Vitamin E: A Current and Never Ending Issue

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The study of the physiological functions of vitamin E began more than a hundred years ago and it has generated hundreds of scientific works; however, there are a lot of aspects that still remain not so clear: (1) Due to the capacity to catch free radicals and by virtue of its antioxidant properties it is believed that vitamin E would have a relevant role in the prevention of carcinogenesis and atherosclerosis. (2) Llorens et al.’s work (3) which is published in this issue of the Journal evaluates the effect of vitamin E over oxidative stress in an animal atherogenic model, as a result of hyperfibrinogenemia. Authors show that the supplement with vitamin E increases the levels of nitric oxide (NO), superoxide dismutase enzymes (SOD) and promotes a recovery of endothelial denudation and a decrease of intimal thickness in rats with hyperfibrinogenemia. The final conclusion is that vitamin E would stop the chain reaction started by free radicals and as a consequence would decrease the superoxide anion, stimulating an increase in the nitric oxide bioavailability and normalizing the concentrations of plasma fibrinogen.

The potential role of vitamin E in the prevention of cardiovascular disease was originally proposed by Gey (4) in the “antioxidant hypothesis of atherosclerosis”. This hypothesis considers the effect of imbalance between pro-oxidant and antioxidant substances in the oxidative stress associated to different pathological processes. (2.5). This theory was perfectly complemented with the following hypotheses. Steinberg’s hypothesis which refers to LDL role and its oxidation in the subendothelium (6), Ross’ hypothesis about cellular interaction in response to inflammation (7) and Jackson’s hypothesis which describes cytokine response in the arterial inflammatory process. (8)

Actually, what we call vitamin E is a group of eight liposoluble complexes, named α, β, γ and δ-tocopherols and α, β, γ and δ-tocotrienols. The commercial forms of vitamin E contain natural RRR- α-tocopherol and synthetic α-tocopherol, or a mixture of both. The different vitamin E complexes have different bioavailability, they are carried in plasma by HDL and LDL lipoproteins creating complexes and protecting them from peroxidation on the part of free radicals. (9) At molecular level, the main role of vitamin E is the protection against lipid peroxidation, role that is performed through its function of hydrogen donor to liperoxide radicals. One of the main actions of vitamin E results in the protection against LDL oxidation, an undeniable step at the beginning of the atherosclerotic process. Beyond this function, more recently and through basic studies, vitamin E is associated to the decrease of the atherosclerotic process due to the inhibition in smooth muscle cells proliferation, the maintenance of a normal endothelial function, the decrease in levels of soluble adhesion molecules, inhibition in secretion of reactive oxygen species (ROS) and proinflammatory cytokines as interleukin (IL)-6, la IL-1 and tumor necrosis factor-alpha (TNF-α). (10) This last function is mediated through nitric oxide bioavailability which suppresses the expression of several genes in proinflammatory molecules. The action of vitamin E in the inhibition of plasminogen activator inhibitor (PAI-1) and platelet aggregation was also described. (9) Likewise, there are works that associate vitamin E to synthesis regulation and enzyme expression related to cholesterol synthesis (hydroxymethylglutaryl-CoA reductase), phospholipases, cyclooxygenases and LDL receptors.

Despite the extensive scientific evidences related to the numerous atherogenic actions of vitamin E, there is a real discrepancy between these actions and clinical study results in primary and secondary prevention, although in many of them a decrease in biomarkers associated to cardiovascular risk was observed, a decrease in mortality was not verified. On the other hand, most of the observational studies describe a negative association between the consumption of vitamin E (whether from the diet or dietary supplements) and events (fatal or nonfatal) of cardiovascular disease (myocardial infarction and/or cerebrovascular accident). Different meta-analyses which were done from the main observational studies have shown that after adjusting the results due to different variables (age, energy consumption) a minor incidence of coronary disease when increasing the dosis of vitamin E was verified. (11) With more strict adjustments, the association is only significant for women. (12) However, most of the randomized clinical trials did not confirm a protective effect of vitamin E supplement over cardiovascular disease, though in some primary and secondary prevention trials, a mortality risk reduction due to cardiovascular disease has been communicated in patients treated during long periods and with high dosis of vitamin E.

To what is attributed the inconsistency between evidence from cohort studies and results from randomized clinical trials? Some of these discrepancies arise from the different ways of vitamin administration (from food, dietary supplements, pharmaceutical forms), different ways of informing the consumption (self-administered surveys, food-cooking), different treatment durations.

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Moreover, we should not ignore the fact that metabolism of vitamin E is intimately associated to that one of lipoproteins and, nevertheless, most of the prospective studies have not evaluated the lipid-lipoprotein profile in patients. Another factor of relevant importance is that an important interaction between different antioxidant agents is produced in the organism, synergism that has not been considered in some studies. Seasonal variations in the consumption, variations in the treatment of serum samples for the evaluation of α-tocopherol plasma concentration or the different bioavailability of molecular variants of vitamin E which constitute pharmaceutical forms have not been taken into account.

The concept that the action of antioxidant substances is mainly shown in early stages of cardiovascular disease arises above all these limitations; in fact, there were differences in the protective effect between young and old people. (13) However, most of the studies, up to now, have included people of mean age and elder ones. It is important to consider that a pro-oxidant state with high ROS production is associated mainly to the beginning of the atherosclerotic process more than with the crucial process of infarction or cerebrovascular accident, which are the analyzed events in most of the observational and randomized clinical studies. Llorens et al.’s work (3) puts emphasis on these protective actions of vitamin E in early stages of the atherosclerotic process which is associated to an inflammatory phenomenon. Many studies that included patients with no evidences of oxidative stress could have diluted the beneficial results in this therapy. Long-term studies which include populations with low oxidative stress and/or inflammation and with determinations such as those presented in this work would allow a more precise evaluation of the benefits of vitamin E therapy.