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Vitamin D supplementation to prevent the progression of pre-diabetes to diabetes: Getting closer to a recommendation

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In addition to its more well-known properties of preventing osteomalacia and building bone density, Vitamin D has been touted as a supplement with claims that it can help prevent cancer, treat heart disease and high blood pressure, help to fight tuberculosis and other infectious diseases and most interestingly, prevent or treat diabetes. Vitamin D supplementation improved insulin release in some,^{1–3} but not all,^{4,5} small-scale short-term randomized trials. Vitamin D may have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptor and thereby enhancing insulin responsiveness for glucose transport,⁶ or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes.⁷

However, in humans, the majority of evidence linking vitamin D and diabetes are based on correlation studies in which levels of 25-hydroxy vitamin D (25-OHD), which is the most valid measure of vitamin D status, have been correlated with increased incidences of heart disease, cancers, infection, and diabetes. Our group examined data from the Third National Health and Nutrition Examination Survey (NHANES III) and found a high prevalence of low serum 25-OHD levels that was more prevalent in women, elderly persons, racial/ethnic minorities and subjects with diabetes, hypertension and obesity.⁸ Most importantly, the prevalence of diabetes was 2-fold higher in participants in the first compared to the fourth quartile of serum 25-OHD levels. These correlation studies have been confirmed by many other groups (reviewed in⁹). Of course, we all know correlation studies do not prove causation, and it has also been speculated that low 25-OHD levels are a marker for morbidity including the amount and duration of obesity, staying inside too much, not enough exercise, and overall ill health.¹⁰

In terms of intervention studies, a *post hoc* analysis of a trial designed for bone-related outcomes that demonstrated that combined supplementation with 700 IU of vitamin D3 and 500 mg of calcium as calcium citrate malate had no effect on glycemia or insulin resistance in 221 adults over age 65 with normal glucose tolerance at baseline.¹¹ However, among participants with impaired fasting glucose (IFG) at baseline, those who took combined vitamin D3 and calcium supplements had a significantly lower rise in fasting glycemia and insulin resistance at 3 years compared with those on placebo.¹¹ No other time points were examined and hypovitaminosis D was not required for entry. In a presentation at the 93rd

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annual Endocrine Society meeting, Burnett-Bowie et al. showed that in healthy persons with low 25-OHD and no evidence of insulin resistance, vitamin D administration for 12 weeks normalized 25-OHD levels but did not improve insulin sensitivity or secretion.¹²

Importantly, there have also been a few cohort studies showing that low levels of vitamin D can predict development of diabetes. Forouhi et al. used an English cohort in the town of Ely and showed that baseline serum 25-OHD levels were inversely associated with glucose and insulin levels collected 10 years later.¹³ These findings confirmed results from a Finnish cohort study showing an inverse association between baseline serum 25-OHD and 17-year risk of type 2 diabetes.¹⁴ Together, the two articles provide strong evidence that low vitamin D status predicts hyperglycemia. What are needed, however, are prospective studies evaluating whether vitamin D treatment can improve conditions such as diabetes or prevent its onset.

In this issue of *Translational Research*, Nazarian and colleagues¹⁵ performed a non-controlled study in which they studied 8 subjects with vitamin D deficiency and IFG with the modified frequently sampled intravenous glucose tolerance (mFSIGT) test before and four weeks after high dose vitamin D supplementation (10,000 iU/day). 25-OHD levels increased from a mean pre-intervention level of 20 ± 7 ng/mL to a mean post-intervention level 45 ± 8 ng/mL. These patients saw an improvement in insulin sensitivity, suggesting that vitamin D would be useful for preventing progression from prediabetes to diabetes. However, this study has two important limitations. First of all, the number of subjects was low and only eight subjects were included in the analysis. Of the eight patients, seven of them showed an improvement in their insulin sensitivity index, a promising finding, but this is a small number of subjects. The second problem with the study was that it was not placebo-controlled. All patients did get vitamin D, which brings up the issue about what kind of placebo effect can be seen in objective studies such as this studying measuring insulin resistance. Placebo-controlled studies are clearly needed when quality-of-life issues are examined, as just being in a study has been known to improve quality of life measurements. However, this study examines a hard outcome, insulin sensitivity as measured by frequent glucose tolerance testing. In general, prediabetes [either IFG or impaired glucose tolerance (IGT)] usually progresses and not improves with time, and it would be hard to imagine how a placebo group would have a similar improvement as the intervention group.

This study brings up several other issues in evaluating whether vitamin D supplementation can be helpful to either treat or prevent diabetes. First of all, the study used an appropriate target group, patients with prediabetes (either IFG or IGT). This is the group that is desirable for intervention to prevent the progression of diabetes, especially in a cost-effective manner such as vitamin D administration. Once the patient has full-blown diabetes, the patient is already on treatment and it would be very hard to evaluate whether an additional treatment like vitamin D actually affects glycemic status. In fact, interventional trials using vitamin D supplementation in subjects with existing type 2 diabetes have shown no overall improvement in beta cell function or insulin resistance.^{16–18} Additionally, studying normal patient (as done by Burnett-Bowie et al.¹²) is also probably not the correct group, as those patients have a reserve of insulin secretion that makes it unlikely that they will benefit from a treatment like vitamin D supplementation. As the Diabetes Prevention Program (DPP)¹⁹ showed, many patients with prediabetes (impaired glucose tolerance in the case of the DPP) do go on to full-blown diabetes, and treatments such as intensive lifestyle intervention can prevent this progression. It is hoped that vitamin D supplementation may be beneficial as well.

Another issue that the Nazarian study brings up is what should the target levels of 25-OHD be in studies. The optimal range of vitamin D is controversial. For example, the Institute of Medicine recommended a value above 20 ng/mL,²⁰ although many societies have recommended higher levels. For example, the recent consensus statement from the Endocrine Society stated that the target range should have a lower limit at 30 ng/mL and to guarantee sufficiency, levels between 40 and 60 ng/mL for both children and adults should be targeted.²¹ Vitamin D toxicity does not occur until 25-OHD levels are well above 100 ng/mL,²² but the actual target 25-OHD level is unknown. To see the most pronounced effect in a study, one would like to see a 25-OHD level in the upper-normal range, which I would consider between 60 and 80 ng/mL. If a study does not achieve those target levels and did not have an effect, the study could be criticized for not giving enough vitamin D and not achieving high enough levels. Only if a study did achieve high enough levels and still did not have an effect, one could then say that the vitamin D supplementation was not effective to prevent the progression of prediabetes to diabetes.

Our group at Charles Drew University (Mayer B. Davidson, MD and myself) have received funding from the American Diabetes Association²³ to study a 12 month supplementation of vitamin D or placebo to examine the progression from prediabetes to diabetes and glycemic parameters in an inner-city population. We have completed enrollment of 107 subjects and expect analysis to be completed in early 2012. We used a weekly high-dose vitamin D supplementation that was based on the patient's weight, as it is known that patients who are overweight need increased amounts of vitamin D supplementation to achieve target levels, as well as the initial starting level of 25-OHD with the idea that patients with a lower starting level will need a greater supplementation. The study included patients with 25-OHD level less than 30 ng/mL as well as either impaired fasting glucose or impaired glucose tolerance (confirmed by an oral glucose tolerance test). Subjects then received vitamin D drops or placebo drops weekly for 12 months and oral glucose tolerance tests were done every three months. At all time points after baseline mean 25-OHD levels were between 60 and 70 ng/mL in the group receiving treatment and 20–25 ng/mL in the placebo group. There were no adverse events associated with vitamin D supplementation. We anxiously await the results of this study.

In conclusion, while the study by Nazarian and colleagues is helpful towards showing that vitamin D supplementation has benefits in terms of glycemic parameters, only with large, placebo-controlled prospective treatment studies can we actually show that vitamin D is beneficial and should be recommended to prevent the progression from prediabetes to diabetes. If proven, vitamin D supplementation could be quite important to stem the tide of the increasing rates of diabetes.

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