

Should High-Dose Vitamin E Supplementation Be Recommended to Diabetic Patients?

The Diabetes Control and Complications Trial (DCCT) has convincingly shown that complications of diabetes can be delayed and reduced by maintaining tight glycemic control (1). Over the last decade, there has been a significant interest in oxidative stress and its role in the development of complications in diabetic patients (2,3). Various studies have documented elevated blood levels of markers of oxidative stress in diabetic patients, particularly in patients with poor glycemic control (2,3). The increase in the level of oxidative stress in newly diagnosed diabetic children and those with no complications (4–7), as well as in vitro studies (8–10), suggest that the elevated levels of oxidative stress associated with diabetes may not be due to the complications. Oxidative stress could originate from a variety of mechanisms, such as excessive oxygen radical production from the auto-oxidation of glucose (11), glycosylated proteins (12), stimulation of cytochrome P450-like activity by excessive NADPH produced by glucose metabolism (8) and from the ketone body acetoacetate (13), and glycation of antioxidative enzymes, which limits their capacity to detoxify oxygen radicals (2,3).

It is not yet clear whether oxidative stress plays any role in the development of complications in diabetic patients. To explore this question, researchers have determined the effect of antioxidant supplementation on oxidative stress and markers of complications in a diabetic animal model. In diabetic animals, many studies demonstrate a reduction in oxidative stress and complications after antioxidant supplementation (14–20). These studies provide support for the use of antioxidant supplementation in reducing the level of oxidative stress and slowing or preventing the development of complications associated with diabetes. However, in diabetic patients, studies on the effect of vitamin E supplementation are limited to examination of blood levels of biochemical markers of oxidative stress and other risk factors, such as glycosylation of proteins,

as assessed by the glycated hemoglobin and lipid levels, and oxidative susceptibility *ex vivo* of LDL (21–29). The results of these studies are not conclusive. Vitamin E supplementation of diabetic patients has been shown to decrease (22–24) or have no effect on (25,26) blood glycosylated hemoglobin, to reduce (22–24,27) or have no effect on (25) triglyceride levels, and to lower levels of lipid peroxides (28) and thromboxane-B₂ (28,29) and the oxidative susceptibility *ex vivo* of LDL (25,26).

In this issue of *Diabetes Care*, Dr. Bursell and colleagues (30) have for the first time determined the effect of vitamin E supplementation on a biophysical parameter *in vivo*, *i.e.*, retinal blood flow and renal hyperfiltration in type 1 diabetic patients. These investigators took advantage of tools used to measure retinal blood flow to assess a change in the hemodynamic function as the end point to determine the efficacy of vitamin E supplementation in diabetic patients. The results of this study show that high-dose (1,800 IU/day) vitamin E treatment for a short duration of 4 months normalizes retinal blood flow and renal hyperfiltration in type 1 diabetic patients who had <10 years of diabetes and no or minimal diabetic retinopathy and/or microalbuminuria. The improvement in the retinal blood flow could be due to better blood rheology and modification in endothelial cell function associated with the effect of vitamin E on activation of protein kinase C isoforms (14). This study lacks data on the blood level of lipid peroxidation products or other markers of oxidative stress (30). Such data would have provided a mechanistic link between reported blood flow improvement and the potential reduction in the oxidative stress level after vitamin E supplementation of diabetic patients. Nevertheless, this study has clearly demonstrated that vitamin E supplementation can normalize the blood flow in diabetes. Such physiological normalization in the early stages of diabetes could ameliorate the risk for development of retinal or renal complications.

The most important question is whether high-dose vitamin E supplements, such as the 1,800 IU used in this study, should be recommended to diabetic patients. The recommended daily allowance/intake (RDA) of vitamin E is 30 IU (31). Diabetic patients, who experience increased levels of oxidative stress, need higher levels of antioxidants, such as vitamin E, to fight the toxic environment created by reactive oxygen species. Is it justifiable, however, to recommend that diabetic patients take a pharmacological dose of vitamin E when the evidence thus far suggests, at best, only a marginal cellular vitamin E-deficiency association with diabetes (4,32,33)? Available data does not demonstrate any evidence for vitamin E toxicity, even with supplementation of vitamin E as high as 3,200 IU/day for 9 weeks (34). However, there are no data on whether any imbalance or deficiency of other nutrients occurs in individuals being supplemented with such a large dose of vitamin E over a long time period.

At present, there is no data for or against these concerns for the high dose of vitamin E supplementation. Again, it is difficult to suggest what dose of vitamin E supplementation is ideal without clinical trials in which diabetic patients are supplemented with varying doses of vitamin E. However, such a clinical trial is not only time consuming and expensive, but if done, could be inconclusive because diverse markers of oxidative stress and complications may respond differently to a specific dose of vitamin E supplementation. Since the RDA for vitamin E is only 30 IU/day (31) and there are no reports of severe vitamin E deficiency in diabetes, it seems reasonable to evaluate the long-term benefits of vitamin E supplementation at a modest dose, in the range of 100–400 IU/day.

The clinical trial data presented by Dr. Bursell and his colleagues in this issue of *Diabetes Care* (30) suggest that the supplementation of diabetic patients with vitamin E, when used in conjunction with intensive

insulin therapy, can potentially reduce the risk for the development of retinopathy and nephropathy in type 1 diabetes. Vitamin E is a lipid antioxidant. Whether the use of vitamin E in combination with an aqueous antioxidant, such as N-acetylcysteine or glutathione, can increase the benefits and efficacy of vitamin E in the improvement of blood flow, and thus reduce the possibility of the development of retinopathy or nephropathy, needs to be investigated.

Unlike type 2 diabetic patients, those with type 1 diabetes have an additional risk factor, i.e., episodes of ketosis or hyperketonemia. Recent studies have demonstrated that hyperketonemia is an additional risk factor in the development of the oxidative stress associated with diabetes (35). The study in this issue observed that the effect of vitamin E supplementation was predominant in type 1 diabetic patients who had poor glycemic control (30). These patients are also likely to have hyperketonemia in addition to hyperglycemia. Therefore, the question arises whether there are subsets of the diabetic population, such as patients with poor glycemic control or type 1 diabetes, that are more likely to show beneficial effects of vitamin E or other antioxidant intervention. This question needs to be considered in future clinical trials of antioxidants and diabetic patients.

In conclusion, the recommendation for the widespread use of high-dose vitamin E for diabetic patients is premature. Similar to the DCCT, researchers need to do a long-term clinical trial with a larger patient population to assess whether vitamin E supplementation of diabetic patients lowers the incidence of development and progression of complications, such as retinopathy, nephropathy, and neuropathy. The economic burden of diabetic patient care for the U.S. in the year 2000 is likely to be close to \$200 billion. Future clinical trials to assess the benefits of low-cost vitamin E supplementation in lowering the risk of complications in the diabetic patient population could significantly reduce the cost of caring for diabetic patients.

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