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Oxidative stress and atherosclerosis: Basic and clinical open issues

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The oxidative stress theory of atherosclerosis has been coined some decades ago for explaining the key mechanisms accounting for arterial inflammation and ensuing formation of atherosclerotic plaque [1]. According to this theory, upon crossing endothelial wall, low-density lipoprotein (LDL) can become oxidized so eliciting an in situ inflammatory process leading to accumulation of monocytes-macrophages into the vessel wall: uptake of oxidised LDL (oxLDL) by macrophage scavenger receptor begets foam cell formation an eventually atherosclerotic plaque [2]. An open issue regards the initiation phase of atherosclerosis, overall, the intrinsic mechanism causing LDL oxidation; thus, in vitro studies consistently showed that LDL are 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 shift endothelial cells to ROS overproduction. Nonenzymatic oxidation may concur to formation of oxidation

molecule as, for instance, in 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 of oxidation molecule derived from 5-lipoxygenase activation [4]; however, it is unclear how the enzyme is activated upon LDL crossing arterial wall. That LDL oxidation is implicated in arterial inflammation concurring to formation of foam cells has been demonstrated *in vivo* by injection of radiolabelled LDL to patients undergoing endarterectomy given or not high doses of vitamin E, a powerful antioxidant; samples taken from vitamin E-treated patients showed that lowered LDL accumulation within macrophages of atherosclerotic plaque suggesting a key role for oxidative stress as 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 identifying patients at higher cardiovascular risk. Regarding the pro-oxidant pathways up-regulation, elevated levels of myeloperoxidase is associated with a high risk of major cardiovascular event in patients with chronic coronary syndrome as well as increased expression and activity of NADPH oxidase represents pro-oxidant mechanisms favouring 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]. On the side of 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 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 hypothesize that 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, is a further relevant ROS-related damage, and leads to loss of protein's function [14]. Metal-catalyzed oxidation, protein interaction with aldehydes and derivatives 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 ameliorate 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 the current work, the plasmatic level of carbonylated proteins was measured in 178 consecutive patients with advanced stable coronary artery disease that has been 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, and with elevated concentrations of plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor. These data pose 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 larger population will be needed to confirm the results and to validate the usefulness and reproducibility of carbonylated proteins in other clinical setting or patients' population. This finding also reopens the "vexata question" on the potential usefulness of antioxidant administration for cardiovascular disease prevention.

Several studies, overall in general population, has been undertaken in the last decades to assess if single or cocktail of antioxidants vitamins such as vitamin E, vitamin C or beta-carotene were able to reduce the cardiovascular events. Even if the results of experimental studies were promising, data from recent meta-analysis provided equivocal results on the beneficial effect of antioxidants supplementation (e.g., vitamin E) in cardiovascular disease prevention [17]. Thus, almost all meta-analysis negated a clinical efficacy of antioxidants while a more recent one seems to suggest a potential role for MI prevention [17]. There are, however, serious methodological caveats in the study methodology of clinical trials with antioxidants, including, for example, the lack of any information of baseline values of circulating vitamins before supplementation or of circulating vitamins after administration, that is a crucial issue considering that vitamin E, for example, is scarcely absorbed by intestinal gut [18]. Future clinical requisites 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 are able to prevent the oxidative pathway eliciting their formation.

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