Untangling the Gordian Knot of Vitamin D Supplementation and Type 2 Diabetes Prevention

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Approximately one-third of the adult U.S. population has prediabetes, ~5–10% of whom will progress to diabetes per year (1,2). Intensive lifestyle changes delay progression to diabetes; however, sustaining lifestyle changes long term is challenging and often insufficient to prevent development of diabetes (3). Simple, inexpensive, and sustainable approaches to complement lifestyle changes are therefore needed to lower diabetes risk in people with prediabetes.

Over the last decade, vitamin D has emerged as a potential modifier of the pathophysiology of type 2 diabetes and vitamin D supplementation has been hypothesized as a promising intervention to lower diabetes risk (4). Observational studies report consistent associations between higher blood 25-hydroxy vitamin D [25(OH)D] concentration and lower risk of developing type 2 diabetes in diverse cohorts (5). Mechanistic studies provide a strong biological basis for an important role of vitamin D in improving pancreatic β-cell function, but there is less evidence on its effects on insulin resistance (6). Until recently, evidence from trials examining the effect of vitamin D supplementation for diabetes prevention was lacking.

In 2019, the U.S.-based Vitamin D and Type 2 Diabetes (D2d) study reported that participants with prediabetes assigned to vitamin D supplementation had a 12% decrease in risk of developing diabetes compared with placebo, but the change was not statistically significant (hazard ratio [HR] 0.88 [95% CI 0.75–1.04) (7). The effect size in D2d was nearly identical to those reported by two similar but smaller trials (Tromsø [Norway], HR 0.90 [95% CI 0.69–1.18], and Diabetes Prevention with active Vitamin D [DPVD] [Japan], HR 0.87 [95% CI 0.68–1.09]) (8,9). Prior meta-analyses did not include these recent trials; thus, the field is ripe for updated meta-analyses.

In the current issue of *Diabetes Care*, two meta-analyses on this topic are published (10,11). Pramono et al. (10) combined results from 18 small trials (total of 1,220 participants) examining the effect of vitamin D supplementation on insulin sensitivity in adults with or at increased risk for insulin resistance. They report no effect of vitamin D supplementation (standardized mean difference −0.01 [95% CI −0.12 to 0.10]). Zhang et al. (11) synthesized results from eight trials (total of 4,896 participants) examining the effect of vitamin D supplementation on incident diabetes in persons with prediabetes. The authors found a significant benefit of vitamin D supplementation for incident diabetes (risk ratio 0.89 [95% CI 0.80–0.99). Additionally, meta-analysis of five trials (total of 1,080 participants) revealed that participants on vitamin D supplementation were more likely to revert to euglycemia than the non–vitamin D group (risk ratio 1.48 [95% CI 1.14–1.92]).

While meta-analyses increase statistical power, allowing more precise effect estimates, for them to be credible certain methodological criteria must be met. Even if the methodology is sound, the strength of a meta-analysis result is only as high as the quality of the included individual trials. Table 1 summarizes our assessment of the two new systematic reviews.

The meta-analysis by Pramono et al. (10) has major limitations, primarily based on the included studies: *1*) Target populations were people "with or at risk for insulin resistance," but no definition of insulin resistance was provided. *2*) Trial populations were heterogeneous. *3*) Vitamin D could be coadministered with other interventions, which may confound the effect of vitamin D. *4*) The outcome of interest was ascertained by different methods across trials. *5*) In all but one trial, study duration was between 2 and 6 months, which is too brief to achieve steady-state blood 25(OH)D concentration and likely inadequate to affect the pathophysiology of type 2 diabetes.

The main advantage of a meta-analysis is to improve statistical power for the outcome of interest. However, when

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Table 1—Evaluation of systematic reviews

	Pramono et al. (10)	Zhang et al. (11)
Topic	Insulin sensitivity	Clinical outcomes (incident type 2 diabetes)
Sensible clinical question	Insufficiently focused	Yes
Exhaustive search	Yes (except restricted to English)	Yes
Evaluated populations	Differ widely (healthy participants with normal glucose tolerance, overweight, prediabetes, polycystic ovarian syndrome, or established type 2 diabetes regardless of diabetes pharmacotherapy)	Similar and appropriate (prediabetes)
Evaluated interventions	Differ widely (oral or injectable vitamin D coadministered with other interventions, e.g., metformin, hypocaloric diet, cheese); short-term (2–6 months)	Similar and appropriate (oral vitamin D); long-term (all but one trial $\geq$1 year)
Evaluated comparators	Data not provided	Similar and appropriate (placebo); two trials were open-label, i.e., there was no comparator
Evaluated outcomes	Differ widely (insulin clamp, oral glucose or intravenous glucose tolerance test, use of different indices to estimate insulin sensitivity)	Similar and appropriate (incident diabetes, reversion to euglycemia)
Meta-analysis methods	Problematic (combined highly heterogenous studies)	Problematic (fixed-effects model meta-analysis, ecological fallacy)
Results reporting	Appropriate but difficult to interpret (standardized mean difference)	Appropriate and easy to interpret (risk ratio, HR)
Risk of bias assessment	Appropriate	Appropriate
Risk of bias	Mostly low (blinding unclear)	Mixed (lack of blinding)
Quality/strength of evidence	Not evaluated	Moderate/high
Generalizability of findings	Unclear	Not evaluated

there are many differences in participant characteristics, interventions, outcome assessment methods, and study quality between the included trials, combining data from such trials increases variability, which reduces statistical power, making it difficult to identify real effects (12). Therefore, the meta-analysis by Pramono et al. cannot be conclusive regarding whether vitamin D supplementation improves insulin sensitivity in meaningful populations.

Zhang et al. (11) address a clinically relevant question (does vitamin D supplementation reduce the incidence of diabetes in persons with prediabetes?), and its main strength is inclusion of trials that are concordant in populations (prediabetes), intervention (oral vitamin D), and outcome ascertainment (diabetes based on glycemic criteria). This meta-analysis incorporates results from the three largest trials (7–9), which had not been included in prior meta-analyses, and makes an additional contribution by summarizing data on the outcome of reversion to normoglycemia, which is often overlooked in diabetes prevention trials.

However, five of the included trials had major limitations, including not being designed for incident diabetes as the primary outcome (13–16), short duration ($\leq$1 year) (13–16), open-label study design (i.e., not placebo) (15,17), and small sample size (13–17). Therefore, results from these five trials provide limited information to test the hypothesis. To address these limitations, the authors conducted several sensitivity analyses. The resultant point estimates changed minimally, likely because these five trials contributed only 8% of the weight in the summary estimate. Indeed, when data were combined from the three large randomized, placebo-controlled trials that were specifically designed and conducted for prevention of diabetes (7–9), vitamin D supplementation reduced diabetes risk by 12% compared with placebo (HR 0.88 [95% CI 0.78–0.99).

Zhang et al. reported a benefit of vitamin D supplementation on incident diabetes in nonobese participants only (BMI $<$30 kg/m^2); however, such a subgroup claim is highly problematic and may be erroneous (subject to ecological fallacy) because the analysis was generated based on the average BMI of each trial cohort rather than the BMI of each participant (18). There are similar concerns in their analyses of baseline and achieved blood 25(OH)D concentration and follow-up duration. Hence, in the absence of within-trial subgroup results or individual participant data, such subgroup results are uninterpretable.

Nevertheless, assuming the findings of the two systematic reviews are correct raises the question of why they seem to disagree: vitamin D supplementation does not substantively affect insulin sensitivity, yet it reduces diabetes risk among people with prediabetes. We posit several potential explanations: *1*) The effect of vitamin D supplementation may not be evident in the short term (2–6 months across the insulin sensitivity trials in Pramono et al.) compared with the longer-term finding on incident diabetes (2–3 years across the diabetes prevention trials in Zhang et al.). *2*) The effect of vitamin D supplementation is difficult to demonstrate in populations with a wide range of "risks" (e.g., overweight, polycystic ovarian syndrome, established diabetes on pharmacotherapy). *3*) Given that the apparent effect of vitamin D on diabetes risk is relatively small ($\sim$12%), it may be that improvement in insulin sensitivity is relevant in only a "hidden" small subset and may not be noticeable when averaged with the larger subset whose insulin sensitivity is not affected by vitamin D.

4) Vitamin D does not have a detectable effect on insulin resistance and works mostly via augmenting β-cell function (19).

Where do we go from here? Answers to important clinical questions are rarely clear-cut, and the truth is almost never dichotomous ("effective" or "ineffective"). The evidence for vitamin D in favor of diabetes prevention is accumulating, and these meta-analyses were worthwhile attempts to assemble pieces of the vitamin D and diabetes prevention puzzle. We are not aware of any ongoing trials specifically designed and powered to test the effect of vitamin D supplementation for diabetes prevention. We expect ongoing or completed large trials that were designed and conducted to test the effect of vitamin D supplementation on nondiabetes outcomes to also report on incident diabetes as a secondary outcome. However, these reports will require careful interpretation due to several expected limitations, e.g., enrollment of populations at low-average risk for diabetes, inadequate vitamin D dose, and insufficiently defined diabetes outcome.

Although the summary estimate of 11–12% relative risk reduction reported by Zhang et al. may appear relatively small, it can have important public health implications when applied in the expanding prediabetes population. We should also not discount the benefit of reversal of prediabetes to euglycemia. Hence, in evaluation of the overall benefit of vitamin D supplementation, this higher likelihood of reversal to euglycemia (~48% more likely in the report by Zhang et al.) should be added to the 12% lower risk of progression to diabetes.

These findings may warrant a recommendation for vitamin D supplementation in adults with prediabetes, particularly given its apparent safety, as evidenced from the two largest trials, Tromsø and D2d (7,8), and low cost. However, given limitations of the evidence base, and thus of these new meta-analyses, final recommendations must await full publication of the second-largest trial (DPVD [9]) and results from individual participant data meta-analyses. Compared with study-level meta-analyses, individual participant data meta-analyses can provide precision of the estimate for progression to diabetes, regression to euglycemia, and safety using time-to-event analyses. They can also overcome the problem of ecological fallacy and, thus, can evaluate heterogeneity of treatment effects across participant subgroups to better define who is most likely to benefit (20). Unlike in Greek mythology, it will take more than a sword to untangle the "Gordian knot" of vitamin D supplementation and type 2 diabetes prevention.

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