Vitamin E and the Treatment and Prevention of Diabetes: A Case for a Controlled Clinical Trial

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ABSTRACT

Strategies to delay the onset and ameliorate the sequelae of type 2 diabetes are urgently needed in Singapore. Diabetes is accompanied by severe oxidative stress (especially lipid peroxidation) due to increased oxygen free radical production. Oxidative stress in part results from hyperglycaemia, but it may also precede, and accelerate the development of overt type 2 diabetes and then of diabetic complications. Epidemiological evidence indicates low vitamin E intake as a risk factor for development of type 2 diabetes, and small scale human intervention studies have indicated benefit of vitamin E in improving endothelial function, retinal blood flow and renal dysfunction. Animal studies also support its usefulness. The weight of evidence available supports the suggestion that a major double-blind controlled clinical trial of antioxidants in prevention and treatment of type 2 diabetes should be undertaken.

Keywords: Diabetes, Vitamin E, lipid peroxidation, oxidative damage, free radical

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INTRODUCTION

Type 2 diabetes is a major and growing problem in Singapore[1] and novel strategies to delay its onset and to ameliorate the side-effects of poor diabetic control are urgently needed. The purpose of the present article is to marshal the growing evidence that antioxidant interventions could play a significant part in the therapeutic arsenal, and to argue the need for a rigorous clinical trial of this concept.

WHAT IS THE EVIDENCE?

Diabetes is accompanied by severe oxidative stress

Oxygen free radicals and other "reactive oxygen species" are constantly produced in the human body, both by unavoidable spontaneous chemical reactions (such as oxidation of adrenalin, dopamine and tetrahydrofolate)[2] and deliberately, an example of the latter being the production of bursts of reactive species by activated phagocytes (monocytes, macrophages, neutrophils and eosinophils) in order to help kill invading micro-organisms[2,3].

The damage done to biomolecules by reactive oxygen species (*oxidative damage*) is kept in check by a complex network of antioxidant defence and repair systems synthesised within the human body[2]. In addition, certain antioxidants are obtained from the diet[2,4]. One of the best characterised of these is vitamin E, a fat-soluble vitamin that helps prevent damage to lipids by oxygen free radicals[4]. When highly-reactive species attack lipids within membranes or lipoproteins, they set off the chain reaction of *lipid peroxidation*[2]. Vitamin E halts this chain reaction, e.g. it acts as a chain-breaking inhibitor of lipid peroxidation[4]. Elevated lipid peroxidation has been observed in many human diseases, especially in atherosclerosis[5]. Eight different compounds found in the human diet exert vitamin E activity, but the most important is RRR-α-tocopherol, sometimes called d-α-tocopherol[4,6].

Multiple studies (e.g. references 7-13) have shown that type 2 diabetes is accompanied by increased oxidative damage to all biomolecules, especially lipids. Elevated lipid peroxidation in type 2 diabetic patients has been demonstrated by a range of assays, of which the most reliable is probably elevated production of F_2-isoprostanes[9,12,13]. This increased oxidative damage may, at least in part, be a consequence of hyperglycaemia. For example, hyperglycaemia has been shown to increase oxygen free radical production by vascular endothelial cells[14-16] nervous tissue[17,18] the rodent embryo[18,19] and human monocytes[20-22]. The hyperlipidaemia associated with diabetes may also lead to increased lipid peroxidation[23,24] perhaps because an increased lipid load allows lipoproteins to reside for longer periods in the circulation and in vessel walls, giving them a greater exposure to any free radicals

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generated[25]. Hyperketonaemia may also promote lipid peroxidation[26] and glycation of lipoproteins appears to render them more susceptible to peroxidation[27].

The oxidative stress may precede the development of type 2 diabetes

Increased lipid peroxidation can be detected in the early stages of type 2 diabetes, well before the development of any diabetic complications[10,11,28-30]. Since lipid peroxides are well-known to cause tissue damage[2] the possibility arises that nephropathy, retinopathy, endothelial dysfunction and peripheral neuropathy associated with poor diabetic control involve free radical damage[2,7,21,31-36]. It is also possible that elevated lipid peroxidation precedes the development of diabetes. There is a considerable variation in levels of lipid peroxides even in healthy subjects, and it has been proposed that persons with elevated lipid peroxidation may be more prone to develop type 2 diabetes and cardiovascular disease[37-42]. Indeed, Facchini et al[43] commented that lipid peroxidation may be increased in insulin-resistant individuals well before the onset of type 2 diabetes. Gopaul et al[42] found increased lipid peroxidation in Indian Mauritian subjects with impaired glucose tolerance compared with control subjects. In other words, not only may the sequelae of type 2 diabetes (hyperglycaemia and hyperlipidaemia) cause elevated peroxidation, but pre-existing high rates of lipid peroxidation may predispose to diabetes. Such elevated rates may reflect poor antioxidant intake[38-40], but could also involve inherited differences in rates of peroxidation and metabolism of lipid peroxides[37,41,43,44].

Diabetes in animal models involves oxidative stress and can be ameliorated by antioxidants

Most animal studies of diabetes are induced by administration of alloxan or streptozotocin, toxic agents that target β-cells. They are thus essentially models of type 1 diabetes. Nevertheless, such animals show increased lipid peroxidation[45] and several studies indicate that supplementation of them with vitamin E decreases the extent of diabetic complications, including renal damage[36], embryopathy[46], nerve damage[47] and vascular dysfunction[48,49].

However, some more relevant animal models exist. One is the "prediabetic" obese Zucker rat, which exhibits fasting hyperinsulinaemia, impaired glucose tolerance, and increased lipid peroxidation[50,51]. Administration of a pro-oxidant chemical was observed to accelerate the onset of type 2 diabetes in this model[51], although it had no effect on control animals. This suggests that animals already showing insulin resistance could be driven to develop type 2 diabetes by a pro-oxidant challenge. Pro-oxidant challenges could include exposure to free radical-generating toxins[2], and/or insufficient intake of dietary antioxidants such as vitamin E[28,39]. In another animal model, the GK rat, which manifests fasting hyperglycaemia and insulin resistance, administration of vitamin E improved glycaemic control[52].

There is also animal evidence that hyperglycaemia may cause damage to islet β-cells, an event which may play a secondary pathogenic role in type 2 diabetes. The data suggest that free radicals are involved in this effect and that antioxidants such as vitamin E could be beneficial in preventing islet damage[53-55].

WHAT EVIDENCE SUGGESTS THAT VITAMIN E MIGHT BE BENEFICIAL IN HUMANS?

We have already reviewed the data showing that type 2 diabetes in humans is accompanied by increased oxidative damage, even prior to complications. Two important questions arise therefore;

A. In subjects with metabolic syndrome/insulin resistance, could decreasing free radical damage prevent or delay the onset of type 2 diabetes?
B. In subjects with type 2 diabetes, could decreasing free radical damage prevent or delay the development of diabetic complications?

Epidemiological evidence

In susceptible persons, the development of type 2 diabetes appears to be facilitated by lack of exercise, cigarette smoking, and diets rich in calories (especially from saturated fat) and poor in fruits and vegetables[56-58]. Such diets often have low levels of antioxidants[2,59]. Indeed, a low lipid standardised plasma vitamin E level has been proposed as a risk factor for subsequent development of type 2 diabetes[38,39]. Consistent with this, vitamin supplement intake was associated with decreased risk of diabetes development in the National Health and Nutrition Examination Survey I (NHANES I) in the USA[40]. Most of the supplements taken by the study subjects contained vitamin E[40]. Obesity and high fat diets seem to lead to increased free radical generation and lipid peroxidation and low antioxidant levels[60-63]. An inherited defect in the antioxidant defence enzyme catalase was reported to be associated with increased incidence of diabetes[64].

Human intervention studies

What evidence exists to suggest that antioxidants such as vitamin E might be beneficial in the treatment of diabetes? To demonstrate benefit, vitamin E must be administered in doses sufficient to decrease the "extra" oxidative stress associated with diabetes, so that low doses (below several hundred of units per day) are unlikely to be effective (JD Morrow, personal communication and[41,59,65]).

Jialal et al[21,66] supplemented type 2 diabetic patients with 1,200 units/day of d-α-tocopherol for three months. Compared with placebo, this amount decreased both levels of lipid peroxidation and free radical production by circulating monocytes. It also decreased markers of inflammation, including C-reactive protein, (an effect confirmed in another study using 800 units/day of vitamin E for four weeks[67]), IL-1β and IL-6, but had no effect on the extent of protein glycation[21,66]. In another study, 1,800 units/day of α-tocopherol for four months improved retinal blood flow and renal dysfunction in patients with type 1 diabetes without changing glycated haemoglobin levels[32].

The majority of published studies have shown improved vascular endothelial function in diabetic patients treated with vitamin E at doses ranging from 600-1,000 units/day for two to three months[13,68-70]. Other antioxidants such as ascorbate[13,67], and the synthetic antioxidant raxofelast[31] were also effective. Hyperglycaemia has been shown to attenuate endothelium-dependent vasodilation even in non-diabetic adults, and a role for free radicals is suggested by the observation that administration of a mixture of vitamins C (2g) and E (800 units) restored endothelial function[71]. Vitamin E at 900 mg/day for four months improved insulin responses in diabetic patients[72]. In elderly type 2 diabetics 900 mg/day of vitamin E produced a modest improvement in metabolic control[73]. Some studies suggest that E improves nerve function in type 2 diabetes; 600 mg/day for four months appeared to improve cardiac autonomic nerve function[74] whereas 900 mg/day for six months improved peripheral motor nerve conduction velocity[75].

Some Caveats

Nevertheless, some contrary data exist. Skrha et al[76,77] in the Czech Republic found that 600 mg of vitamin E for three months appeared to worsen diabetic control in a small cohort of obese type 2 diabetics and raised glycated haemoglobin levels, although these data contradict the previous studies reviewed above and the rise in glycated haemoglobin is suggestive of poor and worsening glycaemic control during the study, which could have concealed any beneficial effect of vitamin E. Ferber et al[78] found that 800 units of vitamin E per day for six months decreased platelet expression of adhesion molecules (in agreement with other studies showing decreased platelet aggregation[79,80]) but aggravated leukocyte-platelet-coaggregation *in vitro*. This did not appear to translate into a clinical effect. Nevertheless, a wide range of studies have suggested that high doses of vitamin E for prolonged periods are safe[6]. However, they do have a mild anticoagulant effect and are contraindicated in subjects on anticoagulant therapy[6]. Another question often raised is the failure of most intervention trials[81-84] with high-dose vitamin E to affect cardiovascular events in high-risk subjects, including those with diabetes[85]. However, the correct hypothesis to test is that vitamin E, by preventing free radical damage, will delay the onset of atherosclerosis and prevent or delay cardiovascular disease[2,5,86]. Once extensive atherosclerosis has developed, there is no reason to suppose that vitamin E would be helpful, and indeed the trials indicate that it is not[81-85]. Nor would I expect it to be helpful in subjects who already have extensive diabetic complications.

CONCLUSION

The weight of evidence from animal, epidemiological and human studies supports the view that high-dose vitamin E, possibly in combination with vitamin C[87,88], could be beneficial in the treatment of type 2 diabetes. First, the studies on the obese Zucker rat and epidemiological studies suggest that vitamin E may help in delaying the development of type 2 diabetes in insulin-resistant subjects. Second, it may delay or prevent the onset of complications in subjects with type 2 diabetes.

A role for vitamin E in the prevention and treatment of diabetes has been discussed for many years, as my lengthy reference list shows, but has not translated into clinical recommendations. In my view, it is time for a well-controlled double blind placebo-controlled clinical trial to be performed to address these two questions.

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