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LETTERS

On the antiatherogenic effects of vitamin E: the search for the Holy Grail

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In a recent edition of *Vascular Health and Risk Management*, Kirmizis and Chatzidimitriou have published a review article, "Antiatherogenic effects of vitamin E: the search for the Holy Grail".

Beside a general evaluation of the literature on vitamin E and CVD prevention, the authors pointed out the possibility that vitamin E therapy may have particular efficacy in kidney patients. In this sense, they may represent an elective population with high susceptibility to such a secondary prevention effect, that was not identified in other cardiovascular (CVD) patient populations studied in the largest randomized controlled trials. The SPACE study,[1] indeed, provided one of the most striking findings in support of this assumption.

The reason for this could be inherent to a defect in the levels and metabolism of vitamin E in kidney patients documented in previous studies,[2,3] but also in the higher demand of vitamin E that these patients may have as a consequence of the exposure to chronic inflammation and uremic toxicity. This higher than normal demand of vitamin E may translate into a higher need for antioxidant protection, but also of other biological functions of this vitamin that include homeostatic effects on genes involved in immuno-inflammatory and vascular protection pathways.[4]

The authors have highlighted the unconventional vitamin E therapy that some of these patients follow while treated with extracorporeal hemodialysis therapy (HD). This consists of the use of a special biomaterial developed to produce hollow-fiber hemodialysesrs that are coated on the blood surface with a layer of *all-rac*-α-tocopherol, ie, the synthetic form of vitamin E that predominates in our tissues and body fluids.[4,5] These hemodialyser membranes, also known as vitamin E-modified membranes, were developed in the 1980s in Japan as cellulosic membranes that were introduced in the clinical practice in the early 1990s in Japan and then in Europe. The first clinical observation on these innovative membranes was published in a peer-reviewed journal on 1997.[6] In recent years, this cellulosic prototype has been substituted with a new generation of vitamin E-modified (or -interactive) membranes that possess the highest depurative and biocompatibility standards in HD being produced using a polysulfone-like fiber backbone with an advanced filtration geometry. Other than biocompatible, these synthetic membranes have now a well characterized antioxidant activity profile that was recent described and quantitated *in vitro*.[7]

However, this should not lead to consider the antioxidant activity of these dialysers as fully available for an antioxidant effect *in vivo*, during the extracorporeal circulation.

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Actually, since from the first researches by us and other groups in the late 1990s, it was clear that the clinical effects of these membranes could not be explained simply with the concept that the chromanols bound to the dialysis membrane surface may produce an *in vivo* scavenging effect on peroxyl radicals, ie, producing an antioxidant therapy effect.

In other words, the antioxidant activity as well as the other beneficial properties of this vitamin E (bound to the dialyser membranes), are probably different from those of the vitamin E form introduced with the diet or supplements, which is present in the circulation within the lipoprotein particles and in the cell membranes.

Thus, the interpretation of possible therapeutic mechanisms by these modified membranes needs more careful dissection and further studies aimed to verify underlying events. To explain the benefical effects of these membranes reported in literature, they have used expressions such as "pharmacokinetic factors", "the type of the α-T molecule used", "form of the drug" or "pharmacokinetic conditions", which are obviously inappropriate in this context and may generate confusion in the readers.

In the case of these membranes, indeed, the form of vitamin E that should be taken into account is exclusively that present in synthetic coating on the blood surface of the hollow fiber, ie, *all-rac*-α-tocopherol, and this vitamin E form does not seem to be released even under drastic *in vitro* recirculation conditions.[7] Thus, there is no reason to discuss clinical effects of vitamin E-modified membrane dialysers in terms of "pharmacokinetics".

As Kirmizis and Chatzidimitriou briefly discussed in their review paper, the antioxidation and anti-inflammatory protection claimed in several studies on these membranes are probably the result of a complex series of effects. According to the available evidence in literature already reviewed by us[8,9] and others,[10] even the previous generations of less biocompatible (cellulosic) vitamin E-modified hemodialyser membranes were observed to produce a better control of antioxidant parameters and lowered oxidative stress markers,[11–14] but at the same time these membranes were found to provide a better control of leukocyte activation and apoptotic death,[8,15,16] of erythrocyte integrity and lifespan,[17,18,a] and to afford higher protection of low-density lipoproteins and endothelial cells.[19,20] Probably, the interaction of all these effects is responsible for the improved CVD outcome observed in a series of promising small clinical studies that examined aortic calcifications,[21] carotid atherosclerosis[17,22] and the nitric oxide-dependent vasodilation response during HD.[23]

In conclusion, it is my belief that all these effects and the efforts made by the authors to explain them in this review paper can be summarized in the concept of "superior biocompatibility" that these vitamin E-modified membranes may have with respect to several other dialyser membranes particularly in the recent interactive polysulfone-based version.

Disclosure

The author reports no conflicts of interest in this letter.

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Reply to Galli letter

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We thank Dr Galli for his interest in our paper[1] and his useful remarks. We also appreciate his encouraging comments on our concerns regarding the possibility that the benefits from the α-T supplementation treatment might be accentuated particularly in special patient populations, such as diabetics or end-stage renal disease patients, ie, patients with high degrees of both oxidative stress and chronic inflammation. Furthermore, in accordance to the comments on vitamin E-modified membrane dialyzers pointed out in the letter, we ourselves have stated in our paper the importance of *in situ* action of the membrane-bound α-T, arguing that "the beneficial effects of the membrane-bound α-T probably take place through the protection it provides to circulating leukocytes against their repeated activation by the otherwise bioincompatible synthetic dialysis membrane and the abatement of the inflammatory reaction might secondarily lead to the antioxidative effects of α-T". Therefore, in order to avoid any confusion, we would like to underline that we agree that any discussion on "pharmacokinetics" refers exclusively to α-T supplementation studies and does not apply in vitamin E-modified membrane dialyzers.

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