CORRESPONDENCE

Vitamin D and Risk for Type 2 Diabetes in People With Prediabetes

TO THE EDITOR: Pittas and colleagues' systematic review and meta-analysis (1) showed that higher-dose oral vitamin D supplementation is associated with a reduced risk for type 2 diabetes mellitus (T2DM). Of interest, the authors report that this effect may be greater in "leaner" persons, especially those with a body mass index less than 31.3 kg/m^2. To explain this variance, they chiefly speculate that obesity suppresses the activation of key cytochrome P450s (CYPs)—namely, CYP2R1 and CYP27B1—which jointly function to endogenously convert vitamin D_3 into its biologically active form, 1,25-dihydroxyvitamin D_3. Although this analysis from Pittas and colleagues is thoughtful, the explanation offered for the differential effects on younger, leaner participants is probably misattributed to CYP regulation.

In both relative and absolute numbers, immune-mediated destruction in those diagnosed with T2DM is substantial; a median of approximately 10% of participants in large, representative "T2DM cohorts" test positive for at least 1 autoantibody, including glutamate decarboxylase (GAD), islet cytoplasmic antibodies, insulinoma-associated protein 2, or zinc transporter 8. In general, these patients are given a diagnosis of latent autoimmune diabetes.

Several prominent population studies have affirmed this finding. The 1997 UKPDS (UK Prospective Diabetes Study) tested 3672 White patients with T2DM aged 25 to 65 years for autoantibodies (GAD and islet cytoplasmic antibodies); 10% of patients newly diagnosed with T2DM tested positive for 1 or both of these (2). Patients who tested positive for GAD and islet cytoplasmic antibodies and were younger than 35 years had a body mass index that was significantly lower (24 vs. 31.7 kg/m^2; $P <$ 0.001). A 2004 multinational cohort (ADOPT [A Diabetes Outcome Progression Trial]) of 4134 patients newly diagnosed with T2DM similarly reported a positivity rate of 4.2% for GAD antibodies and found that GAD-positive patients were less likely to have classical features associated with metabolic syndrome, such as low high-density lipoprotein cholesterol, high triglyceride, and elevated fasting insulin levels (3). More recently in 2018, HUNT (Trøndelag Health Study) documented more than 7% to 8% positivity for GAD among 2002 Norwegians recently diagnosed with diabetes (4). Altogether, a distinct subpopulation of those diagnosed with T2DM probably have clinical markers of autoimmunity and therefore islet destruction that contributes to insulin dependence.

Vitamin D's role in the primary prevention of autoimmune-associated diseases such as latent autoimmune diabetes has shown compelling results. In a 2012 trial of 38 participants recently diagnosed with type 1 diabetes mellitus, Gabbay and associates (5) reported that in those randomly assigned to receive 2000 IU of vitamin D per day, only 18.5% progressed to undetectable C-peptide levels versus 62.5% of control participants.

We applaud Pittas and colleagues for this systematic review and meta-analysis but cautiously advocate for a more nuanced understanding of the differential effects on subpopulations of persons with prediabetes at risk for T2DM potentially driven by a distinct autoimmune pathology and attenuated by higher doses of vitamin D supplementation.

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IN RESPONSE: We thank Mr. Hands and colleagues for their insightful comment. Our hypothesis that suppression of CYP2R1 in persons with obesity leads to reduced production of blood 25-hydroxyvitamin D may explain why vitamin D seems to work better in leaner people with prediabetes. However, it does not preclude other explanations.

Several lines of evidence support a beneficial role for vitamin D in pancreatic β-cell function—either directly by binding to β-cell vitamin D receptors or indirectly by regulating calcium flux through the β cell, which is important for calcium-mediated insulin secretion (1). Vitamin D therefore may work better for diabetes prevention in leaner persons because they are more likely to have predominantly impaired pancreatic β-cell function leading to insulin deficiency. Indeed, in the DPVD (Diabetes Prevention with active Vitamin D) study, eldecalcitol had a favorable effect on diabetes risk among participants with insufficient insulin secretion (2).

Pancreatic β-cell autoimmunity may be present in more than 10% of persons diagnosed with T2DM (3). We agree with Mr. Hands and colleagues that this autoimmunity leading to pancreatic β-cell destruction is 1 pathway toward insulin deficiency. We also agree that high-dose vitamin D may attenuate the autoimmune-mediated pathology. Because none of the 3 trials measured circulating β-cell autoimmune markers, we cannot test the hypothesis that vitamin D benefited predominantly participants who had prediabetes and evidence of β-cell autoimmunity.

This would be a compelling area for future research to better identify subpopulations at risk for diabetes who are most likely to benefit from vitamin D.

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