response in atherosclerotic areas, in peripheral blood mononuclear cells from healthy men. Several data on the effect of olive oil phenolic compounds on the postprandial oxidative stress have been reported. They are, however, difficult to compare because some studies do not mention whether or not postprandial lipemia and/or hyperglycemia, which could lead to oxidative stress, occur after olive oil ingestion, while in other studies neither hyperlipemia nor hyperglycemia occur at postprandial state after the olive oil ingestion [19]. The ingestion of a 25 mL olive oil dose did not promote postprandial oxidative stress with independence of the phenolic content of the olive oil [74], whereas single doses of 40 mL [75] and 50 mL did [76]. With olive oil doses at which oxidative stress occurs, data from randomized, cross-over, controlled studies in humans showed: (i) an increase in the serum antioxidant capacity after VOO ingestion, but not after ordinary olive oil, in comparison with corn oil, suggesting a role for the phenolic compounds of the VOO [77]; and (ii) the phenolic content of an olive oil modulates the degree of lipid and LDL oxidation, the lipid oxidative damage being lower after high- than after low-phenolic content olive oil [75, 78] (Fig. 1).

Concerning sustained doses of olive oil phenolic consumption, controversial results were also obtained in several randomized, cross-over, controlled studies performed up to year 2004 (66, 68, 79 – 82). A review on this topic has been recently published [19]. It must be pointed out that extensive differences existed among the studies in the experimental

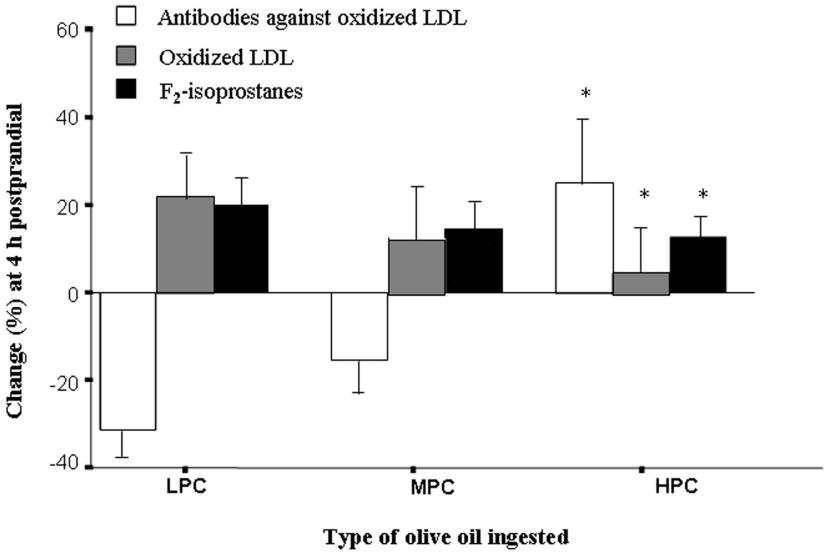

Figure 1. Changes in plasma oxidative stress markers at 4 h after ingestion of 40 mL olive oil with low (LPC), medium (MPC), and high (HPC) phenolic content. * $p < 0.05$ for linear trend. (Adapted from [75]).

design, control of diet, sample population, age of the participants, measurement or not of markers of the compliance of the intervention, and in the sensitivity and specificity of the oxidative stress biomarkers evaluated. On the basis of the studies referred to above, the Consensus Report made by the Expert Panel in the International Conference of Olive Oil and Health held in Jaen, Spain, October 2004 [19, 83] concluded: (i) data regarding the benefits of olive oil phenolic compounds in humans from real-life daily doses of olive oil were still controversial; (ii) the protective effects on lipid oxidation in these trials were better displayed in oxidative stress conditions and in those markers directly associated with LDL oxidation; and (iii) carefully controlled studies in appropriate populations (individuals with high oxidative status), or with a large sample size (in the case of healthy individuals), were required to definitively establish in which conditions phenolics from olive oil can exert their most beneficial effect controlling oxidative stress.

The results of the EUROLIVE study, however, have recently provided evidence of the *in vivo* protective role of phenolic compounds from olive oil on lipid oxidative damage in humans, at real-life olive oil doses [84]. The EUROLIVE (The effect of olive oil consumption on oxidative damage in European populations) study was a large, crossover, multicentre, clinical trial performed in 200 individuals from five European countries. Participants were randomly assigned to receive 25 mL/day of three similar olive oils, but with differences in their phenolic content (from 2.7 mg/kg to 366 mg/kg of olive oil), in intervention periods of 3 weeks preceded by 2 week washout periods. All olive oils increased the HDL-cholesterol and the ratio between the reduced and oxidized forms of glutathione. The antioxidant activity of HDL on LDL lipid peroxidation is well known [8], and reduced glutathione is a major mechanism for cellular protection against oxidative stress [85]. In the EUROLIVE study, consumption of medium- and high-phenolic content olive oil decreased lipid oxidative damage biomarkers such as plasma oxidized LDL, uninduced conjugated dienes, and hydroxy fatty acids, without changes in F_2-isoprostanes. The increase in HDL cholesterol and the decrease in the lipid oxidative damage was linear with the phenolic content of the olive oil consumed. The results of the EUROLIVE study provided first level evidence that olive oil is more than a MUFA fat. Table 1 summarizes the results obtained in the randomized, crossover, controlled studies performed up to date in humans on the *in vivo* antioxidant effects of the sustained consumption of olive oil phenolic compounds.

In the EUROLIVE study [84], in agreement with previous ones [19, 68, 81], systemic markers of lipid oxidation as F_2-isoprostanes, derived from arachidonic acid and with a broad spectra of sources in blood (*i.e.* cell membranes), despite their high sensitivity [86] were not modified by the consumption of either olive oil or its phenolics. Two factors could explain this fact. On one hand, further results of the EUROLIVE study show an increase in the plasma oleic acid content after all type of olive oils ingestion [87]. Thus, a concomitant increase in the LDL fatty acid content could be assumed in agreement with other previous reports [88]. On the other hand, polyphenols bound to human LDL increase in a dose dependent manner with the phenolic content of the olive oil administered [75]. De la Torre *et al.,* have recently reported the binding to human LDL of hydroxytyrosol and tyrosol metabolites, glucuronides and sulfates, after VOO ingestion [89]. The susceptibility of LDL to oxidation depends not only on its fatty content, but also on the LDL antioxidant content (*i.e.* vitamin E and polyphenols) bound to the LDL [90]. Phenolic compounds which can bind LDL are likely to perform their peroxyl scavenging activity in the arterial intima, where full LDL oxidation occurs in microdomains sequestered from the richness of antioxidants present in plasma [5].

Table 1. Randomized, crossover, controlled studies on the antioxidant effect of sustained consumption of phenolic compounds from olive oil on *in vivo* markers of lipid and DNA oxidation

	Olive oil intervention (time)	Daily olive oil dose	Subjects	Washout period	Oxidative markers	Effects
Vissiers *et al.* (2001) [79]	High-phenol vs Low-phenol (3 weeks)	69 g (in sauces, or baked products)	46 healthy (31 women, 15 men)	2 weeks without olives and olive oil	MDA, FRAP LP, PC LDL-resistance[a)] to oxidation	None
Moschandreas *et al.* (2002) [80]	High vs Low phenol (3 weeks)	70 g raw	25 healthy (14 women, 11 men)	2 weeks without olives and olive oil	MDA, FRAP LP, PC LDL resistance[a)] to oxidation	None
Marrugat *et al.* (2004) [66]	Virgin vs Common vs Refined (3 weeks with refined olive oil for cooking)	25 mL (22 g) raw	30 healthy men	2 weeks with refined olive oil for raw and cooking purposes	Plasma oxidized LDL LDL resistance[a)] to oxidation Antobodies against oxidized LDL HDL-cholesterol	Decrease with olive oil phenolics None Increase after virgin olive oil
Weinbrenner *et al.* (2004) [68]	High vs Meium vs Low phenol (4 days with low phenolic olive oil for raw and cooking	25 mL raw	12 healthy men	10 days: low phenol olive oil for raw and cooking; very-low antioxidant diet	Plasma oxidized LDL MDA in urine 8oxodG in urine and lymphoctyes F_2-isoprostanes GSH-Px HDL cholesterol	Decrease with olive oil phenolics None Increase with olive oil phenolics
Visioli *et al.* (2005) [81]	Virgin vs refined (raw)	40 mL raw	22 lipemic patients (12 men, 10 women)	4 weeks with	Plasma antioxidant capacity F_2-isoprostanes	Increase with olive oil phenolics None
Fitó *et al.* (2005) [82]	Virgin vs Refined (raw) (3 weeks, refined olive oil for cooking)	50 mL, raw	Coronary heart disease patiens (40 men)	2 weeks withrefined olive oil for all purposes	Plasma oxidized LDL, LP GSH-Px	Decrease with olive oil phenol ics Increase with olive oil phenolics
Salvini *et al.* (2006) [103]	High vs Low (8 weeks) phenolics	*ad libitum* in substitution of other fats	10 post-menopausal women	2 weeks (usual diet)	Comet assay for DNA oxidation	Decrease with olive oil
Covas *et al.* (2006) [84]	Virgin vs Common vs Refined (3 weks)	25 mL, raw	200 healthy men	2 weeks without olives and olive oil	Plasma oxidized LDL Uninduced dienes Hydroxy fatty acids Antiboides against oxidizee LDL F_2-isoprostans GSH/GSSG Antioxidatn enzymes	Decrease with olive oil phenolics None Increase nonrelated with olive oil phenolics N one
Machowetz *et al.* (2006) [104]	Idem	Idem	Idem	Idem	8oxodG 8-oxo-guanine 8-oxo-guanosine	Increase nonrelated with olive oil phenolics None

a) *In vitro* test.

MDA, malondialdehyde; FRAP, ferric reducing ability of plasma; LP, lipid peroxides; PC, protein carbonyl; 8oxodG, 8-position to 8-oxo-deoxyguanosine; GSH-Px, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione.

4 DNA oxidative damage

Dietary fat and fatty acids are considered important risk factors in carcinogenesis, but, it is not known whether genotoxic or epigenetic aspects of the process of carcinogenesis play the major role [91]. For genotoxicity, lipid peroxidation products of PUFAs are one of the candidates [92]. Among them, malondialdehyde and 4-hydroxy-2-nonenal have been identified as binding to DNA and forming promutagenic exocyclic DNA adducts (*i.e.* 1, N^6-ethenoadenine (εAde); 1, N^6-etheno-2′-deoxyadenosine (εdA); 1, N^4-etheno-2′-deoxycytidine (εdC)) which may lead to mutations, initiation of cancer cells, and cancer progression [93]. The most abundant DNA modification, however, is the hydroxylation of guanine in the 8-position to 8-oxo-deoxyguanosine (8oxodG) [9, 94]. The urinary excretion of 8oxodG is advocated as a biomarker of the whole body DNA oxidation [95]. A predictive value for 8oxodG in lung cancer for non smokers has been reported [96].

Some *in vivo* studies have examined the effect of olive oil and/or that of its phenolic compounds on DNA oxidation, but data from randomized, controlled human intervention trials are scarce. VOO was more beneficial than sunflower olive oil in preventing the age-associated effects on the antioxidant capacity and on the DNA double-strands breaks in rats [97]. Higher adduct levels of εdC and 8oxodG were seen in the liver of female rats fed with a sunflower oil rich-diet in comparison with those fed with olive or rapeseed oil [98]. The intake of ω6-PUFA has been associated with an increase of etheno-DNA adducts in urine [99] and in white cells [100] in female subjects. In contrast, consumption of 25 mL/day of VOO during 3 weeks did not modify the urinary excretion of etheno-DNA adducts in healthy volunteers [101]. In the study referred to [101], the dietary intake of linoleic acid was the highest predictor (45%) of the urinary εdA excretion and, together with the dietary iron intake, predicted a 46% of the urinary εdC excretion. Concerning olive oil phenolic compounds, they reduced the levels of hydrogen peroxide-induced DNA damage in experimental studies [102]. Protective effects of olive oil phenolics on *in vivo* DNA oxidation, measured as 8oxodGuo in mononuclear cells and in urine, were found in healthy male subjects in a short-term study in which participants were submitted to a very low antioxidant diet [68]. A protective effect on DNA oxidation, measured by the comet assay in peripheral blood lymphocytes, was observed in postmenopausal women [103]. Recent results of the EUROLIVE study, however, show that consumption of 25 mL of olive oil per day during 3 weeks reduced DNA oxidation in 182 healthy males, as measured by the 24 h urinary excretion of 8oxodGuo, irrespective of the olive oil phenolic content [104]. The beneficial effect of olive oil consumption on DNA oxidation with a magnitude of decrease of 13% was comparable to that observed with smoking cessation [105]. It must be pointed out that the decrease in oxidative damage to DNA after olive oil consumption observed in the EUROLIVE study, in spite of the consistency of the results through three randomized intervention periods, was evaluated on a linear basis, due to the lack of a placebo group other than the low phenolic olive oil group. Further studies are required to definitively establish the effect of olive oil and its phenolic compounds on the oxidative damage to DNA in front of other types of fat. The randomized, crossover, controlled studies on the effect of olive oil phenolics sustained consumption on DNA oxidative damage performed up to date in humans are summarized in Table 1.

5 Oxidative stress associated processes

Oxidative stress and lipid oxidation are linked with other atherosclerosis associated processes such as inflammation and endothelial dysfunction. Oxidized lipids activate an NFκB-like transcription factor and induce the expression of genes containing NFκB binding sites. The protein products of these genes initiate an inflammatory response that initially leads to the development of the fatty streak [106]. The anti-inflamatory properties of olive oil as MUFA fat, and those of the phenolic compounds from olive oil [107] have been displayed in several experimental models and in some human studies, and have been recently subject of review [108, 109]. In two randomized, crossover, controlled studies, VOO, rich in polyphenols, was shown to be more effective in lowering LTB_4 and TXB_2 than refined olive oil, with a low phenolic content, both at postprandial state in healthy subjects [110] and after sustained consumption in mildly dyslipidemic patients [81]. The anti-inflammatory effects in humans of olive oil and its phenolic compounds is a promising field, and further studies are required to obtain full evidence on the topic. Oxidative stress and LDL oxidation are also related with endothelial dysfunction and hypertension [111].The vasculoprotective and anti-hypertensive role of olive oil will be described in other articles of this issue.

6 Comments

On the basis of the information discussed above olive oil, as source of dietary fat, could provide benefits on oxidative stress associated processes. With the present knowledge, olive oil consumption could reduce oxidative damage, on one hand, due to its richness in oleic acid, and on the other hand, due to its minor components of the olive oil particularly the phenolic compounds. Olive oil seems to be more protective on oxidative lipid and DNA damage than PUFA fat. Oleate-rich LDL is more resistant to oxidative modifications than linoleate-rich LDL, and the protection against oxidative lipid damage appear to be in a dose-dependent manner with the phenolic content of the olive oil. The anti-

oxidant capacity of minor components of olive oil, other than phenolic compounds, remains to be tested in human, randomized, controlled studies. Besides the free radical scavenger activity olive oil phenolics could exert their antioxidant action by promoting an increase in antioxidant molecules, such as HDL cholesterol or GSH-Px , as has been reported in both human [66, 68, 82, 84] and animal studies [112] and in cell culture models [60]. Olive oil phenolic compounds are able to bind the LDL lipoprotein and to protect other phenolic compounds bound to LDL from oxidation. The role of phenolic compounds from olive oil on DNA oxidative damage remains controversial, and perhaps more sensitive methods would be required to detect differences among the types of olive oil consumed. The protective role of olive oil phenolic compounds on DNA oxidative damage has been displayed in studies, but with low sample size, where the DNA oxidative damage was measured in mononuclear cells or lymphocytes from peripheral blood. There is still a debate concerning the best method for DNA oxidative damage measurement, the steady-state levels of 8oxodG in lymphocytes being at present considered the best biomarker for oxidative damage to DNA [113, 114]. Unfortunately, at present, this method is difficult to apply in large sample size intervention studies. Further studies are required to establish the potential benefits of olive oil and those of its minor components on DNA oxidative damage.

7 References

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