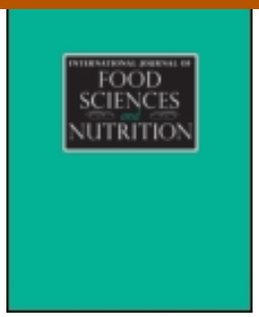

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Nutrition and oxidative stress: a systematic review of human studies

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Abstract
Oxidative stress (OS) – defined as the imbalance between free radical production and antioxidant defences – is a condition associated with chronic-degenerative disease, such as cancer, metabolic and disease cardiovascular diseases (CVDs). Several studies have shown that diet and some of its components could influence the intensity of OS damage. The aim of this review was to critically examine some pieces of evidence from observational and intervention study in human beings to assess whether diet and its components can really modify OS *in vivo*. Furthermore, we tried to find out the possible mechanism behind this association. We considered all studies in MEDLINE which fitted with the following criteria: (1) adult subjects who were healthy or affected by metabolic disease and CVDs; (2) no food supplements, pillows, powder but only common foods and beverages and (3) OS assessment with well-known and validated *in vivo* biomarkers.

Keywords: *oxidative damage, biomarkers, chronic diseases, diet, dietary components*

Abbreviations: *8-OH-dG, 8-hydroxy-2-deoxyguanosine, AHA, American Heart Association, BMI, body mass index, CVDs, cardiovascular disease, DASH, Dietary Approach to Stop Hypertension, DNA, deoxyribonucleic acid, EIA, enzyme immunoassay, ELISA, enzyme-linked immunosorbant assay, FFQ, food frequency questionnaire, GC–MS, gas chromatography–mass spectrometry, HPLC, high-performance liquid chromatography, HPLC–MS, high-performance liquid chromatography–mass spectrometry, LC–MS, liquid chromatography–mass spectrometry, LDL, low-density lipoprotein, MDA, malondialdehyde, MUFA, monounsaturated fatty acids, NECP, national cholesterol education program, OS, oxidative stress, ox-LDL, oxidized LDL, PUFA, polyunsaturated fatty acids, RCTs, randomized controlled trials, RIA, radio immunoassay, RNA, ribonucleic acid, SFA, saturated fatty acids, TBARS, thiobarbituric acid reactive substances, TFA, trans fatty acids, UPLC, ultra performance liquid chromatography*

Introduction

Oxidative stress (OS) represents a disturbance in the balance between prooxidant and antioxidant reactions in living organisms. Free radicals overproduction can lead to an oxidative damage to biological molecules (DNA, proteins and lipids), which has been associated with chronic-degenerative disorders, especially cancer, metabolic diseases and cardiovascular diseases (CVDs; Morrow 2005; Stephens et al. 2009). Several studies have shown increased levels of OS biomarkers in subjects with CVDs or risk factors (dislipidaemia, hypertension, smoke, diabetes and metabolic syndrome; Hopps et al. 2010). Many physiopathological mechanisms have been proposed to explain this association but, however, the *primum movens* seems to be the endothelial dysfunction, a well-known condition linked to atherosclerosis. Free radicals can react with nitric oxide, and the result is a reduction in vasodilatation capacity. Furthermore, endothelial dysfunction is coupled to chronic inflammation, which increases free radicals production (Leopold and Loscalzo 2009).

Moreover, the relationship between oxidative DNA damage and cancer is well known. Reactive compounds can form DNA adducts, and this may give rise to carcinogenic activity (Prado et al. 2010). In addition to this, OS can activate a variety of transcription factors leading to the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines and cell cycle regulatory molecules (Reuter et al. 2010).

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Table I. OS biomarkers *in vivo* and analytical methods for their detection.

Target molecule	Oxidative stress biomarker	Analytical methods
Lipid	MDA	TBARS assay
		Colorimetric assay
		Fluorimetric assay
		HPLC
		GC–MS
	Isoprostanes	GC–MS
		LC–MS
		HPLC
		ELISA
		EIA
		RIA
	ox-LDL and their antibody	ELISA
		EIA
DNA	Oxidized purine and pyrimidine bases (8-OH-dG)	Labelling
		GC–MS
		LC–MS
		HPLC
		ELISA
Protein	Protein carbonyls	Electrophoresis
		Spectrophotometry
		ELISA
	Oxidized aminoacids	GC–MS
		LC–MS
		HPLC
		ELISA

Notes: 8-OH-dG, 8-hydroxy-2-deoxyguanosine; DNA, deoxyribonucleic acid; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; LC–MS, liquid chromatography–mass spectrometry; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; RIA, radio immunoassay; TBARS, thiobarbituric acid reactive substances

Prooxidant species are the result of energy metabolism; besides, recent studies have shown that they play as true second messengers that control important cellular functions, i.e. chemical mediators production, cellular division and migration (Janssen-Heininger et al. 2008, Pérez-Matute et al. 2009). Hence, oxidative damage can occur if there exist two conditions: first, an increased production of reactive species as a consequence of chronic diseases or exogenous sources and second, from diminished levels of dietary antioxidants and enzymatic cofactors.

Moreover, diet composition can influence both the intensity of oxidative damage and antioxidant mechanisms and this explains, at least in part, the relationship among diet and some chronic diseases, such as atherosclerosis, diabetes and cancer (Pérez et al. 2002).

The purpose of this study was to review some pieces of evidence from studies to evaluate whether macronutrients, bioactive compounds or some food and beverages can affect OS parameters *in vivo*.

We considered all observational studies (Table II) and randomised-controlled intervention trials (RCTs, Tables III–VIII) published in MEDLINE (US National Library of Medicine, National Institutes of Health) which fitted with the following criteria: (1) adult subjects who were healthy or affected by metabolic disease and CVDs; (2) no food supplements, pillows, powders but only common foods and beverages and (3) OS assessment with well-known and validated *in vivo* biomarkers (Table I).

First of all, we discuss results from the studies which considered energy balance modification; then evidence on the relationship between nutrients, some foods and beverages and OS *in vivo* biomarkers is presented.

Body weight/energy balance and OS

Epidemiological and clinical evidence suggests that excessive adiposity is associated with increased OS, which could be the mechanism behind the comorbidity in overweight/obese subjects.

An observational study (Sakano et al. 2009) shows that body weight and body mass index are positively associated with urinary isoprostanes and 8-hydroxy-2-deoxyguanosine (8-OH-dG) levels in overweight healthy subjects (Table II).

RCTs seem to confirm the relationship between body weight and OS (Table III).

In fact, it has been observed in a long-term trial that weight loss (−10% of body weight) leads to a significant reduction in DNA oxidation biomarkers (Hofer et al. 2008).

Instead in a short-term trial (4 weeks), there is no consistent effect of weight reduction on urinary isoprostanes excretion. This suggests that long-period intervention trials are needed to establish whether weight loss can affect lipid oxidation (Rankin and Turpyn 2007).

Weight loss induced through exercise (−8% of body weight) results in significant and similar improvements in OS biomarkers when compared with ipocaloric diet (−10% of body weight) (Hofer et al. 2008).

Nutrients and OS

Proteins. Little is known about the association between protein quality and OS; furthermore, we did not find trials that have tested the effect of protein amount on OS biomarkers.

Only one trial fitted with our selection criteria (Azadbakht et al. 2007; Table III). Postmenopausal women affected by metabolic syndrome were randomly assigned to three isoenergetic diets (DASH diet) differing only in the use of protein sources: meat for the control diet and soy nuts and soy proteins for the other two intervention periods. Comparing malondialdehyde (MDA) levels, there was a significant reduction in all groups but it was higher after consuming soya products. These results suggest two considerations: (1) DASH diet, rich in fruit, vegetables, whole grains, low-fat dairy

Table II. Observational studies considering the association between dietary components and OS *in vivo*.

Ref.	Subjects	Methods	Results*
Sakano et al. (2009)	$n = 677$ (293M–384F) Healthy	FFQ Isoprostanes (EIA) 8-OH-dG (ELISA)	+: weight, BMI, alcohol intake −: retinol and vitamin C intake
Hu et al. (2006)	$n = 292$ (113M–179F)	Block FFQ	+: glycaemic index (MDA and isoprostanes)
	Healthy	MDA (spectrophotometry) Isoprostanes (GC–MS)	+: glycaemic load (MDA load)
Couillard et al. (2006)	$n = 56$ men Healthy	3-day food record ox-LDL (ELISA) Isoprostanes (EIA)	+: fat intake and ox-LDL No association with isoprostanes
Tomey et al. (2007)	$n = 1610$ Postmenopausal women	Block FFQ Isoprostanes 0–5 years (EIA)	+: TFA and SFA intake −: fruit and vegetables intake
Kim et al. (2010)	$n = 264$ women Healthy	Tertiles of lycopene serum levels (UPLC) ox-LDL (EIA)	−: higher tertiles of lycopene intake versus ox-LDL
Helmersson et al. (2009)	704 men 9% diabetes 29% hypertension 36% hyperlipidaemic 16% smokers	7-days food record Isoprostanes (RIA) (control after 20 and 27 years)	−: ascorbic acid intake −: α-tocopherol intake
Lecomte et al. (1994)	$n = 417$ men Healthy	Alcoholic beverages: 1. low intake (10.6 ± 9.9 g/day) 2. medium intake (59 ± 25.7 g/day) MDA (fluorimetry)	+: alcohol intake and MDA
Panagiotakos et al. (2004)	$n = 2282$ (1128M–1154F) Healthy	FFQ ox-LDL (ELISA)	−: Mediterranean diet compliance and ox-LDL
Azzini et al. (2011)	$n = 131$ (64M–67F) Healthy	4-day food record MDA (ELISA)	−: Mediterranean diet compliance and MDA

Notes: 8-OH-dG, 8-hydroxy-2-deoxyguanosine; BMI, body mass index; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; FFQ, food frequency questionnaire; GC–MS, gas chromatography–mass spectrometry; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; RIA, radio immunoassay; SFA, saturated fatty acids; TFA, trans fatty acids; UPLC, ultra performance liquid chromatography; * +, positive association; −, negative association.

products and low in saturated fat, total fat, cholesterol, refined grains and sweets can be a dietary strategy to improve OS; (2) probably, MDA reduction after soy consumption is mediated by antioxidant phytochemical compounds and not by any difference in protein quality.

We have to underline that authors do not explain which soy protein source was used and so we cannot rule out that it is a protein hydrolysate/powder.

Carbohydrates. The association between carbohydrates (CHO) and OS has been poorly explored; moreover, more attention has been paid to glycaemic index and glycaemic load than CHO amount.

An observational study (Hu et al. 2006) has shown that glycaemic index is positively associated with lipid peroxidation (MDA and isoprostanes), while glycaemic load was positively associated only with MDA levels (Table II).

However, the association between glycaemic index and lipid peroxidation has not been confirmed by a short-term trial (Botero et al. 2009). Healthy subjects were assigned to follow diets differing for glycaemic index but no differences were detected at the end of the study period (Table III). Long-period RCTs with adequate sample size are needed.

Fats. The association between fats intake and OS has been widely investigated with more attention to the effects of fatty acids than the amount of fats (Tables II and IV).

A significant relationship between dietary fat and OS has been shown by an observational study (Couillard et al. 2006), but it has not been confirmed by RCTs considered in this review (Table IV).

In these trials, subjects were randomly assigned to diets differing in the amount of total fats (38% vs. 28% of energy intake) and fatty acids composition (Perez-Martinez et al. 2010; Petersson et al. 2010). After 12 weeks, no effects on OS biomarkers were observed.

More evidence is available for fatty acids effects. As shown by observational (Tomey et al. 2007) and intervention studies (Jenkins et al. 2008; Perez-Martinez et al. 2010; Petersson et al. 2010), monounsaturated fatty acids (MUFA) seem to improve lipids and proteins oxidation, whereas saturated fatty acids (SFA) have a negative effect on OS status (Tables II and IV). These effects could be related to different chemical properties of fatty acids. In particular, the degree of unsaturation of carbon chains could influence biological membranes fluidity and sensitivity to oxidation. In addition, the presence

Table III. Body weight/energy balance, proteins, carbohydrates and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Body weight and energy balance				
Hofer et al. (2008)	$n = 34$ (12M–22F)	Parallel groups (1 year)	DNA and RNA oxidized bases	↓ DNA oxidized bases in 'buffy coat' after ipocaloric diet ($p < 0.001$) and physical exercise ($p < 0.05$)
	Healthy	(a) Ipocaloric diet (b) Physical exercise (c) Healthy lifestyle (control)	'Buffy coat' (HPLC) Urine (GC–MS)	↓ RNA oxidized bases in 'buffy coat' in both groups ($p < 0.05$)
Rankin et al. (2007)	$n = 32$ women Healthy	Parallel groups (4 weeks) (a) Ipocaloric diet (60% carbohydrates, 20–25% fats, 15–20% proteins) (b) Atkins diet (10% carbohydrates, 60% fats, 30% proteins)	Isoprostanes (ELISA)	No change
Proteins				
Azadbakht et al. (2007)	$n = 42$ women Metabolic syndrome	Crossover (8 weeks-washout 4 weeks) (a) DASH diet* + red meat/day (control) (b) DASH diet + soy nuts (30 g/day) (c) DASH diet + soy proteins (30 g/day)	MDA (HPLC)	↓ All groups versus baseline Significance reached only in soy groups versus control (higher for soy nuts)
Carbohydrates				
Botero et al. (2009)	$n = 16$ men Healthy	Crossover (10 days-washout 2–12 weeks) (a) High glycaemic index diet (b) Low glycaemic index diet	Isoprostanes (GC–MS)	No change

Notes: ↓, reduction; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbant assay; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; RNA, ribonucleic acid; *DASH (Dietary Approach to Stop Hypertension) = diet rich in fruit and vegetables, low-fat milk and dairy products.

of MUFA or SFA in lipoprotein could affect receptor responsiveness in the liver, inducing an increase in low-density lipoprotein (LDL) levels and making LDL more prone to oxidation.

Another interesting point is the relation between dietary polyunsaturated fatty acids (PUFA) and OS. PUFA have a lot of double carbon—carbon bond in their chains, and it makes them the major target of oxidative damage. Moreover, PUFA are precursors of arachidonic acid; through cyclooxygenases and lypoxygenase, this acid generates the eicosanoids, which are involved in inflammatory and prothrombotic processes.

However, PUFA effect on OS has not been clarified yet. In fact, some trials have shown no effect of PUFA on OS biomarkers (Freese et al. 2002, 2008; Wu et al. 2006), while some authors have observed that ω3 improve lipid peroxidation (Parra et al. 2007) and ω6, on the contrary, have a detrimental effect (Turpeinen et al. 1998). These conflicting results are probably due to different designs of study protocols, duration and kind of intervention (Table IV).

Finally, it has been hypothesized that dietary trans fatty acids (TFA) act negatively on human health and one of the possible mechanisms could be OS induction. An observational study (Tomey et al. 2007) shows a positive association between TFA intake and OS (Table II), but RCTs do not confirm this connection (Turpeinen et al. 2002; Tholstrup et al. 2006; Table IV).

However, these trials have tested vaccenic acid, a natural TFA, while negative effects on human health have been demonstrated for TFA derived from industrial hydrogenation.

Foods

Fruit and vegetables. Observational evidence shows a negative association between levels of OS biomarkers and intake of vitamins and bioactive compounds contained in fruit and vegetables. This association was significant in healthy subjects (Tomey et al. 2007; Kim et al. 2010) as well as in people affected by metabolic disease and CVDs (Helmersson et al. 2009; Table II).

All RCTs we considered in this review have confirmed this relationship in healthy subjects

Table IV. Dietary fats and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Perez-Martinez et al. (2010)	$n = 75$ Metabolic syndrome	Parallel groups (12 weeks) Isoenergetic diet: (a) SFA-rich high fat diet (38% energy) (b) MUFA-rich high fat diet (38% energy) (c) Normolipidic diet (28% energy) + 1.24 g/day ω3 (d) Normolipidic diet (28% energy) + 1 g/day oleic acid-rich sunflowers oil	MDA (TBARS) Protein carbonyls (spectrophotometry)	↑ MDA and protein carbonyls after SFA-rich diet versus other diet ↓ Protein carbonyls after MUFA-rich diet
Pettersson et al. (2010)	$n = 486$ (254M–232F) Metabolic syndrome	(as above)	Isoprostanes (RIA)	No change
Jenkins et al. (2008)	$n = 27$ (15M–12F) Hyperlipidaemic	Crossover (1 month-washout 2 weeks) NCEP diet* + snack: (a) Control (Muffin; MUFA = 9.0 ± 0.5%) (b) 'Half' (37 ± 2 g/day almonds + half muffin; MUFA = 14.5 ± 0.5%) (c) 'Full' (73 ± 3 g/day almonds; MUFA = 18.9 ± 0.6%)	MDA (HPLC) Isoprostanes (GC/MS)	MDA: ↓ 'full' versus control Isoprostanes: ↓ 'full' and 'half' versus control
Wu et al. (2006)	$n = 27$ Postmenopausal healthy women (vegetarian)	Parallel groups (6 weeks) Run-in: habitual diet + corn oil (2 weeks) Intervention: (a) Habitual diet + 6 g/day DHA-rich oil (2.14 g/day) (b) Habitual diet + 6 g/day corn oil	Isoprostanes (EIA)	No change
Freese et al. (2002, 2008)	$n = 77$ (20M–57F) Healthy	Parallel groups (6 weeks) (a) Linoleic acid-rich/fruit and vegetables-low diet (b) Linoleic acid and fruit and vegetables-rich diet (c) Oleic acid-rich/fruit and vegetables-low diet (d) Oleic acid and fruit and vegetables-rich diet Habitual diet (control)	MDA (TBARS) Isoprostanes (RIA) Protein carbonyls (fluorimetric assay) 8-OH-dG (HPLC)	No change
Parra et al. (2007)	$n = 276$ (118M–158F) Obese	Parallel groups (8 weeks) (a) Cod fish diet (ω3 = 227 ± 29 mg/day) (b) Salmon diet (ω3 = 1418 ± 34 mg/day) (c) Fish oil diet (ω3 = 3003 ± 128 mg/day) (d) Control diet (↓ fish intake; ω3 = 5.6 ± 0.2 mg/day)	MDA (colorimetric assay)	↓ After cod fish diet versus baseline No change for other group
Turpeinen et al. (1998)	$n = 38$ (18M–20F) 13 control subjects Healthy	Parallel groups (4 weeks) (a) Controlled diet + linoleic acid-rich sunflowers oil (MUFA 18.7%, PUFA 4.6%) (b) Controller diet + oleic acid-rich sunflowers oil (MUFA 11.4%, PUFA 12.3%) (c) Habitual diet	Isoprostanes (RIA)	↑ After linoleic acid intake versus control group ($p < 0.04$) No change after oleic acid intake
Turpeinen et al. (2002)	$n = 30$ (8M–22F) Healthy	Parallel groups (9 days) Run-in: oleic acid-rich diet (2 weeks) Intervention: (a) Vaccenic acid 1.5 g/day (b) Vaccenic acid 3.0 g/day (c) Vaccenic acid 4.5 g/day	Isoprostanes (RIA)	↑ versus baseline in all groups ($p < 0.001$) No change between groups

Table IV – *continued*

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Tholstrup et al. (2006)	$n = 42$ men Healthy	Parallel groups (5 weeks) (a) Vaccenic acid-rich diet (3.6 g/day) (b) Control diet	Isoprostanes (RIA)	No change

Notes: ↑, increase; ↓, reduction; 8-OH-dG, 8-hydroxy-2-deoxyguanosine; DHA, docosahexaenoic acid; EIA, enzyme immunoassay; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acid; RIA, radio immunoassay; SFA, saturated fatty acids; TBARS, thiobarbituric acid reactive substances; *NCEP diet (National Cholesterol Education Program) = SFA < 7% of energy intake and cholesterol < 200 mg/day.

(Visioli et al. 2003; Thompson et al. 2005a, 2005b; Crujeiras et al. 2009; Table V).

This effect could be triggered by several mechanisms. First of all, these foods are rich in vitamins (A, C and E) and precursors (carotenoids), of which the antioxidant capacity is well known; furthermore, as shown by several studies, vitamins can improve DNA repair enzymes, such as enzymes involved in DNA methylation or base excision repair. In this way, they contribute indirectly to decrease oxidative damage (Go et al. 2003; Tudek et al. 2006; Alleva et al. 2012).

In addition to this, minerals act as enzymatic cofactors improving antioxidant defences against free radicals, and dietary fibre can reduce glucose absorption in the gut avoiding postprandial hyperglycaemia, which increases reactive species production.

Finally, fruit and vegetables are rich in phytochemicals, bioactive compounds that increase antioxidant activity and could play a role in glucose homeostasis, as shown by *in vitro* and animal studies (Srinivasan et al. 2007) and in the up-regulation of DNA repair mechanisms-related genes (Guarrera et al. 2007).

Nuts. Many RTCs have investigated the relationship between intake of nuts and OS biomarkers (Table IV). It should be noted that the trials are different for duration, study population considered, type of nuts and OS biomarkers used. Then, in order to make it easier to discuss, we present trials grouped by the type of populations studied.

In healthy subjects, pistachios supplementation significantly reduces lipid peroxidation (Kogyt et al. 2006; Sari et al. 2010) while intake of walnuts is not effective (McKay et al. 2010; Table V).

RCTs which enrolled hypercholesterolaemic subjects have shown that walnuts supplementation does not affect oxidative damage (Ros et al. 2004; Table V), whereas almonds, on the contrary, significantly improve it (Jenkins et al. 2008; Table IV).

In addition, almonds seem to play a protective role against oxidative damage in type 2 diabetic subjects too (Liu et al. 2012; Table IV).

Finally, supplementation with 30 g of nuts (15 g of walnuts, 7.5 g of almonds and 7.5 g of hazelnuts) significantly reduces oxidative damage to nucleic acids and improves other OS biomarkers in subjects affected by metabolic syndrome (Lopez-Uriarte et al. 2010; Table V).

We address these conflicting results to heterogeneity of trials and small sample size. Despite this, intake of nuts seems to improve OS, even if in some trials this effect is not statistically significant.

Whole grains. Scientific evidence, based in particular on epidemiological studies, suggests a potential role of whole grains in the prevention of chronic-degenerative diseases. One of the possible mechanisms behind this

Table V. Fruit and vegetables, nuts, whole grain and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Fruit and vegetables				
Visioli et al. (2003)	$n = 12$ women Healthy	Crossover (4 weeks) (a) Low β-carotene diet (< 600 μg/day) (b) Low β-carotene diet (< 600 μg/day) + supplementation with tomato and its products + 5 g olive oil/portion to improve lycopene absorption	Isoprostanes (EIA)	↓ Isoprostane after tomatos and its product supplementation
Thompson et al. (2005a)	$n = 64$ women Healthy	Parallel groups (14 days) (a) 3.6 portion of fruit and vegetables/day (L) (b) 12.1 portion of fruit and vegetable/day (H)	8-OH-dG (HPLC) Isoprostanes (ELISA)	↓ 8-OH-dG and isoprostanes in group 'H' versus baseline ($p < 0.01$) and versus 'L' ($p = 0.04$)
Thompson et al. (2005b)	$n = 208$ women Healthy	Crossover (8 weeks-washout 2 weeks) Isoenergetic diet: (a) 3.6 portion of fruit and vegetables/day (L) (b) 9.2 portion of fruit and vegetables/day (H)	Isoprostanes (ELISA)	↓ Isoprostanes in group 'H' versus baseline ($p < 0.01$)
Crujeiras et al. (2009)	$n = 15$ women Obese	Parallel groups (8 weeks) (a) Fruit-rich ipocaloric diet (− 600 kcal; fructose 15% of energy intake) (b) Low fruit ipocaloric diet (− 600 kcal; fructose 5% of energy intake)	MDA (colorimetric assay)	MDA improvement after fruit-rich diet
Nuts				
Kogyt et al. (2006)	$n = 44$ (24M–20F) Healthy	Parallel groups (3 weeks) (a) Habitual diet + 65–75 g/day of pistachios (b) Habitual diet	MDA (TBARS)	↓ MDA after pistachios supplementation ($p < 0.05$)
Sari et al. (2010)	$n = 32$ Healthy	Parallel groups (8 weeks) (a) Mediterranean inspired diet (b) Mediterranean inspired diet + 60–80 g pistachios	MDA (HPLC) ox-LDL (EIA)	↓ MDA after pistachios supplementation ($p < 0.001$) No change for ox-LDL
Mckay et al. (2010)	$n = 21$ (9M–12F) Healthy	Crossover (12 weeks-washout 6 weeks) (a) Habitual diet + 21 g/day walnuts (b) Habitual diet + 42 g/day walnuts	MDA (HPLC)	No change
Ros et al. (2004)	$n = 20$ (8M–12F) Hypercholesterolaemia	Parallel groups (4 weeks) (a) Mediterranean inspired diet + 40– 65 g/day of walnuts (b) Mediterranean inspired diet	MDA (HPLC) ox-LDL (ELISA)	No change
Liu et al. (2009)	$n = 20$ (9M–11F) Type 2 diabetes	Crossover (12 weeks-washout 2 weeks) Isoenergetic diets: (a) NCEP* (control diet) (b) NCEP + almonds 56 g/day	MDA (HPLC) ox-LDL (ELISA) Protein carbonyls (spectrophotometry)	↓ ox-LDL and protein carbonyls after almonds supplementation versus control ($p < 0.05$ and $p = 0.0003$, respectively) No change for MDA
Lopez-Uriarte et al. (2010)	$n = 50$ (28M–22F) Metabolic syndrome	Parallel groups (12 weeks) (a) AHA diet† (control) (b) AHA diet + 30 g nuts/day (15 g walnuts, 7.5 g almonds and 7.5 g peanuts)	8-OH-dG (HPLC) Isoprostanes (EIA) ox-LDL (ELISA)	Non-significant improvement of isoprostanes and ox-LDL ↓ 8-OH-dG after nuts supplementation ($p < 0.001$)
Whole grain				
Andersson et al. (2007)	$n = 30$ (8M–22F) Metabolic syndrome	Crossover (6 weeks-washout 6–8weeks) (a) Habitual diet + whole gain (7 pt) (b) Habitual diet + refined grain (7 pt)	Isoprostanes (RIA)	No change

Table V – *continued*

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Enright et al. (2010)	$n = 20$ (10M–10F) Healthy	Crossover (14 days-no washout) (a) Habitual diet + whole grain (M: 8 pt F: 6 pt) (b) Habitual diet + refined grain (M: 8 pt F: 6 pt)	Isoprostanes (ELISA) MDA (TBARS)	No change

Notes: ↓, reduction; 8-OH-dG, 8-hydroxy-2-deoxyguanosine; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; Pt, portion; RIA, radio immunoassay; SFA, saturated fatty acids; TBARS, thiobarbituric acid reactive substances; TFA, trans fatty acids; ⋆NCEP diet (National Cholesterol Education Program) = SFA < 7% of energy intake and cholesterol < 200 mg/day; † AHA diet (American Heart Association) = diet rich in fruit and vegetables, whole grain, legumes and fish, salt max 6 g/day, SFA < 7% energy intake, TFA < 3% energy intake, cholesterol < 200 mg.

effect could be related to the antioxidant compounds contained in these foods.

However, trials have not demonstrated any effect of whole grain diets on OS biomarkers (Andersson et al. 2007; Enright and Slavin 2010; Table V). Considering the short duration of these trials, we cannot exclude that long-term studies could show that the intake of whole grains can reduce oxidative damage.

Olive oil. Olive oil is naturally rich in antioxidant compounds. The main experimental evidence on olive oil comes from EUROLIVE, a European multi-centre trial, and SOLOS, a Spanish study, both concerning the effects of the intake of olive oils, differing in polyphenols amount, on human health (Table VI). Data on OS show that polyphenols-rich olive oil (366 mg/oil kg) significantly improves isoprostanes (Cicero et al. 2008) and 8-OH-dG levels (Machowetz et al. 2007), but it does not affect other DNA oxidation biomarkers (Machowetz et al. 2007). Conflicting results are available for ox-LDL (Marrugat et al. 2004; Cicero et al. 2008) and their antibody (Marrugat et al. 2004; Castañer et al. 2011).

Two trials (Vissers et al. 2001; Moschandreas et al. 2002) with similar study design have not detected change in protein and lipid oxidative damage after high polyphenols olive oil supplementation (308 mg/oil kg; Table VI).

In spite of these inconclusive results, we cannot neglect that high polyphenols olive oil can affect isoprostanes levels, which are considered the gold standard biomarker to asses OS *in vivo*. Thence, the inconsistency of the results could be due to the low content of polyphenols in some *cultivar* of olives.

Cocoa. Over the last years, authors' awareness for the beneficial effects of cocoa polyphenols on human health has increased. As a consequence, there has been a spread of trials that have explorated the mechanisms behind this effect, including OS reduction.

However, only two studies fitted with our criteria (Table VII). In the first trial (Fraga et al. 2005), healthy subjects were given either milk chocolate or white chocolate. After 15 days, there was a reduction in MDA level in milk chocolate group while, on the contrary, subjects who consumed white chocolate had higher level of this OS biomarker. Nevertheless, in a long-term trial there was no change in OS status after dark chocolate or white chocolate supplementation (Taubert et al. 2007).

Even if these trials give conflicting results, both of them show an association between OS biomarkers levels and chocolate consumption. By the way, dark and milk chocolate seem to improve OS while white chocolate has no effect. These effects are probably triggered by polyphenols, the content of which is higher in dark/milk chocolate than in white chocolate.

Table VI. Olive oil and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Cicero et al. (2008)	$n = 182$ men Healthy	Crossover (3 weeks-washout: 2 weeks) Habitual diet + 25 ml/day of oil: (a) High polyphenols olive oil (366 mg/kg) (b) Medium polyphenols olive oil (164 mg/kg) (c) Low polyphenols olive oil (2.7 mg/kg)	ox-LDL (EIA) Isoprostanes (HPLC–MS)	No change for ox-LDL ↓ Isoprostanes versus baseline
Machowetz et al. (2007)	$n = 182$ men Healthy	(as above)	DNA and RNA oxidized bases (HPLC–MS)	↓ 8-oxo-dG versus baseline No change for other bases
Marrugat et al. (2004)	$n = 30$ men Healthy	(as above)	ox-LDL (ELISA) ox-LDL antibody (ELISA)	↓ ox-LDL after high polyphenols olive oil consumption
Castañer et al. (2011)	$n = 182$ men Healthy	(as above)	ox-LDL antibody (ELISA)	No change for ox-LDL antibody ↑ ox-LDL antibody
Vissers et al. (2001)	$n = 46$ (17M–32F) Healthy	Crossover (3 weeks-washout 2 weeks) (a) Habitual diet + high polyphenols olive oil (308 mg/kg) (b) Habitual diet + low polyphenols olive oil (43 mg/kg)	MDA (HPLC) Protein carbonyls (ELISA)	No change
Moschandreas et al. (2002)	$n = 25$ (11M–14F) Healthy	(as above)	MDA (HPLC) Protein carbonyls (ELISA)	No change

Notes: ↑, increase; ↓, reduction; DNA, deoxyribonucleicacid; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; HPLC, high-performance liquid chromatography; HPLC–MS, high-performance liquid chromatography–mass spectrometry; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; RNA, ribonucleic acid

Further studies are needed to elucidate the relationship between polyphenols and OS.

Beverages

Alcoholic beverages. Observational studies have shown a positive association between alcohol intake and oxidative damage to lipid and DNA (Lecomte et al. 1994; Sakano et al. 2009; Table II).

RCTs give conflicting results (Table VII). All trials have considered alcoholic beverages effects on lipid peroxidation in healthy subjects. Duration of treatments was 4 weeks in one trial and almost 2 weeks in others. Evidence suggests that alcohol has detrimental effect on OS because during ethanol metabolism there is an overproduction of free radicals (Caccetta et al. 2001; Addolorato et al. 2008). Despite this, two trials have showed a reduction in lipid peroxidation after red wine assumption compared with white wine and alcohol abstinence (Pignatelli et al. 2006; Micallef et al. 2007). Thence, we can assume that polyphenols of wine, especially red wine, can act against free radicals. However, this effect could be affected by *cultivar* of grapes that influence the amount of polyphenols and their antioxidant power.

Tea. RCTs considering the effect of tea on OS are shown in Table VII.

Trials on healthy subjects have shown that green tea consumption can reduce DNA oxidative damage (van het Hof et al. 1997) but it does not affect lipid peroxidation (Hakim et al. 2003).

Moreover, tea seems to have no effect on subjects affected by hypertension (Hogdson et al. 2002), moderate hypercholesterolaemia (Hogdson et al. 2002; Davis et al. 2003) or type 2 diabetes (Neyestani et al. 2010).

Although trials have shown limited effect of tea consumption on OS, it should be noted that there is a dose–time relationship between OS and intake of tea. Hence, long-term trials are needed to assess whether tea can improve OS *in vivo*.

In addition to this, we underline that it is necessary to know the exact composition in polyphenols of tea in order to well understand whether there is a dose-dependent effect.

Dietary patterns. Mediterranean diet is one of the most recommended dietary patterns for the prevention of chronic-degenerative diseases; the beneficial effect could be triggered also by the high antioxidant capacity of this diet.

ATTICA study has shown a negative association between Mediterranean diet and lipid peroxidation (Panagiotakos et al. 2004). The same result has been detected by an Italian observational study too (Azzini et al. 2011; Table II).

Although RCTs have not confirmed this relationship (Ambring et al. 2004; Fitò et al. 2007;

Table VII. Cocoa, alcoholic beverages, tea and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Cocoa				
Fraga et al. (2005)	$n = 27$ men Healthy	Parallel groups (14 days) Habitual diet + (a) Flavonoids-rich milk chocolate (168 mg) (b) White chocolate (flavonols < 5 mg)	MDA (HPLC) 8-OH-dG (HPLC)	↓ MDA after milk chocolate ↑ MDA after white chocolate No change for 8-OH-dG
Taubert et al. (2007)	$n = 44$ (20M–24F) Healthy	Parallel groups (18 weeks) Habitual diet + (a) Dark chocolate (30 mg polyphenols/day) (b) White chocolate (no polyphenols)	Isoprostanes (EIA)	No change
Alcoholic beverages				
Caccetta et al. (2001)	$n = 18$ men Healthy	Crossover (2 weeks-washout 1 week) Habitual diet + : (a) Red wine 375 ml/day (polyphenols 1200 mg/l) (b) White wine 375 ml/day (polyphenols 345 mg/l) (c) Dealcoholized red wine 500 ml/day (polyphenols 905 mg/l)	Isoprostanes (GC/MS)	↓ After dealcoholized red wine consumption versus other groups ($p < 0.05$)
Addolorato et al. (2008)	$n = 40$ men Healthy	Parallel groups (30 days) Habitual diet + 40 g/day alcohol: (a) Beer (1 l) (b) Wine (400 ml, 11% etanolo) (c) Spirit (120 ml) Abstinence (control)	MDA (TBARS)	↑ All groups versus baseline: (a) + 9.5%; (b) + 19.0%; (c): + 7.3% ($p < 0.05$) No change for control group
Pignatelli et al. (2006)	$n = 20$ (9M–11F) Healthy	Parallel groups (15 days) Mediterranean diet + (a) Red wine 300 ml/day (polyphenols 1.8 g/l) (b) white wine 300 ml/day (polyphenols 0.25 g/l)	Isoprostanes (EIA)	↓ In both groups versus baseline ($p < 0.001$) (↓ % red wine > white wine; $p < 0.001$)
Micallef et al. (2007)	$n = 40$ men Healthy	Crossover (2 weeks-washout 2 weeks) Habitual diet + (a) Red wine 400 ml/day (b) Abstinence	MDA (TBARS)	↓ After red wine consumption ($p < 0.001$)
Tea				
van het Hof et al. (1997)	$n = 133$ (33M–100F) Healthy	Parallel groups (4 months) (a) Water 4 cups/day (b) Decaffeinated black tea 4 cups/day (catechin: 8.11 mg/cup; polyphenols: 111.65 mg/cup) (c) Decaffeinated green tea 4 cups/day (catechin: 73.49 mg/cup; polyphenols 145.75 mg/cup)	8-OH-dG (ELISA)	↓ 8-OH-dG after decaffeinated green tea ($p = 0.002$)
Hakim et al. (2002)	$n = 45$ (24M–24F) Healthy	Parallel groups (4 weeks) Habitual diet + : (a) Black tea 6 cups/day (900 ml; epicatechin 7.17%) (b) Green tea 6 cups/day (900 ml; epicatechin 21.4%) (c) Water 900 ml	MDA (TBARS)	No change

Table VII – *continued*

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Hogdson et al. (2002)	$n = 13$ (10M–3F)	Crossover (7 days-no washout) Habitual diet + : (a) Green tea 5 cups/day (1 l) (b) Black tea 5 cups/day (1 l) (c) Water (1 l)	Isoprostanes (GC/MS)	No change
	$n = 22$ (16M–6F) Hypercholesterolaemic	Crossover (4 weeks-no washout) (a) Green tea 5 cups/day (1 l e 250 ml) (b) Black tea 5 cups/day (1 l e 250 ml) (c) Water (1 l e 250 ml)	Isoprostanes (GC/MS)	No change
Davis et al. (2003)	$n = 15$ (7M–8F) Hypercholesterolaemic	Crossover (3 weeks-washout 4 weeks) NCEP diet⋆ + (a) Black tea 5 cups/day (polyphenols 172 mg/cup) (b) Placebo 5 cups/day (no polyphenols) (c) Decaffeinated placebo 5 cups/day (no polyphenols)	ox-LDL (ELISA) Isoprostanes (ELISA) MDA (TBARS) 8-OH-dG (ELISA)	No change
Neyestani et al. (2010)	$n = 46$ (16M–29F) Type 2 diabetes	Parallel groups (4 weeks) (a) Increasing doses of black tea (from 150 to 600 ml) (b) Black tea 150 ml (control)	MDA (TBARS)	Non-significant improvement

Notes: ↑, increase; ↓, reduction; 8-OH-dG, 8-hydroxy-2-deoxyguanosine; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; SFA, saturated fatty acids; TBARS, thiobarbituric acid reactive substances; ⋆NCEP diet (National Cholesterol Education Program) = SFA $< 7\%$ energy intake and cholesterol < 200 mg/day.

Table VIII. Mediterranean diet, DASH diet, diet with high TAC and OS: human trials.

Ref.	Subjects	Study design	Biomarker and analytical method	Results
Mediterranean diet				
Ambring (2004)	$n = 22$ (12M–10F) Healthy	Crossover (4 weeks-washout 4 weeks) (a) Swedish habitual diet (SFA = 17%; MUFA = 12%; ω3 = 1%; fibre = 19%) (b) Mediterranean inspired diet (SFA = 8%; MUFA = 14%; ω3 = 2%; fibre 40%)	Isoprostanes (RIA)	No change
Fitò (2007)	$n = 372$ (162M–210F) Cardiovascular risk factors	Parallel groups (3 months) (a) Mediterranean diet + virgin olive oil (b) Mediterranean diet + nuts (walnuts 15 g/day, peanuts 7.5 g/day and almonds 7.5 g/day) (c) AHA diet⋆ (control diet)	ox-LDL (ELISA) MDA (HPLC)	↓ ox-LDL and MDA in Mediterranean diets versus control diet
Konstantinidou (2010)	$n = 90$ (26M–64F) Healthy	Parallel groups (3 months) (a) Mediterranean diet + virgin olive oil (VVO) (b) Mediterranean diet + washed virgin olive oil (WVO) (c) Habitual diet (control diet)	ox-LDL (ELISA) Isoprostanes (EIA) 8-OH-dG (HPLC)	↓ Isoprostanes and 8-OH-dG after Mediterranean diets versus baseline ($p < 0.05$ after VVO) No change for ox-LDL
Urquiaga (2010)	$n = 34$ male Healthy	Parallel groups (3 months) (a) Mediterranean diet (b) Western diet	MDA (TBARS assay) 8-OH-dG (HPLC)	↓ 8-OH-dG after Mediterranean diet No change for MDA
DASH diet				
Lopes (2003)	$n = 24$ $n = 12$ (6M–6F) Hypertensive $n = 12$ (6M–6F) Normotensive	Crossover (4 weeks) (a) Habitual diet (1–2 pt of fruit and vegetables/day; SFA 16%; cholesterol 300 mg/day; fibre 9 g/day) (b) DASH† diet (4–5 pt of fruit and vegetables/day; SFA 6%; cholesterol 150 mg/day; fibre 31 g/day)	Isoprostanes (GC/MS)	No change
Azadbakht (2007)	$n = 42$F Metabolic syndrome	Crossover (8 weeks-washout 4 weeks) (a) DASH† + red meat (control diet) (b) DASH + soy nuts (30 g/day) (c) DASH + soy proteins (30 g/day)	MDA (HPLC)	↓ In all groups versus baseline
Diet with high TAC				
Valtueña (2008)	$n = 33$ (19M–14F) Healthy	Crossover (2 weeks-washout 2 weeks) (a) Low TAC diet (b) High TAC diet	MDA (Fluorimetric) ox-LDL (EIA) Protein Carbonyls (ELISA)	↓ MDA after high TAC diet Non-significant improvement for ox-LDL and protein carbonyls

Notes: ↓, reduction; 8-OH-dG, 8-hydroxy-2-deoxyguanosine; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbant assay; GC–MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; ox-LDL, oxidized low-density lipoprotein; Pt, portion; RIA, radio immunoassay; SFA, saturated fatty acids; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TFA, trans fatty acids; ⋆AHA diet (American Heart Association) = diet rich in fruit and vegetables, whole grain, legumes and fish, salt max 6 g/day, SFA < 7% energy intake, TFA < 3% energy intake, cholesterol < 200 mg; †DASH (Dietary Approach to Stop Hypertension) = diet rich in fruit and vegetables, low fat milk and dairy products.

Konstantinidou et al. 2010; Urquiaga et al. 2010; Table VIII), we cannot exclude that Mediterranean diet, rich in antioxidant and bioactive compounds, could affect OS. We suggest that long-term trials which consider all OS biomarkers could clarify the relationship between Mediterranean diet and OS.

Furthermore, DASH diet has been proposed as a dietary strategy to reduce OS. This diet is characterized by high amount of fruit and vegetables and use of low-fat milk and dairy products. Unfortunately, only two trials fitted with our criteria and, in addition to this, they have given inconclusive results (Lopes et al. 2003; Azadbakht et al. 2007; Table VIII).

Finally, it has been suggested that a diet with a high total antioxidant capacity (TAC) could improve the oxidant status. TAC describes the ability of dietary antioxidants to scavenge free radicals and it differs a lot depending on the intake of foods. An intervention trial has tested this hypothesis with two isoenergetic diets differing only in the amount of antioxidant compounds. After the high TAC diet, there was a significant reduction in MDA levels but no changes were detected for ox-LDL and protein carbonyls (Valtueña et al. 2008; Table VIII).

Conclusion

OS is considered as one of the possible mechanisms that trigger metabolic diseases and CVDs, and, in addition to this, it also contributes to cancer development.

Epidemiological studies suggest that diet can influence oxidative damage power, positively and negatively. Hence, changes in diet composition could be a useful strategy in the prevention of chronic-degenerative disease and CVDs.

RCTs have not given convincing results in the majority of cases.

Fruit and vegetables consumption and MUFA-rich diet seem to improve OS *in vivo*. Also weight loss, as a consequence of ipocaloric diet or physical exercise, affects OS biomarkers, but duration of the treatment is important for greater efficiency. Detrimental effects on OS have been reported for SFA and alcoholic beverages.

Several studies have investigated the effect of polyphenols from different sources on oxidative damage but trials have given conflicting results. In particular, the antioxidant power of polyphenols in wine and olive oil seems to be influenced by grapes and olives *cultivar*. Instead, a time-related relationship between tea polyphenols and OS can be hypothesized. Anyway, the weak effects of polyphenols could be related to their rapid elimination, which may produce inactive compounds, or to plasma protein bindings.

Evidence from trials which have explored the effect of dietary patterns suggests that beneficial effects of diet on OS may be related to the synergistic action of different dietary compounds rather than single food or bioactive substance effect.

In conclusion, evidence shows that diet composition can influence OS *in vivo*; this effect is almost clear for MUFA, fruit and vegetables, which improve OS, and for SFA and alcoholic beverages, which worsen oxidative *status*. More trials are needed to clarify the effect of whole grain, nuts and other dietary compounds (polyphenols, PUFA and TFA).

Limits of trials until now performed are the short duration of nutritional treatment, heterogeneous doses and small sample size.

Thence, further long-term RCTs with bigger sample size are needed to support the role of some dietary components on oxidative damage and to give possible definitive answers to the many questions still open.

Oxidative processes are closely related to the development of type 2 diabetes, CVDs and cancer. Hence, dietary strategies which can reduce OS *in vivo* could be a valid approach for the prevention of these diseases, which largely affect human health.

Finally, we would like to underline that future studies should consider the relationship between diet, OS and diseases with a nutrigenomic approach because, as told by del Sol and colleagues, 'diseases can be viewed as specific types of network perturbation' (del Sol et al. 2010), so several molecular and physiopathological mechanisms are involved directly and indirectly in this association.

Recently, several studies have been published and they demonstrate how promising this novel approach is because it gives a large-scale profiling of genes, proteins and metabolites. Focusing on the relationship between diet and OS, one more time evidence shows the power of antioxidants in the reduction of oxidative-related process (Bakker et al. 2010; Konstantinidou et al. 2010).

Nutrigenomic approach, through the 'omic techniques', will allow to better understand the connection between dietary compounds and disease-related or prevention-linked genes. In this way, we could improve dietary strategy in the prevention of chronic-degenerative diseases to maintain a good health and to achieve the so-called 'well ageing'.

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