Review

Dietary Antioxidant Vitamins and Flavonoids and Type 2 Diabetes: A Review of Current Epidemiologic Evidence

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Given the increasing incidence of type 2 diabetes, the identification of effective and safe preventive measures that offer even modest reductions in incidence could have a significant public health impact. One promising but as-yet unproven nutritional strategies for the prevention of diabetes or diabetic complications are dietary antioxidants. Several lines of evidence from laboratory research and observational studies has suggested increased oxidative damages on insulin resistance and pancreatic β-cell insulin secretion, indicating a role of oxidative stress in the etiology of type 2 diabetes. Ample non-human experimental evidence has demonstrated that dietary antioxidants such as vitamins C and E and flavonoids, protect against free radical-mediated damage by reducing free oxygen radicals and replenishing antioxidant reserves. While there is a longstanding interest in the diabetes community regarding the promising yet unproven role of antioxidants in the prevention of diabetes and diabetic complications, available human epidemiologic data provide equivocal information. Evidence from prospective cohort studies generally supports an inverse association between dietary, serum, or plasma levels of vitamins C and E and flavonoids and risk of type 2 diabetes. However, available data from randomized controlled trials did not seem to support the antioxidant hypothesis by showing the null effect of vitamins E and C and beta-carotene on type 2 diabetes among initially nondiabetic individuals. In this article, we review the available literature concerning the efficacy of antioxidants from diets or supplements in reducing the risk of type 2 diabetes.

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INTRODUCTION

Insulin resistance and progressive pancreatic β-cell dysfunction are well-established defects in the pathogenesis of type 2 diabetes.[1] Tissue resistance to the action of insulin is believed to be a common antecedent to both type 2 diabetes and atherosclerotic disease.[2-4] Much research has also demonstrated that both insulin resistance and hyperglycemia increase oxidative stress and thus accelerate the atherosclerotic process.

Considerable evidence supports the theory that free radicals play an important role in the development of many chronic degenerative diseases of aging, including type 2 diabetes.[5,6] Highly reactive free radicals can oxidize and damage such essential molecules as DNA, proteins, and lipids,[6] and accumulation of damaged, oxidized, and dysfunctional peptides is one of the most fundamental manifestation of aging.[5] To guard against oxidative damage caused by free radicals, two major defense mechanisms - the enzymatic (intracellular defense) and the non-enzymatic (intercellular defense) - are found in the human body. The antioxidants such as vitamin E and vitamin C constitute the primary intercellular defense against free radicals.[7,8] In laboratory research, vitamin C, vitamin E, and other antioxidants have been shown to prevent tissue damage by trapping organic free radicals and/or deactivating excited oxygen molecules, which are byproducts of many metabolic functions.[9] This antioxidant activity may slow or prevent atherosclerotic plaque formation by inhibiting oxidation of low-density lipoprotein cholesterol (LDL) and thus protecting the vascular wall from oxidized LDL and other cytotoxic oxidative products.[10] Vitamin E may also modify platelet activity,[21-23] reduce thrombotic potential,[24] and modify vascular reactivity[25-27] via antioxidant-related modifications in prostaglandin metabolism and nitric oxide production.

Basic biologic and clinical data suggest that inadequate antioxidant vitamins contribute to a decrease in plasma concentration of antioxidants, which in turn impairs the ability of insulin to stimulate glucose disposal by peripheral tissues, leading to type 2 diabetes.[32] While there is a

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longstanding interest in the diabetes community regarding the promising yet unproven role of antioxidants in the prevention of diabetes and diabetic complications, human evidence linking antioxidants to the incidence of type 2 diabetes has been inconsistent and controversial. Therefore, in this review, we reviewed the available literatures concerning the efficacy of antioxidant vitamins and flavonoids to clarify whether the evidence from human data support the hypothesis of benefit of antioxidants on type 2 diabetes.

OBSERVATIONAL EVIDENCE OF DIETARY ANTIOXIDANTS AND TYPE 2 DIABETES

Much of the epidemiologic evidence supporting the role of antioxidants in prevention of type 2 diabetes has been indirect. Ecological studies have suggested that populations with a high intake of animal products but a low intake of dietary antioxidants from fruits, vegetables, and whole grains tend to have high prevalence of type 2 diabetes.[11,12] However, such comparisons among populations cannot provide definitive answers because this approach cannot fully adjust for other important factors such as exercise and other lifestyle behaviors that may confound the diet-diabetes association. Moreover, since the diagnosis of diabetes is often followed by alterations in diet, physical activity, and other lifestyle practices, the value of retrospective studies is limited. Prospective cohort studies are better suited to evaluate the role of diet in the development of type 2 diabetes because diets are assessed prior to the outcome and reporting of intake is not biased by a recent diagnosis of diabetes.

Only a few prospective studies have directly examined the relations between dietary antioxidant vitamins and diabetes incidence. In a 20-year prospective study of the Dutch and Finnish adults, Feskens and colleagues found similar inverse relations between dietary vitamin C and glucose intolerance or incidence of diabetes.[13] In the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study of 9,573 men and women, Ford reported that in comparison to non-supplement users, those who used vitamin supplements had a 24% (95% CI, 7%-37%) lower risk of developing diabetes over 20 years of follow-up.[14] In particular, participants who used vitamins regularly and consistently over a 10-year period had a larger reduction in risk (RR, 0.47; 95% CI, 0.27-0.81) than those who used vitamins irregularly, suggesting a dose-response relation.

Flavonoids are a group of naturally occurring polyphenolic compounds primarily from fruits and vegetables.[15] Several small dietary intervention trials have shown that consumption of flavonoid-rich foods such as tea and onions was associated with a significant increase in plasma levels of flavonoids in diabetic patients.[16,17] Flavonoids have high antioxidant activities as free radical scavengers and potent metal chelators.[15,16,18] Flavonoids may preserve β-cell function by reducing oxidative stress-induced tissue damage and therefore protect against the progression of insulin resistance to type 2 diabetes. A prospective study in Finland recently showed that the intakes of some specific types of flavonoids including quercetin and myricetin were inversely associated with risk of incident type 2 diabetes.[19] In the Women's Health Study of 38018 women, Song et al. reported that none of total flavonols and flavones, quercetin, kaempferol, myricetin, apigenin, and luteolin was significantly associated with risk of type 2 diabetes.[20] Among flavonoid-rich foods, apple and tea consumption was associated with diabetes risk. However, flavonoids consist of six major subgroups, including flavonols, flavones, flavanones, isoflavones, anthocyanins, and catechins, and have more than 4,000 different compounds. Even within the same subclass, flavonoids may differ considerably in bioavailability and bioactivity. However, depending on the food-composition databases, most of early observational studies were unable to assess intakes of all constituents such as catechins and isoflavones. Recently, the European Prospective Investigation into Cancer and Nutrition (EPIC)–InterAct case-cohort study was conducted in 8 European countries with 340,234 participants and 12,403 incident type 2 diabetes cases to examine the association between individual flavanol and flavonol intakes and risk of developing type 2 diabetes.[21] Dietary flavonoid intake at baseline from validated dietary questionnaires was evaluated using an updated food composition database. This large study showed inverse associations between all individual flavan-3-ol monomers, proanthocyanidins with a low polymerization degree, and flavonol myricetin and type 2 diabetes, and indicated different roles of individual flavonoids in the etiology of type 2 diabetes.[21]

OBSERVATIONAL EVIDENCE OF SERUM ANTIOXIDANT LEVELS AND TYPE 2 DIABETES

The bioavailability of antioxidants can be reflected by their plasma concentrations.[22,23] Plasma levels of vitamin E correlate very well with dietary intakes and supplements, after appropriate adjustment for confounding factors such as age, sex, smoking status, and blood lipids.[24] It is thus important to evaluate directly the relation between plasma levels of antioxidants and risk of type 2 diabetes. Recently, Salonen et al. reported a strong independent association between low levels of plasma vitamin E and excess risk of type 2 diabetes among 944 men followed for 4 years in Eastern Finland.[25]

In cross-sectional studies, plasma levels of antioxidants have also been related to prevalence of diabetes or glucose intolerance,[26-28] lending further support to the proposition that maintaining certain physiological levels of antioxidants play an important role in the prevention of type 2 diabetes. In a small nested-case-control study of 106 Finns with diabetes and 201 controls, serum alpha-tocopherol was not significantly related to diabetes incidence after adjustment for known diabetes risk factors.[29] In a review of 30 published studies, Will and Byers found that diabetic individuals tend to have at least 30% lower plasma vitamin C levels than people without diabetes,[26] suggesting a potential link between plasma vitamin C and glucose level. More recently, in a large population-based study in Europe, Sargeant and colleagues reported a significant inverse association between plasma vitamin C levels and HbA1c.[30] Observational data, however, cannot definitively determine whether low plasma concentrations of antioxidants preceded the onset of diabetes and thus acted in its causation or whether the low concentrations were consequences of latent diabetes at the time of the measurement.

Other biochemical markers such as urinary excretion of select flavonoid and phenolic acid metabolites, were also used as biomarkers of polyphenol intake. The Nurses' Health Study (NHS) measured eight polyphenol metabolites (naringenin, hesperetin, quercetin, isorhamnetin, catechin, epicatechin, caffeic acid, and ferulic acid) in spot urine samples by liquid chromatography/mass spectrometry.[31] During the early follow-up period (≤ 4.6 y (median) since urine sample collection), markers of flavanone intakes (naringenin and hesperetin) and flavonol intakes (quercetin and isorhamnetin) were significantly associated with a lower type 2 diabetes risk. None of these markers was associated with type 2 diabetes risk during later follow-up.[31]

Table 1. Main results of 9 randomized double-blind controlled trials for dietary antioxidant vitamins and type 2 diabetes

Author	Publication year	Supplements, dose, and duration	Main results
Bishop N[41]	1985	500 mg/day vitamin C;4 months	No significant difference in fasting blood glucose, serum cholesterol, triglycerides, and glycosylated hemoglobin levels.
Paolisso G[37]	1995	1g/day vitamin C; 4 months	Beneficial effects upon glucose and lipid metabolism in aged non-insulin dependent (type 2) diabetic patients.
Liu S[45]	1999	50 mg beta-carotene on alternate days; 12 years	No effect on the risk of subsequent type 2 diabetes.
Mullan BA[36]	2002	500 mg/day ascorbic acid; 4 weeks	Lowered blood pressure and improved arterial stiffness in patients with type 2 diabetes.
Darko D[40]	2002	1.5 g/day vitamin C; 3 weeks	No significant improvement of oxidative stress, blood pressure or endothelial function in patients with type 2 diabetes.
Regensteiner JG[38]	2003	9 g/day oral L-arginine or 1800 mg/day vitamins E and 1000 mg/day vitamin C; 1 week	Significant improvement in measures of endothelial function in people with type 2 diabetes.
Chen H[39]	2006	800 mg/day vitamin C; 4 weeks	Effective improving endothelial dysfunction and insulin resistance in Type 2 diabetes.
Liu S[46]	2006	alternate-day doses of 600 IU vitamin E; 10 years	No significant benefit for type 2 diabetes in initially healthy women.
Song Y[44]	2009	500 mg/day vitamin C; vitamin E 600 IU/other day, 50 mg /other day beta-carotene; 9.2 years	No significant overall effects on risk of developing type 2 diabetes in women at high risk of CVD.

RANDOMIZED TRIAL DATA OF SUPPLEMENTAL ANTIOXIDANTS AND TYPE 2 DIABETES (TABLE 1)

One national survey indicated that 32% of men and 45% of women regularly use nutritional supplements,[32] and the doses of supplementation often exceed the recommended dietary allowance (RDA).[33]

With the relative safety and inexpensiveness, multivitamin supplements are the most commonly used dietary supplements in the U.S. and are advocated as an attractive option for preventing chronic diseases, such as cancer, cardiovascular disease, and type 2 diabetes.[34,35] Approximately 50 percent of U.S. adults routinely take multivitamin supplements[34] and the trend remains increasing in the general population of the US.

One major gap in the current knowledge of vitamin supplementation is the lack of direct evidence from long-term, randomized, and primary prevention trials. Some,[36-38] but not all,[39-41] short-term randomized trials in patients with type 2 diabetes showed the beneficial effects of oral supplementation of vitamin C or vitamin E at high doses on risk factors linked to insulin resistance and diabetes, including oxidative stress, blood pressure,[36] lipid metabolism,[37] endothelial function,[38] or insulin-mediated glucose disposal.[37] However, few large trials with long treatment duration have addressed the primary prevention of vitamin supplements for type 2 diabetes in general populations. Vitamin C is a potent water-soluble antioxidant and can effectively scavenge several reactive species and regenerate tocopherols and tocotrenols from their respective radical species.[42] Vitamin C may also have a role in the energy-dependent release of insulin from pancreatic islets.[43] Some small and short-term randomized trials have been conducted among patients with type 2 diabetes; some reported that vitamin C supplementation (1-2 g/day) reduced oxidative stress and improved endothelial function in diabetic patients.[42] Further, a recent trial has shown suggestive evidence for vitamin C (500 mg/day) in preventing type 2 diabetes among women at high risk of cardiovascular disease.[44] Two previous randomized trials of women (WHS and WACS) did not support either a beneficial or detrimental effect of vitamin E (600 IU every other day for 10 years) on the primary prevention of type 2 diabetes in apparently healthy women.[44,45] Secondary analyses of randomized clinical trials on cardiovascular events and cancers found no significant effects of vitamin E or β-carotene supplementation on the incidence of type 2 diabetes.[44,46] Of note, case misclassification due to the underdiagnosis of type 2 diabetes is a concern in previous trials, because the different criteria of type 2 diabetes were used for exclusion at screening participants and outcome at end of study. In addition, virtually no randomized controlled trial data are available relating dietary flavonoid supplements to subsequent risk of type 2 diabetes. Due to limited data from randomized trials, these data alone are inadequate to answer definitely whether these single antioxidants have a long-term effect on risk of type 2 diabetes.

In addition, antioxidants are members of a rather large and actively cooperating family of phytochemical substances. Synergistic interactions between antioxidants have been described in many experimental studies and may, in part, involve the regeneration of antioxidant. For example, a certain level of vitamin E may be sufficient when the levels of all the other antioxidants are sufficient, but the protective effect of that level of vitamin E may become inadequate when levels of other antioxidants fall.[47] There is some evidence to suggest that a mixture of two or more antioxidants administered in combination may reduce oxidative stress more than a single antioxidant alone. In particular, vitamin C and β-carotene regenerate vitamin E from its oxidized form. The Women's Health Study and the Women's Antioxidant Cardiovascular Study randomized trials of female health professionals both examined the potential synergistic effects among vitamins C and E and -carotene.[44,46] However, compared with placebos, there were no significant differences in diabetes incidence with any antioxidant alone or in combinations of two or three.

Besides single vitamin supplements, multivitamin supplements contain large amounts of variety of vitamins and minerals that approximate or exceed the recommended micronutrient intakes. Multivitamin supplement use may contribute a considerable proportion of nutrient intakes in most dietary supplement users and may contribute to risk of excessive intakes of micronutrients in some subgroups.[35] Despite the widespread use of multivitamins in the US population, few epidemiologic studies have been evaluating the overall benefit and safety of multivitamins for chronic disease prevention. Evidence from basic research and observational studies has suggested that adequate intake of antioxidant vitamin or minerals, may protect against the development of type 2 diabetes via reduction of oxidative stress and its associated metabolic abnormalities including systemic inflammation, endothelial dysfunction, hypertension, and dyslipidemia.[36-38] These metabolic abnormalities act individually or synergistically to impair pancreatic β-cell insulin secretion and interfere with glucose disposal in peripheral tissues,[48] thereby accelerating the development and progression of both atherosclerosis and type 2 diabetes. Recent study also showed that multivitamin use is associated with longer telomere length, which is a reliable marker of biological aging as a result of multiple metabolic disorders, especially oxidative stress and chronic inflammation.[49] However, Recent data from the National Institute of Health-AARP Diet and Health (NIH-AARP DH) cohort found no significant association between multivitamin use and diabetes risk.[50]

CONCLUSIONS

As discussed above, however, abundant experimental and observational data suggest that increased oxidative stress plays an important role in the pathogenesis of diabetes and its complications. Given the increasing public health burden of type 2 diabetes in the US and around the world, the identification of effective and safe preventive measures have a significant public health impact. Antioxidant vitamins agents represent such a promising intervention. However, considerable uncertainty exists regarding the efficacy of dietary antioxidants, and current epidemiologic and clinical data cannot provide definitive answers regarding their use in the primary prevention of type 2 diabetes. A major problem is the lack of long-term, large-scale randomized clinical trials. Evidence from secondary analyses of existing randomized trials did not find any statistically significant benefits or risks of antioxidant vitamins supplementation on the primary prevention of type 2 diabetes. In conclusion, currently, there is insufficient evidence to support a potential beneficial effect of dietary antioxidant supplementation on primary prevention of type 2 diabetes.

CONFLICT OF INTEREST
All authors have no conflicts of interest to disclose.

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