Vitamin D and Type 2 Diabetes

Are We Ready for a Prevention Trial?

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Diabetes rates are increasing around the world, mainly driven by increasing levels of obesity (1). The dilemma for diabetes prevention is that the main risk factor—obesity—is a product of our modern lifestyle (the so-called obesogenic environment) (2). Immediate prospects for changing the environment to reverse rising obesity levels are not promising, and there is a need to consider other options for preventing diabetes.

One of these options—vitamin D—is addressed in the article by Forouhi et al. (3) in the current issue of *Diabetes*. The sun is the primary source of vitamin D, which is synthesized endogenously in skin to produce cholecalficerol (vitamin D_3), although a small proportion (<20%) of vitamin D comes through diet from a limited range of foods (in the form of ergocalciferol [vitamin D_2] and vitamin D_3) (4). The main marker of vitamin D status is the metabolite 25-hydroxyvitamin D [25(OH)D], which is synthesized in the liver. The epidemiology of vitamin D status is inverse to that of diabetes, since blood levels of 25(OH)D decline with age and are lower in populations with increased skin pigmentation, such as African Americans and South Asians, and in people with obesity, while diabetes increases with age and obesity and is higher in these ethnic groups (5).

Animal studies published nearly 30 years ago identified a pancreatic receptor to the active metabolite (1,25-dihydroxyvitamin D) (6) and showed that vitamin D deficiency decreased insulin secretion (7). Since then, numerous human studies of vitamin D and type 2 diabetes have been published, but the quality of these studies is mixed (8). Many are case-control studies flawed by the measurement of 25(OH)D status on blood samples collected after diabetes diagnosis. Several population-based cross-sectional studies have been published showing inverse associations between 25(OH)D and undiagnosed diabetes risk, including two large national surveys (9,10), but this study design provides only moderate evidence regarding causation because of the simultaneous measurement of 25(OH)D and diabetes status. Stronger evidence comes from prospective studies, of which there have been two that show inverse associations between dietary vitamin D and diabetes risk (11,12); however, these studies are limited because they did not assess the major nondietary component of vitamin D from sun exposure.

The potentially strongest evidence comes from intervention studies. Again, there are limitations with these because of small sample sizes and short intervention time periods. Only three intervention studies had more than 100 participants and also administered vitamin D for long periods (2–3 years). One study did not find any effect from a vitamin D_3 dose of 2,000 IU/day but had only 25 people on this dose (13). Another was a post hoc analysis of a trial designed for bone-related outcomes that found that 700 IU/day of vitamin D_3 (combined with calcium) decreased homeostasis model assessment of insulin resistance in participants with impaired glucose tolerance but not in those with normal fasting glucose (14). The largest sample to date of 33,951 women in the Women's Health Initiative study did not observe any effect from vitamin D (15). Again, there are major limitations with this study due to the low vitamin D_3 dose of 400 IU/day, which only increases blood 25(OH)D levels by about 7 nmol/l (16); less-than-ideal compliance; and the presence of contamination, since control subjects were able to take vitamin D.

In the absence of well-designed clinical trials, the strongest evidence to date is provided by cohort studies comparing baseline measures of blood 25(OH)D (which reflect vitamin D status from both sun and dietary sources) and subsequent glycemic status. The study by Forouhi et al. provides such evidence from an English cohort in the town of Ely by showing that baseline serum 25(OH)D levels are inversely associated with glucose and insulin levels collected 10 years later (3). These findings confirm recent results from a Finnish cohort study showing an inverse association between baseline serum 25(OH)D and 17-year risk of type 2 diabetes, which was attenuated after adjustment for confounders (17). Together, the two articles provide strong evidence that low vitamin D status predicts hyperglycemia. In addition, the current article provides new prospective evidence that low levels of vitamin D also predict hyperinsulinemia, a finding that confirms previous cross-sectional studies (9,18) and suggests that vitamin D may act to prevent type 2 diabetes by decreasing insulin resistance, although it may also inhibit insulin secretion (18).

The strengths of the Ely study, in addition to its prospective design and use of 25(OH)D to measure vitamin D status, include its community-based sampling, which increases the generalizability of the results, and the controlling of the most important confounders (obesity and physical activity) in statistical analyses. Its limitations are its relatively small sample size (n = 524) and the 50% loss to follow-up after 10 years. The authors report that participants included in the 10-year follow-up analyses were healthier at baseline than those excluded, and as they state, this is likely to have resulted in a more conservative

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estimate of the association between vitamin D and glycemic status.

Despite evidence from the current article (3) and the Finnish study (17), doubts still remain about whether low vitamin status is a cause of type 2 diabetes. Further cohort studies are required, assessing baseline vitamin D status using blood 25(OH)D to be sure that the Ely and Finnish studies are not false-positive results. Glucose clamp studies are also required because we are still not sure of the mechanism influenced by vitamin D—whether it is insulin resistance, secretion, or both. But most importantly, given that nearly three decades have passed since the first studies linking vitamin D with insulin metabolism (6,7), well-designed clinical trials of the effect of vitamin D supplementation on glycemia status and diabetes risk are urgently required to settle this question. And they need to prevent past mistakes. In particular, the vitamin D dose given in such trials needs to be high enough—above 2,000 IU per day (19)—to raise blood 25(OH)D levels above 80 nmol/l because diabetes risk is lowest at this level (9,20). If well-designed trials are carried out and confirm a protective effect from vitamin D, it could be used by the general population as a simple and cheap solution to help prevent the diabetes epidemic.

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