VITAMIN E STATUS AND HYPERLIPIDEMIA

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Introduction

The oxidative modification hypothesis of atherogenesis suggests that the oxidation of low density lipoproteins (LDL) plays an important role in the progression of the disease [1]. This theory implies that antioxidants, such as vitamin E (the major lipophilic antioxidant in the body), should be beneficial in protecting and preventing atherosclerosis. A cardioprotective role for vitamin E is further supported by observational studies. Epidemiology studies have consistently demonstrated a negative correlation between both vitamin E intakes [2-4], and steady-state plasma vitamin E concentrations [5,6], with the risk of coronary heart disease (CHD). Vitamin E has been shown to inhibit LDL oxidation in vitro [7] and ex vivo after supplementation and emerging evidence now suggests that vitamin E has alternative molecular roles in cell signaling and gene expression, unrelated to its antioxidant action. α-tocopherol can inhibit smooth muscle cell proliferation [8], decrease expression of adhesion molecules [9], and inhibit platelet aggregation [10]. It is likely that a combination of these actions is responsible for the observed beneficial effects, suggesting that an adequate supply of vitamin E to the vasculature, and critical cells in atherosclerotic progression is important to decrease disease risk.

Hyperlipidemia, Cardiovascular Disease, and Vitamin E

The hyperlipidemias are independent risk factors for heart disease [11]. High plasma levels of both cholesterol [12] and triglycerides [13] have been linked to increased mortality from coronary heart disease (CHD). The cholesterol hypothesis arises from large-scale epidemiological surveys [12] and the observations relating to the uptake and deposition of oxidized LDL-derived cholesterol into the artery wall. Serum triglycerides have re-emerged as a risk factor for CHD based on a meta-analysis of prospective studies [13]. Raised triglycerides are associated with abnormalities in circulating lipoproteins, collectively known as the atherogenic lipoprotein phenotype (ALP) [14], which predispose to increased cardiovascular risk. The ALP is also associated with a preponderance of small dense LDL particles, and a reduced level of HDL [14]. Triglycerides are associated with the ALP because of the product-precursor relationship between VLDL and LDL [11]. In essence, raised plasma triglycerides result in the synthesis of large VLDL particles which, after hydrolysis, lead to the formation of small dense LDL. Small dense LDL have been found to be more susceptible to oxidation [15], indeed LDL isolated from hyperlipidemias is more susceptible to oxidation in vitro [16]. Small dense LDL also contain lower quantities of α-tocopherol [15] and it has been shown that the oxidative susceptibility of LDL subfractions is related to their antioxidant content [17]. Hyperlipidemia also influences critical cells in atherogenesis. Hyperlipidemia is associated with impaired platelet function, with greater platelet-endothelial adhesion [18], and increased platelet activation [19]. It is also associated with impaired lymphocyte function [20,21]. Both platelets and lymphocytes are functionally responsive towards vitamin E treatment, as α-tocopherol has been shown to
modulate platelet adhesion and aggregation in supplementation studies and ex vivo experiments [22], and to enhance lymphocyte differentiation and proliferation in vitro and ex vivo [23].

Vitamin E homeostasis in hyperlipidemia is not well documented. As vitamin E is transported in lipoproteins, vitamin E concentration is closely correlated to that of cholesterol and total lipid [24], hence hypercholesterolemics usually have increased concentrations of plasma vitamin E (uncorrected for cholesterol concentrations) compared to normolipidemics [25], whereas decreased concentrations have been observed in hypocholesterolemia [26]. Similarly, hypertriglycerideremias also appear to have higher plasma vitamin E [27]. Erythrocyte vitamin E concentrations are also lower in hypercholesterolemics, even when plasma levels were similar [25], highlighting that plasma levels are a poor reflection of vitamin E status. Although vitamin E supplementation can increase plasma vitamin E levels in both normolipidemic and hyperlipidemic subjects [28], concentrations are maintained within a narrow range regardless of intake.

Since vitamin E distribution is related to the kinetics of lipoprotein metabolism, abnormalities of the plasma lipid status associated with hyperlipidemia may affect functional vitamin E status and may have implications related to the activity of those cells which are responsive towards vitamin E. Recently we have used stable-isotope labeled vitamin E (deuterated α-tocopheryl acetate) biokinetics to investigate vitamin E status in hyperlipidemia [29]. In this study subjects classified as either normolipidemic (total cholesterol < 5.5 mmol/l and triacylglycerol (TAG) < 1.5 mmol/l), hypercholesterolemic (total cholesterol > 6.5 mmol/l and TAG < 1.5 mmol/l), and combined hypercholesterolemic and hypertriglycerideremic (total cholesterol > 6.5 mmol/l and TAG > 1.7 mmol/l) consumed a capsule containing 150 mg deuterium labeled RRR-α-tocopheryl acetate with a standard meal containing 40 g fat. Blood was collected at frequent time intervals over 48 hours, blood components isolated, and tocopherols analyzed by standard methods [30].

We found differences in the uptake of newly absorbed vitamin E into the plasma, individual lipoproteins, and the blood components erythrocytes, platelets, and lymphocytes between the groups [29]. Within lipoproteins, the hypercholesterolemic group secreted chylomicrons with over 300% more α-tocopheryl per particle than the other groups, but there was no difference in the α-tocopheryl content of VLDL. However, the combined hyperlipidemic group had decreased uptake of α-tocopheryl in their LDL. These differences may be due to the transfer of vitamin E to tissues during lipoprotein lipase (LPL)-mediated hydrolysis of VLDL. Hypertriglycerideremia is associated with reduced activity of LPL. Within LDL subfractions there was more newly absorbed α-tocopheryl in larger less dense particles than in smaller dense particles, in line with previous observations [15], suggesting that less dense particles tend to retain their vitamin E. In plasma the combined hyperlipidemic group had decreased uptake of newly absorbed α-tocopheryl. This is not surprising given that LDL is the major carrier of vitamin E in the circulation.

To see whether the differing plasma responses could impact on the delivery of vitamin E to cells, we also looked at the uptake of labeled α-tocopheryl into erythrocytes, platelets, and lymphocytes between the groups. In each blood component there was a differential uptake of newly absorbed α-tocopheryl over the time period in the order normolipidemic > hypercholesterolemic > combined hyperlipidemic. Thus the combined hyperlipidemic group consistently demonstrated reduced uptake of newly absorbed α-tocopheryl into these blood components.
A number of mechanisms are thought to play a role in cellular vitamin E uptake [31]. Cells containing LDL receptors can take up vitamin E by the LDL receptor pathway. As lymphocytes contain LDL receptors [32], they may obtain their vitamin E in this way. LDL receptors [32] have not been found in platelets; however, studies have suggested that the apoB moiety of LDL does interact with an unidentified receptor on the platelet membrane which allows for the transfer of lipids [33]. Since some hyperlipidemic subjects have reduced binding activity of LDL receptors [34] this may influence their vitamin E uptake, similar to what we have observed. The impaired uptake of α-tocopheryl into platelets and lymphocytes in hyperlipidemic subjects could contribute to the altered platelet and lymphocyte function commonly observed in hyperlipidemia, however further work is necessary to investigate a potential link between platelet and lymphocyte function, and vitamin E status within these components.

In conclusion, hyperlipidemia is associated with differential plasma and lipoprotein uptake of newly absorbed α-tocopheryl, and decreased uptake into blood components. The mechanism for these differences may originate from the transfer of α-tocopheryl during lipoprotein hydrolysis and the formation of LDL. Impairment of vitamin E status in hyperlipidemia could potentially influence the function of critical cells in atherogenesis and therefore further increase the risk of CHD.

References


