

Selenium and Diabetes: More Bad News for Supplements

In this issue, Stranges and colleagues (1) report findings from the NPC (Nutritional Prevention of Cancer) trial that show an increased risk for diabetes among participants randomly assigned to receive supplements with 200 μg of selenium daily for 7.7 years compared with placebo. This effect was largely limited to participants in the top tertile of plasma selenium levels at baseline (>121.6 ng/mL). In this group, the hazard ratio for incident diabetes in persons using selenium supplements compared with placebo was 2.70 (95% CI, 1.30 to 5.61). The NPC trial is the largest and longest available experimental study of selenium supplements compared with placebo. Although diabetes was not a primary end point of the trial and the investigators used self-report and medical records to assign the diagnosis, the results have credibility because of the randomized, double-blind design; the monitoring of baseline and follow-up plasma selenium levels; and other methodological strengths. The public health implications of these findings are substantial: More than 1% of the U.S. population take selenium supplements, and more than 35% take multivitamin and multimineral supplements (2) that often contain selenium.

Before it was found to be an essential nutrient (3, 4), selenium was considered highly toxic to animals and humans (5). The key breakthrough occurred in 1973, when Rotruck and colleagues (3) discovered that selenium protected against oxidative damage by means of selenium-dependent glutathione peroxidase. Selenium is incorporated into selenoproteins as selenocysteine through a complex genetic mechanism encoded by the UGA codon (6). Selenoproteins, including glutathione peroxidases, thioredoxin reductases, iodothyronine deiodinases, and selenoprotein P, have important enzymatic functions. Through selenoproteins, selenium is involved in many biological functions, including protection against oxidative stress, immune function, and thyroid function (6, 7).

The concentration and activity of glutathione peroxidases and other selenoproteins increase with increasing intake of selenium until the dose-response relationship reaches a plateau. With the possible exception of selenoprotein P, this plateau of maximum activity is reached at plasma selenium levels of 70 to 90 ng/mL. At greater levels, additional selenium intake further increases the plasma selenium level because of nonspecific incorporation of selenomethionine into albumin and other proteins rather than increased concentration or activity of glutathione peroxidases (8, 9). In the United States, dietary intake of selenium is relatively high (80 to 165 $\mu\text{g}/\text{d}$) (9). Indeed, 99% and 50% of adults have serum selenium levels greater than 95 ng/mL and 124 ng/mL (9), respectively. In short, the risk for selenium deficiency in the United States is negligible, and the use of selenium supplements in this country is unlikely to increase the antioxidant activity of glutathione peroxidases.

Not only are the benefits of selenium supplementation in the United States uncertain, but selenium has a narrow therapeutic range and may be toxic (5, 9). Overt symptoms of acute and chronic selenium toxicity include brittleness and loss of hair and nails, fatigue, neurologic damage, hepatic degeneration, gastrointestinal disturbances, enlarged spleen, and chronic dermatitis (9).

The Institute of Medicine set the Tolerable Upper Intake Level (UL) for selenium at 400 $\mu\text{g}/\text{d}$ to avoid visible symptoms of selenium toxicity in sensitive persons (5, 9). In the NPC trial, participants in the active intervention group received daily supplementation with 200 μg of selenium in addition to their usual selenium intake (1). The increased risk for diabetes in this group alerts us that asymptomatic yet pathologic changes related to chronic selenium toxicity could take place at intake levels lower than the currently defined UL. If the findings of Stranges and colleagues are confirmed, the Institute of Medicine should revise the current upper UL.

The apparent increase in risk for diabetes with selenium supplementation in persons with a dietary intake of selenium in the high-normal range may be biologically plausible. The potential diabetogenic effect of excess selenium could be explained paradoxically by the ability of some selenium compounds to generate reactive oxygen species (10). Selenium may also accumulate in the pancreatic tissue of several animals (5). Under conditions of oxidative stress, reactive oxygen species may increase insulin resistance and affect pancreatic β -cell function (11).

Corroborative epidemiologic evidence is limited. In NHANES III (Third National Health and Nutrition Examination Survey), which was conducted in a representative sample of the U.S. population, participants in the highest quintile of serum selenium levels (≥ 137.7 ng/mL) had an increased prevalence of diabetes compared with those in the lowest quintile (< 111.6 ng/mL) (12). An observational analysis within the SU.VI.MAX (Supplementation with Antioxidant Vitamins and Minerals) trial also found a positive association between baseline plasma selenium levels and fasting plasma glucose levels at baseline and after 7.5 years of follow-up (13). However, a substudy of the Health Professionals Follow-up Study found an inverse association between toenail selenium levels and the prevalence of diabetes at baseline (14), and a small cross-sectional study of Asian persons residing in Singapore found similar mean serum selenium levels among participants with and without diabetes (15).

High-quality prospective cohort studies and randomized trials investigating the effects of dietary selenium and selenium supplements on the incidence of diabetes are needed. These studies should closely monitor diabetes incidence by measuring fasting plasma glucose and other indices of glucose metabolism in groups with a wide range of

selenium intake. Ongoing trials (16, 17) could also be used to confirm the findings of Stranges and colleagues. These studies can help us to understand the dose–response relationship between selenium intake and health outcomes, the benefits and risks for selenium supplementation on diabetes and other chronic health outcomes, and the existence of vulnerable subgroups at risk for side effects. However, until further randomized, controlled trials show that selenium supplementation does not cause diabetes or establish that the potential risk for diabetes is outweighed by yet unproven health benefits, people with diets that provide the Recommended Dietary Allowance for selenium (55 µg/d) (9) should avoid selenium supplements, except in the context of experimental studies.

Although obesity and lack of physical activity are the major factors responsible for the diabetes epidemic, environmental exposures may also be important. High selenium levels (12) or use of selenium supplements by persons with adequate selenium status (1) may contribute to this problem, although the extent of the role of these factors is unknown. Furthermore, the potential harmful effects of selenium supplementation in persons with high-normal selenium levels could extend beyond diabetes. A secondary analysis of the NPC trial identified some benefit of selenium supplementation for cancer prevention among participants with baseline plasma selenium levels less than 121.6 ng/mL but a possible small increase in total cancer risk among participants with higher levels (hazard ratio, 1.20 [CI, 0.77 to 1.86]) (18).

In the past decade, randomized, controlled clinical trials have shown that β-carotene and vitamin E supplements, which were widely believed to be safe, increase mortality and morbidity (19, 20). No dietary supplement, including selenium, has proven useful so far for the prevention of cardiovascular disease or cancer in the general U.S. population. The balance of the potential benefits and harms of selenium supplementation depends on the dietary selenium intake in different countries. However, the U.S. public needs to know that most people in this country receive adequate selenium from their diet. By taking selenium supplements on top of an adequate dietary intake, people may increase their risk for diabetes.

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