Oxidative stress and atherosclerosis: Basic and clinical open issues

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The oxidative stress theory of atherosclerosis was coined some decades ago to explain the key mechanisms accounting for arterial inflammation and ensuing formation of atherosclerotic plaque [1]. According to this theory, upon crossing the endothelial wall, low-density lipoprotein (LDL) can become oxidized thus eliciting an *in situ* inflammatory process that leads to accumulation of monocytes-macrophages in the vessel wall; uptake of oxidized LDL (oxLDL) by macrophage scavenger receptors begets formation of foam cell and eventually atherosclerotic plaque [2]. An open issue regards the initiation phase of atherosclerosis, overall, the intrinsic mechanism causing LDL oxidation. *In vitro* studies consistently showed that LDL is oxidized by endothelial cells but the triggers as well as intra-signalling pathways implicated in LDL oxidation are still unclear. Overproduction of reactive oxidant species (ROS) by endothelial cells with ensuing interaction with sub-endothelial LDL has been shown *in vitro* and considered a potential mechanism, but it is unclear if and how LDL may prompt endothelial cells to ROS overproduce. Non-enzymatic oxidation may lead to formation of oxidation molecules as, for instance, in the case of F2-isoprostanes that stem from ROS interaction with arachidonic acid; F2-isoprostanes have been detected in macrophages of human atherosclerotic plaque [3]. Enzymatic oxidation may be another mechanism eliciting LDL oxidation, as suggested by HPLC analysis of human atherosclerotic specimens, showing that atherosclerotic plaque is rich in oxidation molecules derived from 5-lipoxygenase activation [4]; however, it is unclear how the enzyme is activated upon LDL crossing the arterial wall. That LDL oxidation is implicated in arterial inflammation ensuing formation of foam cells has been demonstrated *in vivo* by injection of radiolabelled LDL in patients undergoing endarterectomy with or without high doses of vitamin E, a powerful antioxidant. Samples taken from vitamin E-treated patients showed lowered LDL accumulation within macrophages of atherosclerotic plaque, which suggests a key role for oxidative stress as a trigger of sub-endothelial inflammation [5].

Several biomarkers of oxidative stress have been investigated to explore the interaction between ROS formation and cardiovascular disease progression *in vivo* [1]. The use of these biomarkers may help clinicians identify patients at higher cardiovascular risk. Regarding the pro-oxidant pathways up-regulation, elevated levels of myeloperoxidase are associated with high risk of major cardiovascular events in patients with chronic coronary syndrome. Increased expression and activity of nicotinamide adenine dinucleotide phosphate oxidase also represent pro-oxidant mechanisms favoring coronary artery disease [6–10]. The risk of incident myocardial infarction (MI) appeared modestly higher in patients with some common polymorphisms in the 5-lipoxygenase pathway [11]. Concerning anti-oxidant pathways under-regulation, the few available data on humans confirm their role in cardiovascular disease development

and progression [1]. Peripheral and coronary levels of some enzymes (e.g., superoxide dismutase and catalase) and direct antioxidants (e.g., glutathione) were lower in patients with unstable angina than in healthy controls, and a positive association of common nitric oxide synthase gene polymorphisms to coronary artery disease has been identified [12, 13]. These findings lead to the hypothesis that the administration of antioxidants could be an interesting therapeutic option to lower the risk of cardiovascular disease.

Protein carbonylation refers to the introduction of reactive carbonyl groups (e.g., aldehyde, ketone, and lactam) into the side chains of proteins, which is another relevant ROS-related damage that leads to loss of proteins' function [14]. Metal-catalyzed oxidation, protein interaction with aldehydes and derivates of lipid peroxidation, and nonenzymatic glycation reactions represent some mechanisms of proteins' carbonylation [14]. Even if this process is generally irreversible, recent preliminary data showed that pyridoxamine ameliorates ROS-mediated cellular dysfunction by scavenging protein carbonyls [15].

The current study by Mróz and colleagues [16] highlighted the relevance of persistent ROS overproduction in chronic coronary syndrome and the usefulness of carbonylated proteins measurement for patients' prognosis stratification. In that article, the plasma level of carbonylated proteins was measured in 178 consecutive patients with advanced stable coronary artery disease that was clinically evaluated during a mean follow-up of 8.3 years. Patients in the highest quartile showed the highest risk of a composite of MI, ischemic stroke, systemic thromboembolism, and cardiovascular death. A further interesting finding is that protein carbonylation appeared to induce a prothrombotic and antifibrinolytic state. Protein carbonylation levels, indeed, were associated with low clot permeability and prolonged clot lysis time; they were also associated with elevated concentrations of plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor. These data provide the basis for a deeper understanding of the mechanisms linking oxidative stress with clotting system activation and eventually cardiovascular disease progression. However, further studies in a larger population are needed to confirm these results and validate the usefulness and reproducibility of carbonylated proteins in other clinical settings or patient populations. This finding also reopens the *vexata quaestio* on the potential usefulness of antioxidant administration for cardiovascular disease prevention.

Several studies in the general population have been undertaken in the last decades to assess if a single or cocktail of antioxidant vitamins, such as vitamin E, vitamin C, or beta-carotene, can reduce cardiovascular events. Even if the results of experimental studies were promising, data from a recent meta-analysis provided equivocal results on the beneficial effect of antioxidant supplementation (e.g., vitamin E) in cardiovascular disease prevention [17]. Thus, almost all meta-analyses negated the clinical efficacy of antioxidants while a more recent one seems to suggest their potential role in MI prevention [17]. There are, however, serious methodological reservations regarding the methodology of clinical trials with antioxidants, including, for example, the lack of any information on baseline values of circulating vitamins before supplementation or of circulating vitamins after administration. This is a crucial issue given that vitamin E, for example, is scarcely absorbed by the intestinal gut [18]. Future clinical requisities for further investigating the impact of oxidative stress on atherosclerosis should include identification of specific molecules that are sensitive to cardiovascular disease progression and specific antioxidants that can prevent the oxidative pathway from inducing their formation.

Article information

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