EDITORIAL (SEE JOERGENSEN ET AL., P. 1081)

Vitamin D Deficiency Is Not Good for You

In this issue of *Diabetes Care*, Joergensen et al. (1) demonstrate a strong association between severe vitamin D deficiency and increased mortality in patients with type 1 diabetes. This observation confirms previous findings in the general population and in subgroups at high cardiovascular risk such as patients with type 2 diabetes or renal impaired patients (2–4). The data by Joergensen et al. complete the picture while carefully avoiding possible criticisms that have made the vitamin D field so hazardous to tread in recent years. Indeed, rather than hard science, it is hype and media statements that crowd the scene. This article brings with it a breath of fresh air.

Many studies are conducted retrospectively or measure vitamin D levels when patients are already sick. Thanks to the excellent registries present in several Northern European countries—and here in particular thanks to the database and tissue bank of the reputed Steno Diabetes Center—this study is able to assess levels of vitamin D measured within 3 years after diagnosis and during up to 25 years of clinical follow-up. This way of working avoids justified criticisms on studies where vitamin D levels were measured at the time of severe diseases. Obviously, patients with congestive heart failure or cancer are less likely to go out and about in the sun or eat fatty fish. Only prospective studies will help to understand the relationship between vitamin D levels and disease. Because vitamin D deficiency in rodents in the early stages of life is predictive of future disease, it would be of great interest to evaluate vitamin D levels in neonates. We have previously demonstrated a twofold risk for the development of diabetes in NOD mice that had been vitamin D deficient in the first 100 days of their lives (5). As vitamin D levels can be measured on dried spots of blood of Guthrie cards that are routinely obtained from all newborns in many countries, such a study is both feasible and could potentially further elucidate the link between vitamin D levels and the development of a wide range of diseases.

The choice of measuring vitamin D levels using the gold standard method of liquid chromatography followed by tandem mass spectrometry (LC/MS-MS) is a second asset of the present work (6). Although levels of 25-hydroxyvitamin D [25(OH)D] are high enough to allow detection by immunoassay techniques, avoiding the use of antibodies results in much more reliable measurements with LC/MS-MS. Furthermore, novel data indicate that modified forms of 25(OH)D may be circulating that are falsely overdetected or not detected by the antibodies and may have physiological implications. Still, at present only a few laboratories around the world are able to measure 25(OH)D by LC/MS-MS, and most laboratories therefore continue to use kits. Their continued widespread use might lead to an overestimation of both the frequency and magnitude of vitamin D deficiency.

This brings us to the other crucial question of where to put the cutoff that defines vitamin D deficiency, even with LC/MS-MS. We do not know, and we do not have a consensus. In addition, there is ongoing debate concerning the dosage of nutritional and vitamin D supplements required to achieve vitamin D sufficiency (7). The turmoil around a statement released by the Institute of Medicine (IOM) is just an illustration of the problem. For bone health, defining the level of vitamin D deficiency is relatively easy as the rise in parathyroid hormone levels can be used as a marker for vitamin D levels that are too low. When 25(OH)D levels drop below 10–20 ng/mL (25–50 nmol/L), parathyroid hormone levels rise, indicating the switching on of the feedback cascade, suggesting that this is the level below which 25(OH)D levels are really deficient. Here, the authors avoid the cutoff discussion and its clinical relevance by using the lower 10th percentile to define deficiency. As a consequence, this study's conclusion is based on data from very severely vitamin D–deficient individuals. Literature on the effects of vitamin D at levels above 20 ng/mL (50 nmol/L) becomes very difficult to interpret because the only available data are from association or preclinical studies in animal models.

So, what should we conclude with regard to vitamin D deficiency (and here we agree to talk about the true deficiency, the severe one)? The National Health and Nutrition Examination Survey (NHANES) indicated a continuum on mortality risk in the general population with an increased cardiovascular risk in patients with low vitamin D levels. In diseases like type 2 diabetes and chronic renal failure, similar observations were made, suggesting that the excess mortality is related to an increase in cardiovascular events. This hypothesis is strengthened by preclinical and in vitro data. Higher levels of inflammation, higher blood pressure, and increased vascular resistance (via renin-angiotensin-aldosterone system) are observed in vitamin D–deficient patients and animals, whereas supplementing with regular vitamin D or activated forms of vitamin D (native 1,25-dihydroxyvitamin D or a synthetic analog such as paricalcitol) lowers inflammation, lowers blood pressure, and decreases vascular resistance (8). Interestingly, the current study did not find an association between vitamin D deficiency and the onset or progression of nephropathy, whereas in previous studies in patients with type 2 diabetes and in models of chronic renal impairment, vitamin D deficiency is associated with microalbuminuria and supplementing with vitamin D (analogs) prevents progression to proteinuria (9). This finding suggests that the pathogenesis of microalbuminuria in type 1 diabetes is a completely different entity from microalbuminuria in type 2 diabetes or other forms of renal disease. In type 1 diabetes, nephropathy is probably purely microangiopathic and therefore closely related to the development of retinopathy, both of which were uninfluenced by vitamin D status here.

In view of the mean age and the survival curves of the patients, it is questionable that cardiovascular events contribute significantly to mortality in this study. As we have no insight into the direct causes of death, other events such as accidents or cancer may underlie the increased mortality in vitamin D–deficient patients with type 1 diabetes. Accidents are hard to account for by vitamin D deficiency, but an increased cancer risk does come out of other epidemiological studies (10). Almost all cancers are correlated with vitamin D deficiency (with the caution that in most studies, vitamin D is

dosed when cancer is already present), except for pancreatic cancer where several studies point to a lower risk in individuals with lower vitamin D levels (11,12).

What should we do now? Evidence linking true vitamin D deficiency (<10 ng/mL [25 nmol/L]) to adverse outcomes seems solid, and the impact of the vitamin D deficiency happens early in life. Avoiding vitamin D deficiency is thus the message. The IOM has confirmed the nutritional advice that existed: 600 IU of vitamin D per day as supplements or in food (fortified products, or fatty fish like mackerel. . . .) for all and 800 IU for people over 70 years of age (7). One may of course also make his or her own by sitting in the sun. Half an hour of exposure of face and hands daily should suffice to maintain adequate vitamin D levels, but some caveats apply (13). The wavelength of UV light that is necessary to make vitamin D in skin is exactly the same as the one that ages skin and causes skin cancer. Moreover, in winter, the sun does not rise high enough in the sky in large parts of the U.S., Europe, and certainly Canada, to allow us to make any vitamin D. And if one is dark skinned, exposing skin to sun has almost no effect on vitamin D levels. Exciting data point toward an "individual" set point for vitamin D sufficiency determined by the presence of polymorphisms in the carrier protein (DBP), but also polymorphisms in the vitamin D receptor and the enzyme responsible for final activation of vitamin D into 1,25-dihydroxyvitamin D (CYP27B1). This implies one individual may have to take more vitamin D in order to achieve vitamin D sufficiency than another (14).

In this study, no relationship between BMI and vitamin D levels was observed despite overwhelming evidence that a negative correlation exists (15). The reason is that these young Danes were all of normal weight (mean BMI 20 kg/m^2). In overweight patients, vitamin D accumulates in excess fat, leading to low circulating levels. Therefore, doctors should certainly screen for vitamin D deficiency in obese patients with diabetes and replete if necessary. Extra attention should be paid to patients who underwent bariatric surgery causing fat malabsorption. These individuals are at extreme risk of vitamin D deficiency and sometimes need extreme doses to achieve sufficiency (16).

In conclusion, vitamin D deficiency is associated with increased mortality in type 1 diabetic patients as well. Being aware of populations at risk and screening for vitamin D deficiency with appropriate methods is therefore essential. Cutoff levels for deficiency and sufficiency are under discussion, but levels below 10 ng/mL (25 nmol/L) are considered severely deficient and should certainly be avoided and supplemented. Guidelines suggest supplements of vitamin D of 600 IU per day in all and 800 IU in elderly (age >70 years). Many voices shout for higher doses, but only demonstrating these claims by hard clinical data will move the field forward from hype to science.

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