

Review

Use of Antioxidant Nutrients in the Prevention and Treatment of Type 2 Diabetes

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Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), is increasingly common throughout the world. The World Health Organization has predicted that between 1997 and 2025, the number of diabetics will double from 143 million to about 300 million. The incidence of NIDDM is highest in economically developed nations, particularly the U.S., where approximately 6.5% of the population (17 million people) have either diagnosed or undiagnosed diabetes. The two most important factors contributing to the development of NIDDM are obesity and physical inactivity. The leading cause of mortality and morbidity in people with NIDDM is cardiovascular disease caused by macro- and microvascular degeneration. Current therapies for NIDDM focus primarily on weight reduction. Indeed, several investigations indicate that 65% to 75% of cases of diabetes in Caucasians could be avoided if individuals in this subgroup did not exceed their ideal weight. The success of this approach has been, at best, modest. An alternate approach to the control of Type 2 diabetes is to arrest the progress of the pathology until a cure has been found. To this end, some investigators suggest that dietary antioxidants may be of value. Several studies in humans and laboratory animals with NIDDM indicate that vitamin E and lipoic acid supplements lessen the impact of oxidative damage caused by dysregulation of glucose metabolism. In this brief review, we discuss the incidence, etiology, and current therapies for NIDDM and further explore the usefulness of dietary antioxidants in treating this disorder.

Key teaching points:

- The incidence of Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), is increasing throughout the world. The increase is particularly acute in economically developed countries.
- The two most important factors contributing to the development of NIDDM are obesity and physical inactivity. Efforts to reduce the incidence of NIDDM through weight reduction have been, to a large extent, unsuccessful.
- The leading cause of mortality and morbidity in people with NIDDM is cardiovascular disease caused by macro- and microvascular degeneration.
- An increased rate of oxidative damage has been reported in people with NIDDM.
- Supplementing the diet with antioxidant nutrients, particularly vitamin E and lipoic acid, appears to reduce oxidative damage associated with high serum glucose concentrations.

INTRODUCTION

Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), is a multifactorial disease characterized by mild to severe dysregulation of glucose homeostasis. Glucose, an essential nutrient, is the major source of energy in the human body. In healthy individuals, blood glucose concentrations are

effectively held within a relatively narrow range (between 80 and 100 mg/mL in the post-absorptive state) regardless of calorie intake. This is particularly important because, despite variations in the time and amount of food consumed, the glucose requirements of peripheral tissues, especially the central nervous system, are constant. The maintenance of such precise glucose homeostasis is dependent almost entirely upon

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the appropriate secretion of insulin and the efficacy of secreted insulin in peripheral tissues.

Ingestion of carbohydrates causes a momentary increase in blood glucose concentration, resulting in a rapid release of insulin by the β -cells within the islets of Langerhans. Insulin then binds to receptors in target peripheral tissues to produce its effects. Under normal conditions, insulin promotes the transport of glucose into skeletal muscle and adipose tissue. In the liver, insulin suppresses glycogenolysis and gluconeogenesis, and in adipose tissue, it inhibits lipolysis. By decreasing hepatic and adipose glucose production, and by accelerating the uptake of glucose into peripheral tissues, the net effect of insulin's action is to lower blood glucose concentration.

In people with NIDDM, there is a gradual change in glucose homeostasis manifested as glucose intolerance and inefficient uptake of glucose from the blood by peripheral tissues. Glucose intolerance is caused, in part, by an attenuated biological response to normal concentrations of insulin, a condition known as insulin resistance. In addition, NIDDM is often associated with a diminution in the sensitivity of the pancreatic β -cells to glucose stimulation, with a subsequent decrease in insulin secretion. In time, there may be an increased demand for insulin due to worsening insulin resistance. Eventually, the combination of increased insulin resistance and inadequate insulin secretion in response to a glucose challenge will result in hyperglycemia, which is a significant and prolonged increase in blood glucose concentration. Hyperglycemia, the hallmark of NIDDM, can lead to numerous pathological conditions and increased mortality.

BACKGROUND

NIDDM is increasingly common throughout the world. The World Health Organization has predicted that between 1997 and 2025, the number of diabetics will double from 143 million to about 300 million [1]. The incidence of NIDDM is highest in economically developed nations, particularly the U.S., where approximately 6.5% of the population (17 million people) have either diagnosed or undiagnosed diabetes. There are an additional 25 to 30 million people in the U.S. with impaired glucose tolerance. The incidence of NIDDM in the U.S. has increased by about 33% over the past decade and is expected to increase further. However, the greatest rise in the prevalence of NIDDM is projected to occur in developing countries, particularly India and China [2].

The prevalence of both NIDDM and glucose intolerance increases with age. It is estimated that between 25% and 30% of the U.S. population aged 65 and older has NIDDM or impaired glucose tolerance [3]. Older adults exhibiting no clinical signs of diabetes often demonstrate decreased glucose tolerance (i.e., decreased glucose disposal rate as determined by an oral glucose tolerance test). Although it is often considered a disease primarily of the elderly and middle-aged, diabetes has

increased in all age groups over the past 10 years [4]. The greatest increase in diabetes has occurred among persons 30 to 50 years of age. For example, the incidence of NIDDM among people aged 30 to 39 years increased approximately 70% during the past decade [4].

In addition to age, the only other non-modifiable factor associated with an increased risk for the development of NIDDM is ethnic background. During the past 10 years the prevalence of NIDDM in the U.S. has increased across all ethnic groups [4]. However, the greatest increase in the incidence of diabetes has occurred among African-Americans, Hispanics, and American Indians. Persons from these ethnic backgrounds are at significantly greater risk for developing diabetes than are Caucasians. The apparent differences in risk among the various ethnic groups may merely reflect different dietary and lifestyle choices, or they may be due to a combination of genetic and environmental factors.

ETIOLOGY

The development of NIDDM was once thought to be the result of an endogenous, age related alteration in the ability of insulin to mediate uptake of glucose in peripheral tissues. This belief was based on the observation of a gradual but significant rise in insulin resistance with age independent of other variables. However, numerous studies have demonstrated that endogenous factors such as changes in insulin receptor number and affinity do not play a significant role in the development of NIDDM [5]. Also, the dramatic increase in the rate of diabetes among younger populations is evidence that NIDDM is not a disease of aging *per se*, but rather the consequence of modifiable, environmental factors. The two most important factors contributing to the development of NIDDM are obesity and physical inactivity.

The prevalence of obesity in the U.S. population as a whole is about 20%, but it is even higher among certain non-Caucasian groups [6]. During the past decade, the percentage of Americans defined as obese (30 pounds over ideal weight) has increased by about 33%. It is not a coincidence that these figures mirror the dramatic rise in diabetes over the same 10-year period. The association between obesity and the incidence of NIDDM is very strong. The vast majority of recent studies in humans and rodents have demonstrated a positive relationship between obesity and insulin resistance [5,7]. Several cohort studies indicate that weight gain during adulthood, the degree of obesity, and the duration of obesity are all strong and independent risk factors for the development of NIDDM [8].

Decreased physical activity is becoming more common in the U.S. and throughout the world because of the decrease in demand for physical labor and an increase in sedentary occupations. Almost a third of the adult population in the U.S. does not participate in exercise or other physical activity [4]. This

lack of physical activity is a potentially reversible factor contributing to glucose intolerance. Physical inactivity increases the risk of obesity and results in decreased insulin sensitivity and diminished glucose tolerance [9], each of which is associated with the development of NIDDM.

CURRENT THERAPIES FOR TYPE 2 DIABETES

Because obesity and physical inactivity are the major risk factors for the development of NIDDM, the most effective and obvious method for its prevention and treatment is a combination of weight reduction and exercise. Results of numerous studies emphasize the importance of weight loss to control or prevent impaired glucose metabolism, insulin resistance, and diabetes. About 65% to 75% of cases of diabetes in Caucasians could be avoided if individuals in this subgroup did not exceed their ideal weight [10]. For individuals who are already overweight, even modest weight loss is associated with significantly reduced diabetes risk [11].

Exercise is an effective means of preventing and treating impaired glucose tolerance and NIDDM in men and women who already suffer from or are at risk for developing these conditions. Although exercise is known to increase insulin sensitivity and improve glucose tolerance, the mechanism underlying its beneficial effects is unclear. Skeletal muscle responds to exercise training by increasing glucose transporter (GLUT4) concentration, resulting in improved insulin action [12]. However, it should be noted that the improved tissue insulin sensitivity resulting from exercise is not always associated with increased glucose disposal. In addition, an extensive review of the literature reveals that the loss of muscle mass that commonly occurs with advancing age does not contribute to the development of glucose intolerance [5]. Taken together, these findings indicate that weight reduction is more important in the prevention of NIDDM, and that exercise must be accompanied by weight loss to improve insulin sensitivity and glucose tolerance [13].

Most cases of NIDDM could be prevented or treated effectively if diabetics or individuals at risk for diabetes adhered to a strict diet and exercise regimen. In the real world, this does not happen. Genetic, environmental, and social factors conspire to make dieting difficult and exercise inconvenient. There are also some individuals with NIDDM whose hyperglycemia cannot be managed satisfactorily with diet and exercise alone. Faced with these realities, the pharmaceutical industry has developed a number of oral hypoglycemic agents, which, as the name implies, act to lower blood glucose concentrations. Generally, improved glycemic control is accomplished pharmacologically by two means: a) stimulating the release of insulin from functioning β -cells in the pancreatic islets, and b) improving insulin sensitivity in peripheral tissues. Drugs in the first category include the sulfonylureas (glyburide, glipizide) and

the meglitinides (repaglinide). Drugs in the second category include the biguanides (metformin) and the thiazolidinediones (troglitazone, rosiglitazone). The primary mechanism of action of these agents is to reduce hepatic glucose output and decrease insulin resistance in skeletal muscle. Combinations of the insulin secretagogues and the insulin-sensitizing agents, which have complementary mechanisms of action, have been used with varying degrees of success.

ADVERSE EFFECTS OF TYPE 2 DIABETES

Type 2 diabetes is characterized by an increased risk for the development of macrovascular disease (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) and microvascular complications (neuropathy, renal disease, and retinopathy). The leading cause of mortality and morbidity in people with NIDDM is cardiovascular disease [14]. There is little doubt that a close association exists between NIDDM and vascular disease, but what effect(s) of impaired glucose metabolism is so injurious to the vasculature? The answer appears to be hyperglycemia. This is an acute or chronic increase in blood glucose concentration that results from decreased uptake of glucose into muscle and adipose tissue and increased hepatic glucose output. Several studies have demonstrated that even mild increases in chronic (fasting) or acute (postprandial) blood glucose concentration can contribute to macrovascular injury and atherosclerotic changes [15]. A meta-analysis of 20 different studies of 95,783 individuals followed for 12 years led to the conclusion that glucose is a risk factor for cardiovascular events even within a range below the diabetic threshold (<126 mg/dL), and that glucose is likely to be a continuous cardiovascular risk factor, similar to total cholesterol and blood pressure [16]. A close relationship has been established between poor glycemic control and the progression of retinopathy and polyneuropathy [17]. Conversely, intensive glycemic control prevents or significantly delays the development of nerve abnormalities and diseases related to microvascular changes in persons with NIDDM [17].

The mechanisms by which glucose produces its deleterious effects are not completely understood. However, the preponderance of evidence indicates that hyperglycemia increases oxidative stress, defined as the production of reactive oxygen species (free radicals; ROS) beyond the protective capability of the antioxidant defenses. The two primary mechanisms by which hyperglycemia may promote the generation of ROS are activation of the polyol pathway and increased glucose auto-oxidation. Enhanced ROS concentrations resulting from these mechanisms can cause general damage to proteins through cross-linking, fragmentation, and lipid oxidation. Reactive oxygen species may also mediate some of the changes associated with the development of atherosclerosis, for example, activation of coagulation, vasoconstriction, increased expression of

adhesion molecules, and oxidative modification of low-density lipoprotein [18]. Increased uptake of glucose in the artery wall stimulates protein kinase C activity, which activates peroxidase enzymes and the cyclo-oxygenase pathway to produce an overabundance of ROS. In turn, these ROS may increase endothelial permeability, macrophage migration, and the secretion of endothelin, a cytokine believed to be involved in the development of atherosclerosis [18].

Another adverse effect of hyperglycemia is the nonenzymatic glycosylation of proteins. As a function of time and glucose concentration, protein amino groups react with glucose to eventually form advanced glycosylation endproducts (AGEs). The formation of AGEs often involves the participation of free radicals. AGEs can accumulate over time and induce excess cross-linking of collagen and other extracellular matrix proteins. The harmful effects of glycosylation occur in a wide variety of tissues. For example, glycosylation can affect the structural proteins of nerves, such as myelin, tubulin, and neurofilaments, modifying their structure and function with the formation of AGE. Macrovascular and microvascular complications are the most common and significant consequences of glycosylation. The AGE-induced cross-linking of proteins in the vascular wall has been implicated in pathological changes associated with atherosclerosis, such as the accumulation of LDL particles [19]. The thickening, loss of elasticity, and increased permeability of blood vessel walls associated with microvascular complications may be due, in part, to glycosylation of vascular proteins.

There is now considerable evidence that hyperglycemia, hyperinsulinemia, and insulin resistance enhance free radical generation and thus contribute to oxidative stress in NIDDM [20]. Oxidative stress associated with hyperglycemia may lead to a reduced number of glucose transporters and impairment of insulin signaling [21]. Oxidative stress can even have adverse effects on β -cell insulin secretion [22]. Therefore, oxidative stress resulting from hyperglycemia and insulin resistance can worsen NIDDM by promoting further insulin resistance and decreased insulin secretion.

In obesity, a condition normally associated with NIDDM, there is increased oxidative stress that may be attributed to several mechanisms. A significant decline in insulin-mediated glucose uptake, which is often experienced by obese individuals, may result in hyperinsulinemia, which in turn may induce a rise in plasma free radical production. Hypertriglyceridemia and/or hypercholesterolemia observed in obese persons may facilitate the generation of ROS. It has been demonstrated that triglyceride-rich lipoproteins are more susceptible to oxidation, and that pro-oxidation kinetics and a decline in antioxidant effectiveness depend on LDL-cholesterol content [23]. In addition, the observation that obese rats on a calorie-restricted diet have less oxidative stress than obese rats fed *ad libitum* indicates that obesity is associated with an elevated degree of oxidative stress.

ANTIOXIDANT-BASED THERAPEUTIC APPROACHES TO NIDDM

The body possesses defense mechanisms that, in the healthy individual, adequately control plasma ROS concentration under most conditions. However, in persons with NIDDM, increased plasma ROS generation and a marked reduction in antioxidant defenses result in oxidative stress, which in turn can lead to many of the deleterious effects of NIDDM. It is critical, therefore, that any therapies for NIDDM include the direct and/or indirect reduction of oxidative stress. As discussed previously, modifications of certain environmental factors, for example, exercise and especially weight loss, can effectively prevent and even reverse the effects of NIDDM, in part by reducing oxidative stress. Various hypoglycemic agents reduce oxidative stress, indirectly by lowering blood glucose levels and preventing hyperinsulinemia, and directly by acting as free radical scavengers. For example, gliclazide, a sulfonylurea normally used to augment insulin release, is an effective scavenger of superoxide and hydroxyl radicals. Recent studies have demonstrated that gliclazide can decrease LDL oxidation and monocyte adhesion to the endothelium, events that contribute to the development of atherosclerosis in NIDDM [24,25]. The insulin-sensitizing agent troglitazone also appears to possess some antioxidant activity.

Antioxidant nutrients may complement the therapies described above to reduce oxidative stress. In general, exogenous antioxidants can compensate for the lower plasma antioxidant levels often observed in NIDDM and in pre-diabetic individuals, whether their diabetes is primarily genetic in origin or due to obesity and a sedentary lifestyle. It has long been suspected, but only recently demonstrated, that the consumption of fruits and vegetables rich in vitamin and other antioxidants can increase overall antioxidant status [26,27]. In studies of humans and rodents, dietary supplementation with antioxidants is associated with decreased risk of NIDDM and induces changes that could be beneficial in reducing insulin resistance and protecting vascular endothelium [20].

There is mounting evidence that a general increase in antioxidant status achieved by dietary supplementation can help diminish oxidative stress associated with NIDDM. However, certain antioxidants are of particular benefit with regard to the prevention and treatment of diabetic complications. Primary among these are vitamin E (α -tocopherol) and lipoic acid (thioctic acid). Vitamin E is a fat-soluble vitamin that effectively scavenges the peroxy radical in cell membranes, thereby inhibiting lipid peroxidation. Prospective epidemiological studies demonstrate that high serum vitamin E levels are associated with decreased risk of NIDDM [28]. In the GK rat, a model for NIDDM, vitamin E supplementation significantly improves glycemic control, possibly by minimizing free radical damage to the pancreatic β -cells [29,30]. Improvements in glucose metabolism and insulin action in the obese Zucker rat, an animal that exhibits many of the features of NIDDM, may be

mediated by a reduction in oxidative stress. Researchers found that glucose-stimulated hyperinsulinemia and lipid peroxidation in the obese Zucker rat could be significantly reduced with dietary vitamin E [31,32]. A similar finding has been observed in humans. Plasma concentrations of lipid hydroperoxides, an indicator of lipid peroxidation, were higher in healthy, insulin-resistant volunteers as compared to insulin-sensitive ones, while plasma concentrations of vitamin E were significantly lower.

Prospective studies of non-diabetic individuals provide evidence that vitamin E supplementation is associated with a protective effect against coronary heart disease [33]. In humans and in animal models of NIDDM, vitamin E reduces vascular oxidative stress and preserves endothelial function, thus inhibiting the development of atherosclerosis. Specifically, vitamin E supplementation of as little as 400 $\mu\text{g}/\text{d}$ can make LDL less susceptible to oxidation and consequently less atherogenic. In vascular tissue, the protein kinase C pathway regulates basement membrane turnover, cellular proliferation, and endothelial cell permeability. Activation of this pathway by hyperglycemia has been linked to macro- and microvascular dysfunction. Vitamin E supplementation has been demonstrated to prevent the induction of protein kinase C activity in the hyperglycemic aorta, thereby inhibiting the migration and proliferation of vascular smooth muscle cells. This effect of vitamin E can prevent or at least delay many of the vascular complications associated with NIDDM.

Lipoic acid, an essential cofactor of alpha-oxoacid dehydrogenase complexes, is also a potent lipophilic free radical scavenger. Several studies indicate that the decline in insulin-mediated glucose uptake observed in NIDDM is due to oxidative stress, which in turn is associated with reduced glucose transporter (GLUT4) exposure and/or impairment of insulin signaling [34]. Lipoic acid was found to increase glucose transport in muscle cells in culture by stimulating translocation of GLUT4 from internal pools to the plasma membrane [20]. In cultured adipocytes, treatment with lipoic acid protected the insulin receptor from oxidative damage, maintaining its functional integrity. A placebo-controlled explorative study of patients with NIDDM indicated that oral administration of lipoic acid significantly increased insulin-mediated glucose uptake, presumably by modulating insulin sensitivity [35].

Oxidative stress may play an important role in the pathogenesis of diabetic neuropathy, a condition characterized by pain and numbness of the extremities. Antioxidant treatment has been demonstrated to prevent nerve dysfunction in experimental diabetes. Lipoic acid is of particular interest to researchers because it is a powerful free radical scavenger of peripheral nerves both *in vitro* and *in vivo*. It also promotes fiber regeneration and stimulates nerve growth factor. Several clinical studies reveal that lipoic acid is generally safe and effective in reducing symptoms of diabetic peripheral neuropathy. Short-term treatment for three weeks using 600 mg/d

intravenously or 1800 mg/d orally appeared to reduce symptoms and improve neuropathic deficits [36,37,38]. Lipoic acid taken orally (600 mg/d) for 4–24 months reduced neuropathic deficits and improved motor and sensory nerve conduction in the lower limbs [39,40].

A number of other antioxidant nutrients have been reported to be beneficial for subjects with NIDDM. Flavonoids, a group of antioxidant polyphenolic compounds found ubiquitously in commonly consumed fruits and vegetables and in beverages, such as red wine and tea, have been demonstrated to protect against oxidative stress in type 1 and type 2 diabetes [41]. Specifically, the flavonoids inhibit lipid oxidation and delay the depletion of lipid-soluble antioxidants. Serum levels of carotenoids, another group of antioxidant compounds often present in edible plants, were inversely related to fasting serum insulin levels [42]. While not conclusive, this observation is suggestive of a role for carotenoids in the pathogenesis of insulin resistance and diabetes.

Taurine and coenzyme Q₁₀ are endogenous antioxidants that can also be obtained from the diet. In rats with diabetes induced by chemical destruction of β -cells, taurine supplementation (1% taurine in the drinking water) reduced renal oxidant injury by decreasing lipid peroxidation and inhibiting the accumulation of advanced glycation endproducts within the kidney [43]. The effects of oral treatment with coenzyme Q₁₀ (60 mg twice daily) were examined in a randomized, double-blind trial of 30 patients with coronary heart disease. After 8 weeks of treatment, the patients receiving coenzyme Q₁₀ had reduced plasma levels of insulin (fasting and 2-hr), glucose, and lipid peroxides as compared to the control group [44]. These findings indicate that treatment with coenzyme Q₁₀ in this group decreases oxidative stress and improves insulin sensitivity.

CONCLUSION

Type 2 diabetes is a chronic, progressive disease characterized by insulin resistance with an inadequate compensatory insulin secretory response. NIDDM is becoming increasingly common throughout much of the world, and the incidence of this disease is rising most rapidly among younger people. The reason for this dramatic increase in NIDDM is the increased prevalence of obesity and physical inactivity which are becoming more common in a world where physical labor is less necessary and calorie-dense foods are readily available. Proper diet and exercise can effectively prevent or reverse NIDDM in most cases, but patient compliance is difficult. Hypoglycemic agents are an important therapeutic option, especially for patients who do not respond to diet and exercise alone.

Hyperglycemia, an inevitable consequence of NIDDM, is the source of most of the deleterious effects usually associated with this disease. High blood glucose concentrations promote auto-oxidation of glucose to form free radicals. The generation of free radicals beyond the scavenging abilities of endogenous

antioxidant defenses, a condition known as oxidative stress, can result in macro- and microvascular dysfunction and polyneuropathy. Various antioxidant nutrients, particularly vitamin E and lipoic acid, have proven useful in decreasing oxidative stress. In NIDDM, treatment with antioxidants has been demonstrated to preserve beta-cell function, increase insulin sensitivity, protect the vascular endothelium, and ameliorate polyneuropathy. Results of numerous studies indicate that dietary supplementation with antioxidant nutrients may be a safe and simple complement to traditional therapies for preventing and treating diabetic complications.

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