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Antioxidant treatment in peripheral artery disease: the rationale is there, but what about clinical results?

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Peripheral arterial disease is a major cause of morbidity and disability and has been consistently associated with an adverse overall prognosis. Oxidative stress has been linked to vascular disease, with several suggested pathogenetic mechanisms, leading to various insults of the arterial wall and, ultimately, to atherothrombotic disease. Considering that the pathophysiological background is quite compelling, attenuation of oxidative processes by means of various substances with antioxidant properties has been conceived as a promising therapeutic target. However, clinical results have been mostly disappointing and 'antioxidant' therapies are still far from being integrated into treatment algorithms for vascular disease.

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Introduction

Peripheral artery disease (PAD) is a term primarily used for describing obstructive atherosclerotic lesions affecting the arterial vasculature of the lower extremities [1••]. During the last decade alone, global ageing, increased incidence of diabetes and smoking resulted in a 23% increase in the number of PAD patients [2]. Contemporary data show that worldwide more than 200 million people are affected with over 40 million of them living in Europe. Past the age of 65, its prevalence is exponentially increasing and by the age of 80 one fifth of the general population is suffering from PAD. In Western Europe, mortality directly related to PAD was estimated to 3.5 per 100 000 individuals while cardiovascular mortality within 5 years after diagnosis of stable PAD is 11–23% [3] (these patients mostly die from complications related to coronary artery disease and stroke). Risk factors are similar to those for other atherosclerotic diseases (carotid artery disease, coronary artery disease, and so on). Smoking exhibits strong association with PAD and heavy smokers have a four-fold higher risk of developing IC compared to non-smokers [4]. Diabetes is another well-described risk factor with reports showing that for every 1% increase in glycosylated hemoglobin there is a corresponding 26% increase in PAD risk [5]. Important associations with hypertension and hypercholesterolemia have also been described [2].

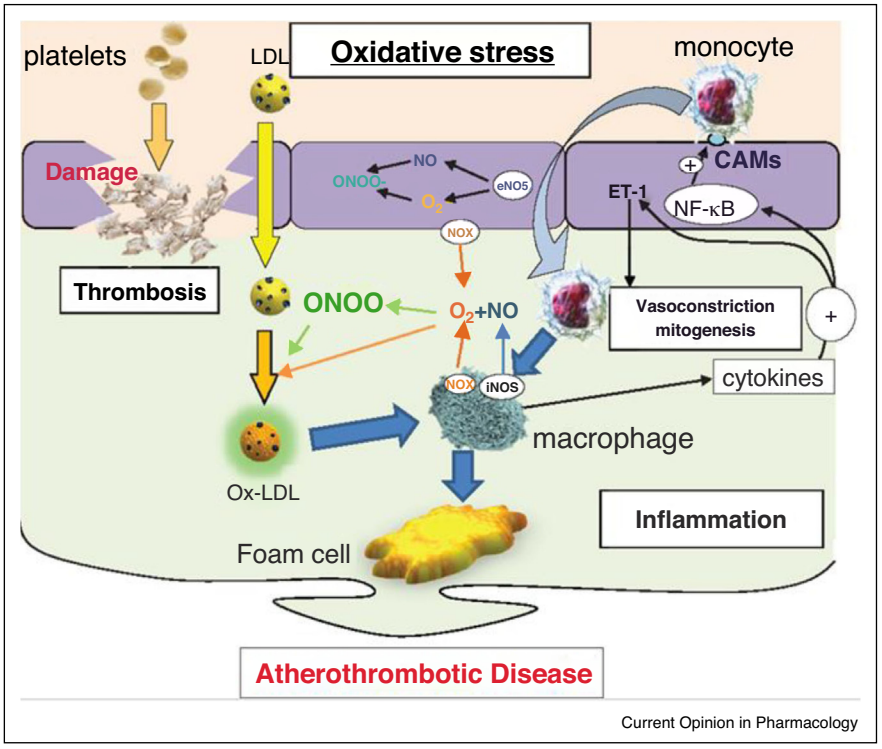
Central to the pathogenesis of atherosclerosis are pathways that result in oxidative stress (Figure 1). Oxidative stress is commonly defined as the redox status present when an imbalance exists between antioxidant mechanisms and oxidative activity species, including reactive oxygen (ROS), nitrogen (RNS), non-radical and free radical species [6]. Its contribution to the atherogenic process has been well described in other papers [7,8•]. In this short review we will focus on the main clinical studies connecting oxidative stress with PAD and discuss the pharmacologic interventions tested so far in an effort to mitigate oxidative damage.

Oxidative stress and peripheral arterial disease — basic research evidence

Effects on vessels

In the majority of clinical trials, investigators measured the level of oxidative stress specific biomarkers [9] in the serum of PAD patients and compared it with controls. Loffredo *et al.* [10] examined whether an imbalance between oxidative stress and nitric oxide (NO) exists in these patients. Nitrite and nitrate (NOx) were selected as markers of NO generation and 8-hydroxy-2-deoxyguanosine (8-OHdG) as a marker of oxidative stress. Samples were collected from 40 PAD patients and 40 controls. Compared with controls, serum levels of 8-OHdG were significantly increased in PAD patients, and serum levels of NOx were significantly decreased. Levels of 8-OHdG and NOx were inversely correlated [10]. One year later, in a similar study, they described the existence of an inverse correlation between oxidative stress, NO, and flow mediated dilation (FMD) [11]. FMD predominantly depends upon release of nitric oxide (NO) from the vascular wall

Figure 1



Under conditions of oxidative stress, endothelial cell damage, loss of the protective effects of NO and enhanced LDL peroxidation combine to drive an inflammatory state, leading to lipid accumulation in the arterial wall. *Abbreviations*: CAMs, cell adhesion molecules; eNOS, endothelial NO synthase; iNOS, indicible NO synthase; NF-κB, nuclear factor kB; ET-1, endothelin-1; LDL, low-density lipoprotein; ox-LDL, oxidized low density lipoprotein; ONOO−, peroxynitrite; O_2^-, superoxide; NO, nitric oxide.
Source: From Goszcz K, *et al*. Front Cardiovasc Med. 2015;2:29 (Creative Commons Attribution 4.0 International Public License).

[12] and is known to independently predict vascular outcome in patients with PAD [13]. It was hypothesized that NOX2 (the catalytic core of nicotinamide-adenine dinucleotide phosphate oxidase) up-regulation might be responsible for increased oxidative stress and endothelial dysfunction. In a cohort comprised of 50 PAD patients and 50 controls they measured serum levels of soluble NOX2-derived peptide (sNOX2-dp), a marker of NOX2 activation, NOx, urinary isoprostanes, a marker of oxidative stress and FMD. PAD patients demonstrated increased sNOX2-dp and isoprostanes levels and reduced levels of NOx and FMD. After multiple linear regression analysis they reported an independent association between FMD and sNOX2-dp [14].

Nonaka *et al*. noted that the serum levels of S-glutathionylated proteins, proteins with oxidized sulfhydryl groups, are positively correlated with the ankle/brachial index and concluded that they can serve as a sensitive risk marker for PAD [15]. Bertoia *et al*. examined the association between primarily oxidized phospholipids (OxPL) on apolipoprotein B-100-containing lipoproteins (OxPL/apoB) and lipoprotein (a) [Lp(a)], and risk of PAD [16•]. They also examined indirect measures of oxidized lipoproteins, including autoantibodies to malondialdehyde-modified low density lipoprotein (MDA-LDL) and apolipoprotein B-100 immune complexes (ApoB-IC). Two parallel case–control studies of 143 men and 144 women with incident confirmed cases of clinically significant PAD and 861 controls served as the study population. They found that OxPL/apoB and Lp(a) levels were positively associated with the risk of PAD in men and women while autoantibodies to MDA-LDL and ApoB-IC were not.

In 2014 Gardner *et al*. compared apoptosis, cellular oxidative stress, and inflammation in cultured endothelial cells treated with sera from subjects with PAD and healthy control subjects free of atherosclerotic disease. They also compared circulating inflammatory, antioxidant capacity, and vascular biomarkers between the two groups. The PAD group had greater endothelial reactive oxygen species (ROS) production than the control group. Furthermore, in the circulation, the PAD group had lower antioxidant capacity, higher levels of inflammation and lower levels of angiogenic biomarkers. A few months later, the same group published a study examining the same parameters but this time around instead of healthy