Vitamin D and diabetes: Much ado about nothing?

Vitamine D et diabète : beaucoup de bruit pour rien ?

At the end of the 1980s, we reported that circulating levels of 25(OH)D were lower in type 1 diabetic patients (T1DM) treated with either subcutaneous multiple injections or continuous infusions of insulin compared with patients treated with continuous intraperitoneal infusions of insulin [1]. At the time of publication, we concluded that insulin per se had a direct stimulatory effect on the activity of the hepatic 25-hydroxylase that converts vitamin D to 25(OH)D [2]. The latter compound is currently the most monitored metabolite in plasma for assessing vitamin D status [2–5]. Yet, the insulin effect was virtually completely ignored 20 years ago because, in the 1980s, no one was really interested in the possible relationships between diabetes and regulation of vitamin D metabolism. At present, however, these relationships are at the forefront of medical debate. Several publications [6,7] and reviews [8–11] have highlighted the possible role of vitamin D deficiency as a risk factor in the development of chronic diseases such as diabetes. More generally, it has been reported that vitamin D deficiency is a common disorder in the developed countries [9,12], even though the nutritional status of the general population as a whole appears to be adequate. Returning to the specific issue of the relationships between diabetes and vitamin D metabolism, the question is whether or not we need to supplement people with vitamin D to prevent the onset or progression of diabetic states.

1. Possible links between diabetes and vitamin D

Most of the clinical studies undertaken to look at the possible role of vitamin D in diabetes are mainly clustered around epidemiological, observational and cross-sectional studies [11]. In contrast, interventional trials have rarely been conducted. At present, we are still searching for results of large interventional studies specifically designed to assess the impact of dietary or pharmacological supplementation with vitamin D on the prevention or progression of diabetes in individuals prone to, or affected by, the condition.

A suggestion of the relationship between diabetes and vitamin D has been provided by the observation of vitamin D deficiency in newly diagnosed T1DM [13] and T2DM [14,15]. With the development of routinely used measurements of vitamin D metabolites and its derivatives in plasma, the definition of vitamin D deficiency is no longer based on clinical criteria, but is now founded on the finding of low circulating concentrations of either 25(OH)D or 1,25(OH)2D [2–5]. As plasma 25(OH)D concentrations are usually considered the most acceptable and easiest functional measure of vitamin D nutritional status [5], this parameter has been used for assessing the degree of vitamin D deficiency in humans, especially in patients with diabetes. In newly diagnosed patients with T1DM, it has been reported that plasma 25(OH)D concentrations are lower than in non-diabetic controls, even though mean levels in both groups are within the normal range [13]. As 1,25(OH)2D, the key and active derivative of vitamin D was described as a potent immunomodulator [2,8,9,16,17], several investigators have postulated that low synthesis of this compound may be in part responsible for, or able to facilitate, the development of T1DM in individuals prone to the condition [8].

To confirm this hypothesis, randomized interventional trials need to be undertaken in a large population of subjects being supplemented with vitamin D or, more preferentially, with 1,25(OH)2D. In such trials, the primary endpoint might be the incidence of T1DM at the end of the study period, after a follow-up of several years or decades. However, for obvious reasons, these types of studies are not easy to perform. As a consequence, there is, at present, no clear evidence that regular supplementation with vitamin D can prevent the onset of T1DM. Over the past decade or so, two studies have attempted to provide an answer to the question [6,7]. The first was a large multicentre trial conducted across different countries in Europe [6]. In this case-control study, patients with an onset of diabetes before age 15 and control subjects without diabetes were compared. Assessment of their dietary intakes of vitamin D was made using questionnaires and interviews. The results showed a protective effect of vitamin D in infancy, as the odds ratio for developing diabetes was significantly lower (0.67) in children exposed to vitamin D supplements in early infancy compared with those who were not [6]. The second study was a follow-up of a Finnish birth-cohort study [7]. The frequency of vitamin D supplementation was recorded in the first year of life, and the primary outcome was T1DM after 30 years of follow-up. The results of this study indicated that regular supplementation with 2000 IU daily during the first year of life reduced the risk of developing T1DM (relative risk = 0.22) compared with those who had regularly received less vitamin D than the recommended amount.
The data from these two studies [6,7] suggests that appropriate supplementation with vitamin D early in life can reduce the risk of developing T1DM. However, it is difficult to firmly assert that vitamin D treatment is an important measure for preventing T1DM as neither the EURODIAB [6] nor the Finnish [7] study provided the highest levels of evidence (A), as those can only be obtained from well-conducted, generalizable, randomized controlled trials, whereas the EURODIAB and Finnish studies can be graded at levels B and C, respectively.

In T1DM, for at least several months or years after the disease has been diagnosed, we found that circulating levels of 25(OH)D were within the normal range, whatever the modality of insulin delivery — multiple injections or continuous infusions using either the subcutaneous or intraperitoneal route — even though intraperitoneal insulin infusion is associated with higher levels of plasma 25(OH)D than is subcutaneous administration [1]. Yet, despite these differences, circulating 1,25(OH)2D was normal and similar in the various groups receiving conventional treatment, subcutaneous infusions or intraperitoneal infusions.

These results taken together appear to suggest that vitamin D metabolism does not exhibit any deficiency in chronically insulin-treated patients with T1DM. On the other hand, there are reasons to believe that vitamin D supplementation may have an impact on the prevention of the disease. Such negative or positive effects need to be confirmed in randomized trials with an A level of evidence using supplementation with 1,25(OH)2D, as this metabolite is a well-known potent immunomodulator [2,8,9,16,17].

In T2DM, some investigators have reported that 25(OH)D levels are decreased compared with control subjects, although the differences are usually relatively small [14, 45]. The meaning of these findings remains unclear, but a possible explanation might be the increase in body weight, a condition frequently encountered in patients with T2DM. In obese subjects, the increase in blood vitamin-D concentration is smaller than in non-obese individuals after an oral dose of vitamin D or following sunlight exposure. These differences could be due to the fact that, in obese individuals, body fat can intervene as an irreversible sink for vitamin D, thereby increasing the risk of vitamin D deficiency [18,19]. The risk of having T2DM also appears to be increased in subjects with a vitamin-D-deficient status [15], but there are many inconsistencies across the results of different studies.

At present, it is difficult to draw any firm conclusions from the available studies, including those in which vitamin D supplementation was undertaken. The restoration of normal vitamin D stores in vitamin-D-deficient patients can improve glucose tolerance, probably by exerting a small — but significant — stimulatory effect on both insulin secretion and insulin sensitivity [20]. In contrast, conflicting results have been observed when patients with impaired glucose tolerance or overt T2DM and no evidence of vitamin D deficiency were treated with vitamin D supplements. The variability of the impact of vitamin D supplementation is so wide that the spectrum of results appears to be a continuum from improvement to worsening, with even the absence of any effect in some studies [8,11,20–22].

2. Conclusion

In the end, it is difficult to determine whether or not vitamin D is involved in either the prevention or progression of diabetes and to conclude whether or not vitamin D deficiency is a consequence or a cause of diabetic states. Considering the latter hypothesis that vitamin D deficiency is a risk factor for diabetes, it remains to be clarified whether vitamin D is a link in a chain or a spoke in a wheel. At present, supplementation with vitamin D might play a role in the prevention of T1DM [6,7]. In contrast, the relationship between T2DM and vitamin D metabolism is not convincing [8], and it would appear to be somewhat precarious to recommend vitamin D supplements for either preventing or treating T2DM except in those patients who exhibit frank vitamin D deficiency. Yet, even in such patients, it is not recommended to use supraphysiologsical doses of vitamin D, as excess intakes of the vitamin can lead to adverse effects [23,24]. In patients with vitamin D deficiency, supplementation with vitamin D exerts beneficial effects on different targets, the most interesting being bone tissue and the immune system. At high doses, however, vitamin D and its derivatives can have a certain degree of toxicity and, thus, can result in such adverse effects as hypercalcaemia, hypercalciuria and the development of renal stones [23,24]. Considering the effects of vitamin D as a whole, and of integrating them in a hormetic model [25] defined by the fact that small doses can elicit opposite responses to those of high doses, but with adverse effects in both cases, it appears that the dose of vitamin D should be maintained within the so-called region of vitamin D homeostasis, defined by lower and upper thresholds.

These remarks can be applied to all effects of vitamin D, including those on glucose metabolism. As a consequence, our final conclusion — as reflected in the title of this editorial — may be summarized by one phrase: much ado about nothing. This suggests that vitamin D supplementation should be reserved only for diabetics who are vitamin-D-deficient. However, it is important to note that, in some countries, the prevalence of hypovitaminosis is relatively high in the general population, especially in winter and spring [12]. As a consequence, the ‘consensus’ should be to firmly recommend effective supplementation in diabetic patients who have been diagnosed as vitamin-D-deficient on the basis of correct determinations of plasma 25(OH)D and its derivatives [26]. In contrast, and despite the fact that the highest tolerated intake level for vitamin D appears to be relatively high [24], the ‘nonsensus’ would be to systematically prescribe supplementation of vitamin D in patients with or without diabetes and who are not deficient in vitamin D.

Conflict of interest statement

The authors declare no conflict of interest with the content of this editorial.

References


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