



## VITAMIN E & CHRONIC DISEASES: FROM RUGS TO RICHES ?

### INTRODUCTION

Ever since its discovery in 1992, vitamin E has been the subject of controversy and indeed, for several decades many scientists were not even sure as to whether vitamin E was an essential nutrient for humans. It was not until the 60's that deficiency states were documented in humans and it was not until the 80's and 90's that scientists finally understood the crucial role of vitamin E in the prevention of long-term oxidative damage to body cells and tissues. Today, vitamin E has become one of the hottest topics in the nutrition research and practice arena. The emerging concepts indicate that vitamin E has an important role to play not only in the preventive but also the therapeutic aspects of disease. In this regard, the purpose of this Update is to highlight some recent findings in this area of nutrition.

### Vitamin E in the Treatment of Alzheimer's Disease

One of the newest and most exciting developments in vitamin E research is the discovery that high doses of this vitamin may help to slow the loss of function that occurs in Alzheimer's disease. Researchers from 23 US medical centers recently completed a trial in which 341 patients with moderately severe Alzheimer's disease were randomly assigned to receive one of four treatments: vitamin E (2000 IU / day), selegiline which is also being tested as a possible treatment for Alzheimer's disease, both vitamin E and selegiline, or an inactive placebo.<sup>1</sup> The primary outcome of the study was the time to occurrence of any of the following : death, institutionalisation, loss of the ability to perform basic activities of daily living, or severe dementia. The investigators specifically chose these outcomes because they reflect the loss of the ability to function independently - an important practical consideration for Alzheimer's patients and their families.

Both selegiline and vitamin E slowed the progression of functional deterioration significantly ( $p < 0.01$ , median time for selegiline = 655 days, for vitamin E 670 days or combination therapy 585 days) as compared with the placebo group (440 days). The patients in the three treatment groups, therefore reached the study endpoints several months later than those in the placebo group. The results of this study indicate that vitamin E may be of value in the treatment of Alzheimer's disease patients – probably as one component of a combined strategy to slow the course of the disease.<sup>2</sup>

Further trials are needed to determine whether vitamin E might also be helpful in delaying the onset of Alzheimer's disease in people who have not yet developed any of the obvious symptoms.<sup>3</sup> It should be noted that there was no difference in the reported beneficial effects between the groups receiving the combination or individual therapy. The absence of an additive effect of treatment may be due to either the two agents exerting their effect through the same mechanism with each agent providing a maximum benefit or to the two agents exerting their effect through an independent mechanism, but the disease was too progressed for an additive effect to be shown. Alternatively, one agent may have interfered with the absorption of the other, thus resulting in an effect that was not additive.

It is also to note that in this study there was no improvement in cognitive test scores in any of the treatment groups. Additionally, falls and syncope were significantly more frequent in the treatment groups, especially the group receiving the combination treatment as compared to

placebo. These events, however, did not lead to the discontinuation of any of the treatment modalities and the authors concluded that each agent alone was relatively well tolerated by the patients. Despite these limitations, the reported findings remain of great interest, because of the important clinical nature of the documented outcomes and also because no other treatment of such patients has shown similar benefits.

The effect of vitamin E on Alzheimer's disease is probably attributable to the vitamin's antioxidant activity. There is evidence that oxidative mechanisms may play a role in the pathological changes characteristic of Alzheimer's disease.<sup>3</sup> Several studies have found evidence of increased oxidative damage, including increased lipid peroxidation and oxidative damage to DNA in patients with this disease.<sup>4-8</sup>

### **Vitamin E and Immune Function in the Elderly**

It is well known that the proportion of elderly people in the developed and developing world is continuously increasing with major and very significant demands on health care costs. In France for instance, although the elderly population represents about 17 % of the total population, nearly half of the health care resources are used by the elderly primarily due to chronic diseases and increased susceptibility to infections. In general, aging is well known to be associated with a reduction in immune responses such as decreased delayed hypersensitivity, decreased lymphocyte response to antigens, low levels of sereconversion, reduced interleukin-2 production and decreased antibody titre after vaccination.

Nutrition plays an important role in the normal functioning of the immune system, and vitamin E may be particularly crucial. Several years ago, researches from Tufts University demonstrated that short-term (one month) supplementation with high doses of vitamin E could improve several measures of immune function in healthy elderly subjects.<sup>9</sup> More recently, a longer term study confirmed and extended these findings and showed that beneficial effects could occur with more moderate levels of vitamin E supplementation.<sup>10</sup> In this study, 88 healthy elderly people were randomly assigned to a placebo group or to groups consuming 60, 200 or 800 mg /day of vitamin E. After four months, supplementation with vitamin E improved several clinically relevant measures of cell-mediated immunity, such as the response to immunisation against hepatitis B and tetanus. The best results were obtained at a vitamin E dose of 200 mg / day. During the study, the incidence of infections in subjects taking vitamin E was 50 % lower than that in the placebo group. On this basis the authors recommended increasing the intake of vitamin E for elderly people.

In agreement with these findings, this year a large (n = 755; 2 x 2 factorial design), randomised, double blind placebo controlled trial of two years duration in institutionalised elderly (>65 years), has shown that the administration of a micronutrient formulation containing trace elements (zinc and selenium) as well as vitamins (beta-carotene, vitamin C and vitamin E) had a beneficial overall effect on defined immunological parameters. Although the nature of the supplement precludes the definition of the effect of the individual nutrients in it, the trial nevertheless underscores the importance of micronutrients in optimal immune function. The trial specifically showed that antibody titres after influenza vaccine were higher in the groups that received trace element supplements alone or in combination with vitamins, whereas the vitamin supplemented group had significantly lower antibody titres (p<0.05). Furthermore, the number of patients without respiratory tract infections was higher in the group that received trace element supplements (p<0.06). However, the micronutrient supplements administered had no effect on the incidence of urogenital infections. These findings are not only of potential public health importance, as the authors conclude, but also emphasise the care that needs to be exercised in terms of recommendations for the supplemental use of micronutrients in relation to immune function<sup>11</sup>.

## Coronary Heart Disease

Studies have shown that vitamin E may also help to reduce the risk or slow the progression of coronary heart disease. The vitamin appears to be of value both in healthy people and in those who already have established heart disease. In most instances, scientific studies have shown protective effects primarily for high doses of the vitamin greater than those that can be obtained from the diet.

The first major studies that provided compelling evidence for a protective effect of vitamin E on coronary heart disease were two very large studies of middle-aged U.S. health professionals published in 1993 by researchers from the Harvard School of Public Health.<sup>12, 13</sup> In these studies, which involved more than 80 000 women and more than 40 000 men, those who had used single-entity vitamin E supplements (generally containing at least 100 IU of vitamin E) for two or more years had a lower risk of myocardial infarction than those who did not use supplements. Among men, vitamin E supplementation was associated with a 37 % reduction in heart disease risk; among women 41 %. In both studies, vitamin E intake from dietary sources or from multivitamins was not associated with any protection against heart disease, presumably because the amount obtained from these sources is far lower than that provided by single-entity supplements. Dietary vitamin E intakes are generally less than 15 IU / day; multivitamins provide 30 IU / day; single entity supplements usually provide more than 100 IU / day.

The association between vitamin supplementation and a reduced risk of heart disease is not limited to middle aged people. A 1996 U.S. study has shown a similar relationship in the elderly – the age group at highest risk of coronary heart disease.<sup>14</sup> In this study, which involved more than 11 000 people aged 67 and older who were followed for up to eight years, those who took vitamin E supplements had a lower rate of death from coronary heart disease and a lower rate of death from all causes than those who did not take supplements.

More specifically, vitamin E supplement users had a 47 % reduction in the risk of death from coronary heart disease when compared with non-users of supplements. Long-term users of vitamin E supplements (those who reported supplement use at two different interviews, conducted two years apart) had an even lower risk of dying from heart disease. So did people who took both vitamin E and vitamin C – a finding that makes good biological sense, since vitamin C has been shown to reinforce the antioxidant effect of vitamin E.

## Secondary Prevention

Vitamin E may be of value in both the primary and secondary prevention of coronary heart disease. The term *primary prevention* refers to prevention of the onset of disease in healthy people; *secondary prevention* refers to prevention of further damage in people who have already shown signs or symptoms of the disease.

The potential benefit of vitamin E supplementation in secondary prevention of coronary heart disease was demonstrated by a recent study from the United Kingdom.<sup>15</sup> In this study, which is known as CHAOS (for Cambridge Heart Antioxidant Study), 2 002 patients with known coronary disease were randomly assigned to received vitamin E supplements (either 400 or 800 IU / day) or an inactive placebo, and they were observed for about a year and a half.

Vitamin E supplementation led to a statistically significant reduction in the risk of cardiovascular death and non-fatal heart attacks combined. (41 vs 64 events : Relative Risk (0.53 (95 % confidence interval (CI) 0.34 – 0.83; P = 0.005) This was due to a large drop in the risk of non-fatal heart attacks. (14 vs 41; RR 0.23; CI 0.11 – 0.47; P = 0.005) The effect of vitamin E on the risk of non –fatal heart attacks was detectable after only 200 days of supplementation.

However, there was a non-significant excess of cardiovascular deaths in the vitamin E supplemented group (27 vs 23 deaths; RR 1.18; CI 0.67 – 2.27; P <0.61). All cause mortality was 36 of 1035 vitamin E treated patients and 27 of 967 patients treated with placebo. Most of the cardiovascular deaths occurred early (before 200 days) in the follow-up

period before any beneficial effect of vitamin E on atheromatous plaques could have occurred. Whether, therefore, there was a true adverse effect on early mortality must await the confirmation of these findings as well as the findings of longer-term trials which have mortality as their primary end point. The authors conclude that in patients with angiographically proven symptomatic coronary atherosclerosis, vitamin E treatment reduces the rate of non-fatal heart attacks. They also urge further studies for the better definition of the effects of vitamin E supplements on early cardiovascular deaths.

Another study that indicates that vitamin E supplementation may be beneficial for patients with coronary heart disease was conducted at the University of Southern California.<sup>16</sup> In this study 156 patients with previous coronary bypass surgery who were participating in a controlled trial of a cholesterol lowering drug combination were asked about their self-chosen use of dietary supplements. Those who consumed more than 100 IU / day of vitamin E in addition to the cholesterol-lowering drugs showed less progression of the narrowing in their coronary arteries than those with lower vitamin E intakes. Thus, vitamin E may be of value as adjunctive therapy in patients who are receiving drug therapy for existing coronary disease.

In a very similar vein, the results of a long-term (4 years duration), large (n = 3 657), currently on-going, randomised, two-by-two factorial design, placebo controlled clinical trial (the MICRO-HOPE trial) are being awaited with interest and should become available within the next three years. The trial compares the effects of an ACE inhibitor and vitamin E on clinical outcomes in patients with diabetes [prevention of diabetic nephropathy, cardiovascular disease and microalbuminuria, and the development of microalbuminuria in normoalbuminuric subjects as well as cardiovascular death, myocardial infarction, and stroke (MICRO)]. The diabetic subjects are a subset of the 9451 high-risk subjects enrolled in the Heart Outcomes Prevention Evaluation study (HOPE) which evaluates the effects of an ACE inhibitor and vitamin E on major cardiovascular events (cardiovascular death, myocardial infarction, and stroke).

### **Can Vitamin E Help to Prevent Cancer ?**

Most of the scientific evidence about vitamin E concerns heart disease rather than cancer. Scientific studies on the role of antioxidant nutrients in cancer have focused primarily on beta-carotene rather than vitamin E. However, vitamin E may also have an important role to play in cancer prevention. In fact, the results of two large epidemiological studies suggest that the use of relatively high doses of vitamin E may be associated with a reduced risk of at least two common types of cancer.

In one of these studies<sup>17</sup>, researchers compared the vitamin E intakes of more than a thousand oral cancer patients with those of healthy people. They found that people who had ever regularly used single-entity vitamin E supplements for a period of six months or more had half the risk of oral cancer seen in non-users of supplements. In the other study, which focused on lung cancer in non smokers, the use of vitamin E supplements was associated with a 45 % decrease in lung cancer risk.<sup>18</sup>

The findings of these two studies should be interpreted with caution, because the studies were observational rather than experimental. The study participants made their own decisions about whether to use supplements – they were not assigned randomly to the use or non-use of vitamin E. In fact, the one large-scale controlled trial of vitamin E supplementation and lung cancer did not show a beneficial effect of supplementation.<sup>19</sup> It is uncertain, however, whether this finding reflects a true lack of benefit of vitamin E or whether the dose used in this trial (50 mg / day) was inadequate.

## Why is Vitamin E Important ?

The ability of vitamin E to inhibit a variety of seemingly unrelated disease processes can probably be attributed to its antioxidant activity. As an antioxidant nutrient, vitamin E plays a crucial role in the complex system of defenses by which the body protects itself against free radicals and other oxidant substances.

In the case of atherosclerosis, vitamin E probably acts at least in part by inhibiting the oxidation of low-density lipoproteins (LDL) in damaged arteries. LDL is one of the lipoproteins that carry cholesterol and other fatty substances through the bloodstream. High levels of LDL are associated with an increased risk of coronary heart disease, but the chemical condition of LDL may be as important as the amount. Recent studies suggest that LDL must be converted into its oxidised form in order to exert adverse effects. Vitamin E taken in large doses has been shown to inhibit the oxidation of LDL in human volunteers.<sup>20, 21</sup>

Vitamin E may also protect against coronary heart disease by other mechanisms. For example, vitamin E may have beneficial effects on platelets that complement those of aspirin, helping to prevent the blood clots that trigger heart attacks and the most common type of stroke.<sup>22, 23</sup>

Vitamin E is also of interest because of its newly emerging role in various phases of the immune response. Immune and inflammatory responses are now recognised as having a major role in the atherogenic process. The vitamin E modulation of these responses suggests a possible link for the beneficial effect of vitamin E on atherosclerosis.

## The Safety of Vitamin E

The potential uses of vitamin E in disease prevention may require doses considerably higher than the amounts usually present in the diet. The safety of these relatively large doses is therefore an important consideration.

In general, vitamin E has a remarkably good safety record. Extensive reviews of the medical literature have concluded that doses of more than 50 times the recommended allowance are safe for long periods of time.<sup>24-27</sup> In clinical trials in older people with Alzheimer's disease or Parkinson's disease, the very high dose of 2000 IU / day was well tolerated by most subjects for as long as two years.<sup>1, 7</sup>

Formal safety evaluations have confirmed the safety of doses of 800 IU / day in elderly subjects<sup>28</sup> and 900 IU / day in young adults.<sup>29</sup>

Certain individuals, however, may not be able to take high-dose vitamin E supplements safely because of the presence of chronic medical problems or the use of medications that are incompatible with vitamin E. Specifically, patients who expect to have surgery within the next two weeks or who are recovering from surgery, those who are taking anticoagulant medications, those with vitamin K deficiency and those with the hereditary eye disease retinitis pigmentosa should not take vitamin E supplements except on the advice of a physician.<sup>25, 30, 31</sup>

## How Much Vitamin E Do People Need ?

The question of how much vitamin E people need for optimal health is a very difficult one to answer. In fact, there may never be a single answer to this question because different amounts of vitamin E may be needed for different purposes.

In general, however, it appears that doses greater than 100 mg per day may be needed to produce significant protective effects against cardiovascular disease and other degenerative diseases of aging and to optimise immune function in older adults. This is far more vitamin E than can be obtained from even an excellent diet. It has been calculated that a diet meeting all the current guidelines for the prevention of chronic diseases would provide about 18 mg / day of vitamin E.<sup>32</sup> According to one recent U.S. survey,<sup>33</sup> mean vitamin E intakes in

various age groups of men range from 9-12 mg / day; among women, typical intakes are about 6-8 mg / day. If the potential benefits of vitamin E in disease prevention are to be realised, supplementation – or perhaps food fortification will be needed.

Research is also needed to assess the potential benefits of more moderate dosages of Vitamin E , or food fortification, over much longer periods and from a younger age. Most studies have only tested the benefits of vitamin E supplements in high-risk age groups for the emergence of coronary heart disease, or in subjects with established coronary artery lesions.

## CONCLUSION

In conclusion, the accumulating evidence is largely confirmatory of a potentially beneficial role for vitamin E both in the prevention and treatment of disease. It would, however, be rather simplistic and irresponsible to impart the impression that vitamin E can exert its beneficial effect in the absence of overall sound and correct nutrition. At present and for certain defined conditions vitamin E supplements may be seen as an adjuvant to, rather than a replacement for, sound and correct nutrition. Future studies will no doubt close the gaps in our current knowledge and put greater perspective on the role of this vitamin in the prevention of chronic disease and the dose(s) needed to derive such benefits.