Diabetes risk: antioxidants or lifestyle?\textsuperscript{1−3}

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It is projected that, by 2025, >300 million people worldwide will have diabetes. In the United States, in the period between the 2 National Health and Nutrition Examination Surveys conducted in 1976 and 1994, the number of people with diabetes almost doubled (1). Obesity, overweight, and physical inactivity are regarded to be the major contributing factors for the development of this disease (2). Many strategies (diet, exercise, drugs, and weight reduction) have been developed to reduce the risk of developing diabetes and its associated cardiovascular complications. Several potential mechanisms are responsible for the disorders associated with diabetes, such as insulin resistance, \( \beta \) cell dysfunction, and insulin production and secretion. These disorders have been associated with increased concentrations of oxidants and reduced concentrations of natural antioxidants.

This association has been the subject of investigation in experimental animal models and in human clinical intervention trials. Several small clinical studies have suggested the benefit of dietary antioxidants on lowering the risk of developing diabetes and its associated cardiovascular complications. In the current issue of the Journal, Song et al (3), in a double-blind, placebo-controlled trial, have examined the long-term effects of supplemental intake of dietary micronutrients vitamin C, vitamin E, and \( \beta \)-carotene and their combinations for >9 y on the primary prevention of type 2 diabetes in middle-aged women with either a history of cardiovascular disease (CVD) or with >3 CVD risk factors. This clinical trial was designed and conducted on the basis of the notion that extensive production of reactive oxygen species (ROS) and the reduction of natural antioxidant defenses potentially contribute to the risk of developing diabetes. Therefore, the expectation would be that supplemental intake of these antioxidants and their combinations might lower the risk of developing type 2 diabetes. However, the results of the study, such as in other clinical trials of antioxidant supplementation (4−6), showed no effect from generous supplemental intake of these vitamins on primary prevention of type 2 diabetes.

Many investigators have implied that oxidative stress is responsible for systemic inflammation, endothelial dysfunction, and diminution of pancreatic \( \beta \) cell secretion and the impairment of glucose utilization in peripheral tissues. All of these phenomena would cooperate in accelerating the development and progression of type 2 diabetes. Because of these assumptions, antioxidants such as vitamin C, vitamin E, and \( \beta \)-carotene were assumed to be ideal supplements to reverse oxidative stress and its consequences. Along these lines, observational studies have found that biomarkers of insulin resistance or glucose intolerance may correlate with a diminution of antioxidants. Unfortunately, 2 intervention studies that used vitamin E or \( \beta \)-carotene supplementation in patients with type 2 diabetes did not show a positive effect on the development of type 2 diabetes (7, 8).

In the study by Song et al (3), vitamin C was included in the supplementation protocol on the correct assumption that this vitamin is needed to regenerate oxidized vitamin E. However, no evidence was found of benefit, nor more importantly of harm, due to supplementation of vitamin C, vitamin E, and \( \beta \)-carotene on the primary prevention of type 2 diabetes. The authors’ conclusions are indeed novel and interesting from a basic science as well as a clinical viewpoint. Regarding the clinical viewpoint: in a random population, similar to that of the trial in women aged \( \geq 40 \) y with a history of or risk factors for CVD, there is not enough evidence to recommend supplementation with vitamin C, vitamin E, or \( \beta \)-carotene. However, this does not exclude the possibility that different populations, possibly with different genetic backgrounds, may receive benefit from additional intake of these vitamins. For example, Milman et al (9) recently reported that middle-aged patients, who had type 2 diabetes and haptoglobin 2-2 genotype and who were under oxidative stress, showed reduced cardiovascular events after receiving supplementation with vitamin E for 1.5 y.

Regarding the first viewpoint mentioned previously, ie, the value of translating evidence from basic science to design of a clinical study, a number of points can be discussed. First, in regard to oxidative stress and its coexistence with type 2 diabetes, should it be considered a cause or a consequence? Moreover, considering that the measures of oxidative stress reflect only a minor component of antioxidant defenses, the question can be

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further extended as follows: Can the replacement of this minor component have a significant effect on disease? An additional point concerns the number of studies that have indicated that the so-called antioxidants may act differently in vivo than in vitro. Consequently, if oxidative stress was indeed present in the body, it would not be reversed by molecules, which are not acting uniquely as antioxidants. It appears, therefore, that the premises of the intervention studies of this type should be revised. If oxidative stress was indeed at the basis of a disease, antioxidants might be useful to prevent it if they were chosen and tested for their in vivo function. As a result, the hypothesis of oxidative stress as a cause or consequence of a disease requires more rigorous analyses. In his article “Total Antioxidant Capacity: Appraisal of a Concept,” Sies (10) concludes, “The concept of ‘total antioxidant capacity,’ which originated from chemistry and then was applied to biology and medicine, and further to nutrition and epidemiology, needs critical appraisal, because there are serious limitations that preclude meaningful application to in vivo conditions” (p 1483). This verification is needed in the case of type 2 diabetes, as well as in the case of other diseases, before more intervention studies are carried out.

Finally, focusing on the simple paradigm of oxidants and antioxidants may divert attention from other dietary and exercise interventions that apparently are much more effective than taking high doses of antioxidant supplements singly or in combination. It is important to emphasize the role of chronic inflammation associated with overweight, obesity, and abdominal adiposity in type 2 diabetes (11) instead of only one of its consequences, ROS. The elimination of ROS by supplemental antioxidants may not eliminate the main cause of the problem, ie, chronic inflammation. Large waist circumferences and high body mass indexes are reported to be powerful independent predictors of type 2 diabetes in US women (12). And, thus far, reduction of body weight and fat by lowering caloric intake and exercise has been proven to be more effective than antioxidant supplementation in lowering the risk of type 2 diabetes and its associated cardiovascular complications.