Nutritional, Dietary and Postprandial Oxidative Stress\textsuperscript{1,2}

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ABSTRACT Nutritional, or dietary oxidative stress denotes a disturbance of the redox state resulting from excess oxidative load or from inadequate nutrient supply favoring prooxidant reactions. Low intake or impaired availability of dietary antioxidants including vitamins E and C, carotenoids, polyphenols, and other micronutrients (e.g., selenium) weakens the antioxidant network. Postprandial oxidative stress, as a subform of nutritional oxidative stress, ensues from sustained postprandial hyperlipidemia and/or hyperglycemia and is associated with a higher risk for atherosclerosis, diabetes, and obesity. In Western societies, a significant part of the day is spent in the postprandial state. Unsaturated fatty acids incorporated into LDL and oxidized LDL are an atherogenic factor. Lipid hydroperoxides present in the diet are absorbed, contributing to the prooxidant load. In hyperlipidemic and hyperglycemic subjects, endothelium-dependent vasodilation is impaired in the postprandial state, making postprandial oxidative stress an important factor modulating cardiovascular risk. Postprandial oxidative stress is attenuated when dietary antioxidants are supplied together with a meal rich in oxidized or oxidizable lipids. Ingestion of dietary polyphenols, e.g., from wine, cocoa, or tea, improves endothelial dysfunction and lowers the susceptibility of LDL lipids to oxidation. Polyphenols affect endothelial function not solely as antioxidants but also as modulatory signaling molecules. J. Nutr. 135: 969–972, 2005.

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Oxidative metabolism is a mainstay of aerobic life. Nutrients serve for energy production by oxidative phosphorylation, and intermediary metabolism includes direct incorporation of oxygen atoms from molecular oxygen into biomolecules. Utilizing oxygen in biological systems includes the formation of reactive oxygen species (ROS), which can damage biological molecules. Thus, central biological processes lead to the generation of oxidative breakdown products; interest has focused particularly on oxidation of DNA, proteins, and lipids. Conversely, there is a multilayered strategy of defense against oxidative damage including enzymatic and nonenzymatic antioxidants as well as adaptive responses (1). An imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage, has been called “oxidative stress” (2–4). The term describes a metabolic condition of cells, organs, or the entire organism characterized by an oxidative overload.

At low levels, ROS mediate cellular functions via intracellular signaling, activated by stimuli that influence the cellular redox state. Changes in the redox state of intracellular thiols, especially glutathione, play a role in the regulation of gene transcription (5). Depending on the pathway of generation, or the major ROS formed, the phenomenon of oxidative stress can be subspecified, e.g., metabolic oxidative stress, environmental oxidative stress, photooxidative stress (6), drug-dependent oxidative stress, or nitrosative stress (3).

This article focuses on nutritional, or dietary, and postprandial oxidative stress, addressing oxidative challenge from prooxidants in foodstuffs and nutrients such as, the generation and release of oxidants and breakdown products, as well as of antioxidants from components of the diet within the organism, and adaptive responses and pathophysiological processes.

Nutritional, or Dietary, Oxidative Stress. Nutritional oxidative stress describes an imbalance between the prooxidant load and the antioxidant defense as a consequence of excess oxidative load or of inadequate supply of the organism with nutrients; the term dietary oxidative stress is often used synonymously. Dietary antioxidants are low-molecular-weight compounds capable of scavenging ROS directly, comprising tocopherols, ascorbate, carotenoids, thiols, polyphenols, and other micronutrients (e.g., selenium-containing amino acids). Epidemiologically, increased ingestion of a diet rich in antioxidants is associated with a diminished risk for degenerative diseases (7). Dietary antioxidants are thought to be responsible, at least in part, for the beneficial effects of diets rich in fruits and vegetables, recommended in a worldwide campaign of disease prevention.

Increased oxidative stress has been associated with disease states such as diabetes, cystic fibrosis, cataract, or infections (8). Interestingly, it was recognized early on by Levander and colleagues (9) that dietary oxidative stress might also be protective, namely, in infections with parasites such as in malaria, where the plasmodium is more sensitive to oxidative challenge than the host cells. The relation between oxidative stress and viral infections has been further scrutinized in an interesting way: oxidative stress is implicated in the pathogenesis of viral infections, including hepatitis, influenza, and AIDS (10). Thus, poor nutrition can affect host response toward infection and, consequently, an adequate supply of antioxidants provided with the diet is required (11).

The levels of antioxidants in the diet vary, depending on source-related factors such as growth conditions as well as food

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processing and storage. Endogenous factors have an effect on bioavailability at the level of absorption, distribution, metabolism, and excretion (12).

Copper, manganese, and selenium are constituents of antioxidant enzymes, gastrointestinal glutathione peroxidase, a selenoenzyme, efficiently reduces lipid hydroperoxides during the absorption of fats (13). Antioxidants such as polyphenols modulate the expression of genes related to oxidative stress or antioxidant defense (14). Variations in nutritional status lead to metabolic adaptations, which are affected by the individual genetic profile. Nutrigenomic approaches link nutrient supply and resulting effects on the molecular basis of gene expression (15,16).

**Postprandial Oxidative Stress.** Postprandial oxidative stress is characterized by an increased susceptibility of the organism toward oxidative damage after consumption of a meal rich in lipids and/or carbohydrates (Fig. 1) (17,18). Thus, macronutrients have an effect on the redox balance in the organism. They are either targets of oxidative modifications after absorption or are present in a prooxidant form in the diet. Hyperlipidemia and hyperglycemia have been associated with increased oxidative damage affecting lipoproteins and the antioxidant status (19). Postprandial increases of lipid and carbohydrate levels lead to increased oxidative stress, which has been associated with increased risk for atherosclerosis and related disorders (20).

LDL are prominent targets for postprandial oxidative modification. Oxidative stress has been implicated in the pathogenesis of cardiovascular diseases or diabetic complications (21,22). Importantly, there is a link to central obesity (23). However, the detailed relations among hyperlipidemia, hyperglycemia, hyperinsulinemia, and oxidative stress are still under research.

Consumption of a meal containing oxidized and oxidizable lipids gives rise to increased plasma levels of lipid hydroperoxides, detectable by sensitive chemiluminescence techniques (17). This is associated with increased susceptibility of LDL to oxidation, apparently due to structural perturbation at the particle surface brought about by lipid oxidation products.

In Western societies, a significant part of the day is spent in the postprandial state. The concept voiced by Zilversmit (24) that atherogenesis is a postprandial phenomenon is gaining momentum. In this view, accumulation of triglyceride-rich lipoproteins in the postprandial state results from lowered clearance rates of chylomicron remnants, and this prolonged hyperlipidemic state contributes to vascular injury and the development of atherosclerosis. For individuals in a continuous postprandial state, levels of chylomicron remnants in the circulation may remain elevated indefinitely. Elevated lipids and lipoproteins are related to coronary artery disease progression; however, factors associated with the postprandial state that predispose individuals to vascular disease remain to be explored.

Flow-mediated vasodilation is largely NO dependent. Hypercholesterolemia causes endothelial dysfunction that is based at least in part on impaired NO production. Impaired NO synthase activity may be due to aberrant signaling of NO synthase in cells containing elevated cholesterol either through compromised post-translational modification of the enzyme and coupled signaling proteins or via downregulation of proteins (e.g., caveolin) that are closely associated with cholesterol (25). Similar effects were reported for lipid hydroperoxides and other ROS (26).

Vogel and colleagues (27) reported that flow-mediated vasodilation was lowered ~50% by 2 h and by as much as 70% at 4 h after a high-fat meal. Flow-mediated vasodilation was not affected by administration of a low-fat meal or a high-fat meal that included 1 g vitamin C and 800 IU vitamin E (28). The change in flow-mediated vasodilation after the low-fat and high-fat meals correlated inversely with the 2-h postprandial change in triglyceride levels. A single high-fat meal transiently impaired endothelial function for up to 4 h in healthy normocholesterolemic subjects; this effect was blocked by antioxidants. Endothelium-dependent vasodilation is impaired in hyperlipidemic subjects, especially in the postprandial state (29). Postprandial hypertriglyceridemia is an independent risk factor for early atherosclerosis.

**Dietary Lipids and Lipoprotein Oxidation.** A strong relation exists between dietary fat intake and atherosclerosis progression as determined by carotid artery wall thickening (30). Fish oil induces hyperlipidemia as well as elevated plasma and tissue lipid hydroperoxide levels in animals fed cholesterol-containing diets. The effects of unsaturated fat intake on lipoprotein oxidation and lipoprotein oxidizability are documented (31), along with the widely accepted in increased antioxidant demand associated with the intake of diets rich in PUFA. Nevertheless, elevations in plasma hydroperoxide levels could arise as readily from the hydroperoxides associated with PUFA-rich foods as from the propensity for PUFA-enriched lipoproteins to undergo peroxidation after assimilation (32). Ingestion of oxidized dietary lipids is associated with oxidized lipid appearing in chylomicrons (33). Prolonged elevations in triglyceride-rich lipoproteins, associated with decreased chylomicron clearance, result in a restriction in vitamin E transfer to LDL and HDL along with greater susceptibility to oxidation (34).

The findings discussed above seem to conflict with the notion that gastrointestinal glutathione peroxidase efficiently reduces lipid hydroperoxides during the absorption of fats (13). Small amounts of lipid hydroperoxides may escape reduction and appear in the plasma because the lipid hydroperoxide

![FIGURE 1](https://academic.oup.com/jn/article-abstract/135/5/969/4663985/1350684639953091)
content in foods can be orders of magnitude higher than that observed in postprandial plasma. The large interindividual variability for the postprandial increase of lipid hydroperoxides in chylomicrons (0.1 to 20 nmol/mg of cholesterol, Ursini, Dept. of Biological Chemistry, University of Padova, Padova, Italy, personal communication) agrees with the variable efficiency for enzymatic reduction in different subjects. Accordingly, a large hydroperoxide burden may overwhelm glutathione pools in some enterocytes, and the capacity of glutathione peroxidase may become transiently limited.

Secondary oxidation products can be absorbed after oral administration of hydroperoxide-enriched lipids (35). They likely do not induce the propagation of lipid peroxidation directly, but may produce cell injury and inflammatory responses to injury that indirectly promote oxidation in target tissues, most notably gastrointestinal tissues. Oxysterols may behave similarly to lipid hydroperoxides because they are absorbed largely via the lymphatics, albeit to a lesser extent than cholesterol. Thus, oxysterols can be considered to be markers of ingested fats that have been subjected to oxidation. Furthermore, oxysterols and other lipid peroxidation products induce cytotoxic responses that can promote the generation of ROS and induce further lipid peroxidation (36). Induction of cytokines (37) and activation of inflammatory cells (38) by oxysterols represent a mechanism by which prandial lipid peroxidation products promote postprandial oxidative stress.

Dietary lipids also interact with nutrient-sensitive transcription factors involved in the regulation of several metabolic pathways (16). Thus, changes in fatty acid pattern affect signaling pathways. The sterol regulatory element-binding protein and nuclear factor-κB are such nutrient-sensitive transcription factors (39).

**Hyperglycemia.** Atherosclerotic diseases are prevalent as secondary complications associated with type 2 diabetes, and a diet high in readily absorbable carbohydrates is associated with increased risk for type 2 diabetes (40). Most epidemiologic data implicate postprandial hyperglycemia in the development of cardiovascular disease, and postprandial hyperglycemia is a predictor of cardiovascular risk. Elevated postprandial glucose levels may have a direct toxic effect on the vascular endothelium mediated by oxidative stress, independent of other cardiovascular risk factors such as hyperlipidemia (41,42). Postprandial hyperglycemia also may exert its effects through its substantial contribution to total glycemic exposure (22). Ischemia-reperfusion causes oxidative damage that is enhanced with repetitive postprandial hyperglycemia (43). Among the cells that can be damaged by diabetes are the primary sensory neurons, also known as dorsal root ganglion neurons. Damage to these cells results in diabetic peripheral neuropathy. An elevated glucose level leads to apoptosis in neurons accompanied by increased oxidative stress (44).

**Metabolic Fine-Tuning.** An important antioxidant function is effective during the process of digestion and assimilation. The postprandial increase in plasma lipid hydroperoxide content and oxidative stress is restricted when a meal containing oxidized and oxidizable lipids is consumed together with red wine (45) or with procyanidins (46). Procyanidins can be found in many plants; important sources are red wine, in particular grape seeds and grape skin, cocoa, pine bark, and green tea. For example, red wine protected diabetic patients from meal-induced oxidative stress (47). This inhibitory action can be explained by the fact that during gastric digestion of food containing oxidized and oxidizable lipids, all of the conditions for lipid peroxidation are satisfied, particularly when the meal contains a catalytic source for hydroperoxide decomposition such as myoglobin (48). This means that the time course and amplitude of the postprandial oxidative load can be modified by dietary components such as procyanidins. Thus, there is a growing body of evidence suggesting that vascular responses can be positively modified by dietary antioxidants.

Intervention studies showed that selected biomarkers of cardiovascular risk are influenced by the consumption of polyphenol-rich foods (49). Apart from wine, major sources of dietary flavanols are cocoa and related products, tea, and a number of fruits and vegetables. High-flavanol cocoa, but not standard low-flavanol cocoa, reverses endothelial dysfunction in subjects at risk for cardiovascular disease (50), and plasma F2-isoprostane concentrations are lowered (51). Similarly, consumption of tea (52) or purple grape juice (53) reverses endothelial dysfunction and reduces the susceptibility of LDL cholesterol to oxidation. Recently, in a study on tea consumption, it was concluded that effects on endothelial function may not be attributable to a systemic antioxidant or anti-inflammatory effect (54). On the other hand, there are distinct effects of cocoa polyphenols on the generation of inflammatory mediators in vitro (55). In an experimental model of inflammation, alcohol-induced liver injury in rats, cocoa extracts were shown to be protective (56).

These observations in vitro and in vivo document the capability of dietary constituents to modulate the postprandial response leading to proatherogenic conditions. This metabolic fine-tuning is a concept that deserves further attention, particularly from the standpoint of polyphenols as important components of the milieu of dietary antioxidants. The concept blends with that of "metabolic tune-up" (57), which focuses on the most favorable intake of micronutrients and metabolites to optimize metabolic reactions, adapting to changing needs. The fine-tuning in postprandial conditions has a modulatory role, preventing adverse reactions, with emphasis on timing and location.

It is evident from the literature to date that a mixture of antioxidant compounds are required to provide protection from the oxidative effects of postprandial fats and sugars. No specific antioxidant can be claimed to be most important because human food consumption varies enormously. However, a variety of polyphenolic compounds derived from plants appear to be effective dietary antioxidants, especially when consumed with high-fat meals.

**LITERATURE CITED**


