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thromboxane $A_2$ ($TXA_2$, a vasoconstrictor, also stimulates platelet aggregation) are believed to be important factors in the pathogenesis of diabetic angiopathy.[15] Decreased platelet vitamin E content and increased release of platelet $TXA_2$ have been demonstrated in diabetic rats and IDDM patients.[15,20,21] While vitamin E deficiency is associated with increased platelet aggregation,[15] vitamin E supplementation in diabetic rats[20] and humans[15] normalizes platelet function. In a recent report by Gisinger et al, supplementation of IDDM patients (n = 22) with 400 mg alpha-tocopherol daily for 4 weeks was associated with a significant decrease in platelet $TXA_2$ production stimulated by adenosine diphosphate (ADP) or collagen.[15] The authors suggest that vitamin E supplementation "could be beneficial with respect to platelet-vessel-wall interaction and thus might be promising for the prevention of diabetic angiopathy."[15]

## Vessel Wall Protection

Vitamin E is also involved in the production of another prostanoid, prostacyclin ($PGI_2$), a potent vasodilator and inhibitor of platelet aggregation which is produced by vascular endothelial cells.[16] It has been suggested that reduced production of $PGI_2$ in the vascular wall may be involved in the pathogenesis of macroangiopathy in diabetic patients.[16] In bovine aortic endothelial cells cultured in a high concentration of glucose (associated with decreased $PGI_2$ levels), vitamin E enhanced the production of $PGI_2$ and restored $PGI_2$ production in these cells.[16] The authors speculate that similar effects may occur in diabetic patients and suggest that vitamin E may be one of the key factors involved in the regulation of $PGI_2$ and $TXA_2$ balance (an important determinant of vascular tone) in diabetes and other pathophysiological states.[16]

It is interesting to note that, in a subsequent investigation, the same authors demonstrated that cultured bovine aortic epithelial cells have specific binding sites for d-alpha-tocopherol.[22] Further, high concentrations of glucose reduced d-alpha-tocopherol binding through mechanisms that the authors believe may involve nonenzymatic glycation of endothelial cells or oxidative damage to intracellular constituents.[22]

## Improved Insulin Action Reported

The potential for vitamin E to improve glucose homeostasis is another area of active investigation. In a recent report by Paolisso et al, vitamin E supplementation for 4 months (900 mg/day) was associated with evidence for both reduced oxidative stress and improved insulin action in patients with NIDDM (n = 15) versus well-matched normal controls (n = 10).[23] In the diabetic patients, greater reductions were documented in microviscosity, plasma oxygen production and the ratio of plasma oxidized glutathione (GSSG) to plasma reduced glutathione (GSH) (changes in this ratio may affect beta-cell insulin response to glucose as well as lipid peroxidation in cell membranes).[23] The authors suggest that reduction in the GSSG-GSH ratio, which was associated with a more marked increase in total glucose disposal and nonoxidative glucose metabolism, may increase glucose transport in diabetic patients.[23] In a related study by the same investigators, vitamin E supplementation for 3 months (900 mg/day) in elderly NIDDM patients (n = 25) was associated with significant declines in plasma levels of $HbA_1$, lipids (triglycerides, total cholesterol and LDL cholesterol) and apoprotein B.[24] Daily vitamin E administration also reduced plasma glucose and the GSSG/GSH ratio, indicating improved metabolic control.[24] No effects on beta-cell insulin response to glucose were observed.

## Vitamin E Levels in Diabetes

There have been conflicting reports on plasma alpha-tocopherol levels in diabetics.[25-27] Since vitamin E is transported in blood by lipoproteins, plasma vitamin E levels may reflect the amount of lipoproteins available as the carrier, as well as the integrity of the enterohepatic pathway.[26] Abnormalities in the utilization and transport of vitamin E in diabetics was suggested by a study of vitamin E levels in the plasma, platelets and erythrocytes of IDDM and NIDDM patients using high-performance liquid chromatography.[28] In this report, plasma vitamin E levels were significantly increased in diabetic patients compared to controls and were also significantly correlated with plasma cholesterol and apoprotein B concentrations. In the diabetic patients, the plasma ratios of alpha-tocopherol/cholesterol and alpha-tocopherol/apoprotein B were elevated, as were triglyceride levels, compared with controls. However, platelet and erythrocyte alpha-tocopherol levels were not significantly different in the diabetic patients versus controls. The authors suggest that the use and transport of vitamin E within cells may be altered in diabetes, particularly if hyperlipidemia is present.[28]

A direct positive relationship between plasma lipids and alpha-tocopherol concentrations in the lipid component of lipoproteins in diabetic patients was suggested in a study by Kokoglu and Ulakoglu.[1] The authors speculate that the increased levels of alpha-tocopherol in the LDL and VLDL fractions and decreased levels in the HDL fraction may be due to impairment of the LDL receptor mechanism, which regulates the delivery of alpha-tocopherol to cells. In a previous study, the authors demonstrated that nonenzymatic glycosylation of LDL is increased in NIDDM and this process is positively correlated with plasma lipid and lipoprotein levels.[29] Of interest, Martinoli et al found that plasma alpha-tocopherol levels were unchanged in IDDM patients, compared with strictly matched controls.[27] Further, they documented significantly higher plasma alpha-tocopherol levels only in IDDM patients with neuropathy and call for further investigations to delineate if and how vitamin E may play a role in the pathogenesis of diabetic microvascular complications.[27]

## Conclusion

There are several mechanisms whereby vitamin E may be hypothesized to affect the pathogenesis of diabetes: as an antioxidant, as one of the regulators of the vasoactive prostaglandins and as a substance which inhibits platelet aggregation. Studying this micronutrient and its relationship to this common disease may not only add to our knowledge of vitamin E's role in health and disease, but increase our understanding of the molecular mechanisms associated with the pathology of diabetes and provide a new modality in the management of diabetes.

While no specific recommendations can be made at present regarding the role of vitamin E as an agent with a potential to reduce the risk of complications in IDDM and/or NIDDM, future clinical trials involving substantial numbers of patients may take this nutrient from the theoretical to the practical.

**References:** **1.** Kokoglu E, Ulakoglu E. *Diabetes Res Clin Pract.* 1991;14:175-181. **2.** Williamson JR, et al. *Diabetes.* 1993;42:801-813. **3.** Baynes JW. *Diabetes.* 1991;40:405-412. **4.** Low PA, Nickander KK. *Diabetes.* 1991;40:873-877. **5.** Sato Y, et al. *Biochem Med.* 1979;21:104-107. **6.** Karpen CW, et al. *Prostaglandins Leukot Med.* 1982;8:93-103. **7.** Matkovics B, et al. *Horm Metab Res.* 1982;14:77-79. **8.** Collier A, et al. *Diabetic Med.* 1990;7:27-30. **9.** Caballero B. *Nutr Rev.* 1993;51(11):339-340. **10.** Douillet C, et al. *Biochem Med Metab Biol.* 1993;50:265-276. **11.** Costagliola C, et al. *Ophthalmic Res.* 1988;20:308-316. **12.** Leske MC, Chylack LT, Wu S-Y. *Arch Ophthalmol.* 1991;109:244-251. **13.** Hurley D. *Med Trib.* 1994;35(10):1,6. **14.** Ceriello A, Quatraro A, Giugliano D. *Diabetic Med.* 1992;9:297-299. **15.** Gisinger C, et al. *Diabetes.* 1988;37:1260-1264. **16.** Kunisaki M, et al. *Metabolism.* 1992;41(6):613-621. **17.** Ceriello A, et al. *Diabetes Metab.* 1988;14:40-42. **18.** Ceriello A, et al. *Diabetes Care.* 1991;14(1):68-72. **19.** Shoff SM, et al. *Am J Clin Nutr.* 1993;58:412-416. **20.** Karpen CW, et al. *Diabetes.* 1982;31:947-951. **21.** Karpen CW, et al. *Diabetes.* 1984;33:239-243. **22.** Kunisaki M, et al. *Diabetes.* 1993;42:1138-1146. **23.** Paolisso G, et al. *Am J Clin Nutr.* 1993;57:650-656. **24.** Paolisso G, et al. *Diabetes Care.* 1993;16(11):1433-1437. **25.** McMasters V, et al. *Am J Clin Nutr.* 1967;20(6):622-626. **26.** Lewis JS, et al. *Am J Clin Nutr.* 1973;26:136-143. **27.** Martinoli L, et al. *Internat J Vit Nutr.* 1993;63:87-92. **28.** Caye-Vaugien C, et al. *Internat J Vit Nutr.* 1990;60:324-330. **29.** Kokoglu E, et al. *Turk J Med Biol Res.* 1990;1:55-61.

# NUTRITIONAL ASPECTS OF AMBULATORY CARE

## DIABETES AND VITAMIN E

Nutritional management of diabetes has traditionally focused on *macro*nutrients, ie, protein, fat, carbohydrate and fiber. However, in the past decade, an increasing number of investigations have suggested that attention to *micro*nutrients may also be warranted when managing both insulin-dependent and non-insulin-dependent diabetes mellitus (IDDM and NIDDM). While the literature reflects an interest in diabetes and several micronutrients (eg, vitamin C, pyridoxine ($B_6$), thiamine ($B_1$) chromium, selenium), this review will concentrate on the clinical and nonclinical research concerning vitamin E (alpha-tocopherol).

A potential supportive nutritional role for vitamin E in diabetes has been hypothesized and studied intermittently for nearly 5 decades.[1] And, although the specific events behind the development of diabetic complications remain to be elucidated, one current theory posits excess free radical activity as an initiator of pathogenic molecular events. Thus, the theoretical potential exists for vitamin E, the major lipid-soluble antioxidant, to reduce and/or ameliorate some of the complications of diabetes.

### Hyperglycemia and Oxidative Stress

Evidence continues to accumulate linking elevated blood glucose levels with increased oxidative stress in both diabetic humans and animals.[2] It is not known to what extent this increased oxidative load reflects enhanced production of reactive oxygen species (free radicals) or decreased efficiency of free radical scavenger systems.[2,3] As indicators of the heightened oxygen free radical (OFR) activity in diabetes (at present, in vivo OFR activity can only be monitored indirectly) various investigators have demonstrated an increase in conjugated dienes in experimental diabetes,[4] increased lipid peroxide levels in diabetic patients,[5] elevated levels of malondialdehyde (MDA) in experimental diabetes [6,7] and reduced levels of superoxide dismutase (the neutralizing enzyme for the superoxide [$O_2^-$] molecule) in the blood of diabetic humans and the tissues of experimental animals.[4,8] It has been suggested that a free radical process involving peroxidation of lipids in cell membranes may be involved in the altered glucose transport and microangiopathic disease associated with diabetes.[9]

Oxidative stress may also be involved in the pathogenesis of ischemic heart disease which occurs earlier and with greater incidence in diabetics than in nondiabetics.[8,10] Finally, numerous reports have indicated that oxidative damage plays a role in the pathogenesis of cataract in diabetes,[11,12] a debilitating complication which also adds to the already staggering cost of diabetes care, the United States total for which was estimated to exceed $105 billion in 1992[13] with costs in other industrialized countries like Canada proportionate to the population.

Among the mechanisms that have been proposed to explain the increased oxidative stress and free radical activity in diabetes are nonenzymatic glycosylation (glycation) and glucose auto-oxidation.[3,14] It is theorized that accelerated nonenzymatic glycosylation (and the free radicals generated in oxidative reactions) may be one of the mechanisms by which hyperglycemia causes diabetic complications.[9,14]

There are several hypothesized ways that vitamin E may potentially affect the clinical course of diabetes, and not all relate to its antioxidant activity: inhibiting protein glycosylation, normalizing platelet activity and helping to maintain vascular tone through its effects on prostaglandin synthesis.[14-16]

### Inhibition of Protein Glycosylation

The hypothesized link between oxidant stress, nonenzymatic glycosylation and tissue damage occurring in diabetes points toward a possible supportive role for antioxidants in diabetes management.[14] Vitamin E has been shown to inhibit protein glycosylation both in vitro[17] and in diabetic patients.[18] A dose-dependent effect of vitamin E on the reduction of protein glycosylation was demonstrated with supplements of 600 to 1,200 mg vitamin E/day administered to diabetic patients (n = 10) for 2 months, compared to matched controls (n = 10).[18] (Please see figure.) Vitamin E appeared to interfere with glycosylation at a very early stage, ie, at the very first step of the Maillard reaction (oxidative browning), leading Ceriello et al to speculate that administration of vitamin E could be "particularly advantageous."[18] Conflicting results were reported by Shoff et al, who found no relationship between vitamin E intake (at nonpharmacologic doses) and glycosylated hemoglobin ($HbA_1$) levels in persons with (n = 172) or without diabetes (n = 1,980).[19] Attempting to explain why their findings are at odds with those of Ceriello et al, the authors suggest that the association between vitamin E and $HbA_1$ may be because the level of blood glucose control in this patient group was better or it may be "limited to individuals consuming pharmacologic [levels] of vitamin E."[19]

**Effects of vitamin E administration on $HbA_1$**

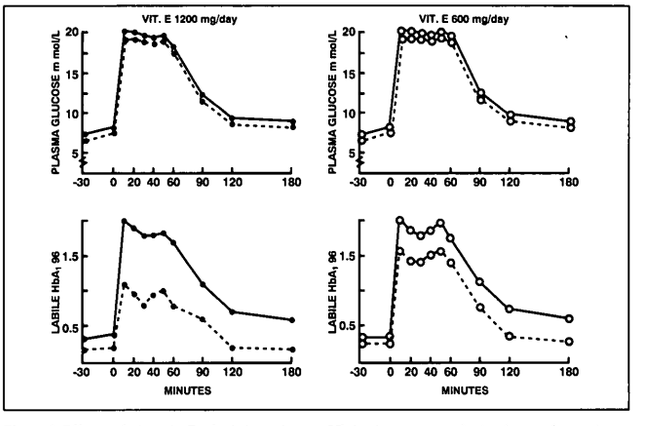


**Figure 1.** Effects of vitamin E administration on $HbA_1$, increments during hyperglycemic clamp in diabetic patients before ( ●—● ) and after ( ●- - -● ) 1200 mg vitamin E/day, and before ( o—o ) and after ( o- - -o ) 600 mg vitamin E/day. Reprinted from Ceriello A, et al. *Diabetes Care.* 1991;14(1);71 with permission of author and publisher. Copyright ©1991 by American Diabetes Association, Inc.

### Normalization of Platelet Activity

Another area in which potential benefits of vitamin E are being evaluated involves platelet function in diabetic patients. Platelet hyperaggregability and enhanced release of