Dietary and Pharmacological Antioxidants

Subjects: Others

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Reactive oxygen species (ROS) have physiological roles as second messengers, but can also exert detrimental modifications on DNA, proteins and lipids if resulting from enhanced generation or reduced antioxidant defense (oxidative stress). Venous thrombus (DVT) formation and resolution are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, as well as the regulation of effector cells such as platelets, endothelial cells, erythrocytes, neutrophils, mast cells, monocytes and fibroblasts. Many conditions that carry an elevated risk of venous thrombosis, such as the Antiphospholipid Syndrome, have alterations in their redox homeostasis. Dietary and pharmacological antioxidants can modulate several important processes involved in DVT formation, but their overall effect is unknown and there are no recommendations regarding their use. The development of novel antioxidant treatments that aim to abrogate the formation of DVT or promote its resolution will depend on the identification of targets that enable ROS modulation confined to their site of interest in order to prevent off-target effects on physiological redox mechanisms. Subgroups of patients with increased systemic oxidative stress might benefit from unspecific antioxidant treatment, but more clinical studies are needed to bring clarity to this issue. (From: Reactive Oxygen Species in Venous Thrombosis, 10.3390/ijms21061918 (https://doi.org/10.3390/ijms21061918))

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1. Dietary

Various nutritional factors and drugs are known to have antioxidant functions. While evidence exists that they influence various distinct processes important for DVT formation, their overall effect on DVT has yet to be established. The antioxidant effects of vitamins A, C and E for instance are well known [1]. Vitamin E reduces cardiovascular events in subgroups of patients with increased oxidative stress [2], but supplementation in the general population holds no cardiovascular benefit, and may even increase all-cause mortality [3]. Data on how vitamin E might influence the formation and/or resolution of DVT are sparse and limited to two components of the DVT formation process, platelet activation and the coagulation cascade. Activation of isolated platelets with collagen can be inhibited by the antioxidative effects of vitamin E [4]. Vitamin E downregulates the in vitro expression of the initiating protein of the coagulation cascade, TF, in monocytes, suggestive of an anticoagulant function [5][6].

In hemodialysis, the extracorporeal circuit leads to activation of the clotting cascade, which is associated with increased ROS generation and reduced antioxidant mechanisms [7]. The use of a less thrombogenic ethylene–vinyl–alcohol (EVAL) dialysis membrane inhibits NOX2-mediated ROS production, and the use of other materials with ROS-scavenging activities results in the reduced activation of clotting [8][9]. The administration of natural antioxidants, such as red grape juice, which has antioxidant properties, reduces neutrophil NOX activity and plasma concentrations of oxidized LDL (ox-LDL) to an even greater extent than vitamin E in patients undergoing hemodialysis [7].

Beer contains a nutritional antioxidant, xanthohumol, for which a direct beneficial effect for the development of DVT has been shown. Xanthohumol, present in hops that are used in beer making, prevents both arterial and venous thrombosis in mice by decreasing ROS accumulation and inhibiting platelet activation without increased bleeding risk [10]. Moderate beer consumption is associated with a decreased risk of venous thrombosis [10][11][12]. Red wine inhibits platelet activation and diminishes experimental venous thrombosis in rats, an effect that was associated with a substantial increase in total radical-trapping antioxidant parameters (TRAP) [13]. Antioxidant polyphenols, present in a variety of foods and drinks, including red wine and chocolate, are known to reduce platelet reactivity [14] and this is believed to be one of the major drivers of improved cardiovascular mortality when wine is moderately consumed [15]. The Mediterranean diet, and olive oil in particular, also favor antioxidant mechanisms. A cross-over study comparing olive oil with corn oil revealed olive oil intake caused a reduced post-prandial ROS increase in serum and platelets via NOX2 downregulation . It appears, therefore, that nutritional antioxidants can modulate several important steps in the DVT formation process, but their overall benefit in reducing this condition remains to be established.

2. Pharmaceutical

The beneficial effects of statins in cardiovascular disease are mainly attributed to their lipid lowering effects, but there is extensive evidence to suggest that they have pleiotropic effects in regulating disease. Statins decrease oxidative stress and platelet activation in hypercholesterolemic patients by an early and late mechanism. The early effect is dependent on the direct inhibition of platelet NOX2 and independent of any lipid lowering effect, while the late effect is associated with LDL lowering including the platelet-activating molecule, ox-LDL [17][18]. These antiplatelet effects could be responsible for the reduction in thrombotic events observed upon pre-procedural statin therapy [19]. The resolution in venous thrombi is also enhanced by statin therapy, although the mechanism has yet to be reported [20]. Antiplatelets (aspirin) and anticoagulants (Xa inhibitor, rivaroxaban) also have antioxidant properties, as they reduce NOX2-mediated platelet ROS production [21][22].

Most of these drugs have already been evaluated for their benefit in DVT patients, but there are also other antioxidant drugs that are used in other fields of medicine. Modified versions and dosages of these drugs could be repurposed for use in thrombotic diseases. Thioredoxin (TRX) inhibitors, for example, are currently under investigation in clinical trials for diseases involving an imbalance in the NADPH/thioredoxin reductase/thioredoxin system, such as cancer. TRX inhibitors also attenuate platelet function and thrombus formation, which could lead to their being repurposed as antiplatelet agents [23]. The oral anti-diabetic drug, Alogliptin, diminishes oxidative stress and the associated prothrombotic state in a mouse model of chronic stress [24].

Drugs with pro-oxidant properties, such as the anticancer, estrogen-receptor-blocker tamoxifen, might negatively impact processes related to DVT. Platelet activation through tamoxifen-mediated NOX upregulation has previously been suggested to be causally involved in the increased risk of venous thrombosis in breast cancer patients treated with tamoxifen [25].

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