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Review

## Vitamin D and type 2 diabetes mellitus: Where do we stand?

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### Abstract

**Aims.** – In-vitro and observational studies have established a link between vitamin D deficiency and different type 2 diabetes outcomes (insulin resistance, insulin secretion, glucose intolerance). Although the number of randomized controlled trials vs placebo is small, vitamin D (VTD) has been shown to prevent increases in glucose concentration and insulin resistance, enhance insulin sensitivity and reduce systolic blood pressure in type 2 diabetic patients.

**Methods.** – In this review, we have focused on the potential mechanisms that might explain the association between VTD and type 2 diabetes mellitus (T2DM). We have also evaluated the different epidemiological and observational studies on the topic, as well as the various interventional studies.

**Results.** – Although the in vitro studies appear to be promising in explaining the link between VTD metabolism and T2DM, the results of in vivo studies are conflicting. This could be related to differences in their methodological approaches.

**Conclusion.** – Although more studies are needed to confirm the role of VTD in the treatment of T2DM, there is nevertheless enough evidence at this time to suggest a need to maintain 25-OH vitamin D levels in T2DM patients around 30 ng/mL over the course of a year.

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**Keywords:** Vitamin D; Type 2 diabetes mellitus; Pathophysiology; Review

### Résumé

Vitamine D et diabète de type 2 : le point en 2011.

**Introduction.** – Des études, tant observationnelles qu'*in vitro* ont établi l'existence d'un lien entre une carence en vitamine D et différentes complications liées au diabète de type 2 (résistance à l'insuline et intolérance au glucose). Le nombre d'études randomisées en double insu contre placebo est malheureusement assez limité, mais il n'empêche qu'il a déjà été démontré que la vitamine D permettait de diminuer les augmentations de la glycémie ainsi que la résistance à l'insuline, augmentait la sensibilité à l'insuline et réduisait la pression artérielle systolique chez le patient diabétique de type 2.

**Méthodes.** – Dans ce travail, nous nous sommes intéressés aux mécanismes pouvant expliquer l'association vitamine D–diabète de type 2. Nous avons également étudié quelques grandes études observationnelles et épidémiologiques et nous nous sommes concentrés sur les études randomisées en double insu contre placebo publiées à ce jour.

**Résultats.** – Les études *in vitro* semblent assez prometteuses, mais les résultats observés dans les études *in vivo* sont assez conflictuels, souvent à cause de différences de méthodologies.

**Conclusion.** – Nous avons encore besoin d'autres études pour clarifier le rôle de la vitamine D dans le traitement du patient diabétique de type 2, mais il semble cependant évident que les concentrations plasmatiques en 25(OH)-vitamine D de ces patients devraient être maintenues aux environs de 30 ng/mL tout le long de l'année.

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**Mots clés :** Vitamine D ; Diabète de type 2 ; Physiopathologie ; Revue générale

### 1. Introduction

Vitamin D (VTD) is, in fact, not a vitamin, but a prohormone. Indeed, only a small amount of VTD can be obtained from the

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Table 1  
Foods that naturally contain vitamin D.

Food	Content (IU/100 g)
Halibut liver oil (D3)	200,000
Cod liver (D3)	8500
Sea eel (D3)	520
Smoked river eel (D3)	3600
Cod (D3)	50
Halibut (D3)	200
Black halibut (D3)	600
Herring (D3)	1250
Sea bass (D3)	20
Mackerel (D3)	40
Sardine (D3)	300
Salmon (D3)	650
Canned salmon (D3)	450
Redfish (D3)	90
Sole (D3)	60
Tuna (D3)	200
Oyster (D3)	300
Butter (D3)	50
Margarine (D3)	300
Crème fraîche (D3)	40
Calf's liver (D3)	130
Poultry liver (D3)	50
Milk (D3)	1
Cheese (D3)	10–20
Egg (D2 and D3)	70
Liquid yolk (D2 and D3)	220

diet, as it is naturally present in very few foods (Table 1). Thus, the main source of vitamin D is sunlight-induced photochemical conversion of 7-dehydrocholesterol after exposure of the skin to ultraviolet B (UVB) rays (wavelength: 270–300 nm). VTD is found in two forms: the first, vitamin D3 (cholecalciferol), is the molecule synthesized in the skin, and is also present in some foods (mainly fatty fish from cold waters); the second, vitamin D2 (ergocalciferol), is the vitamin D found in plants (Fig. 1).

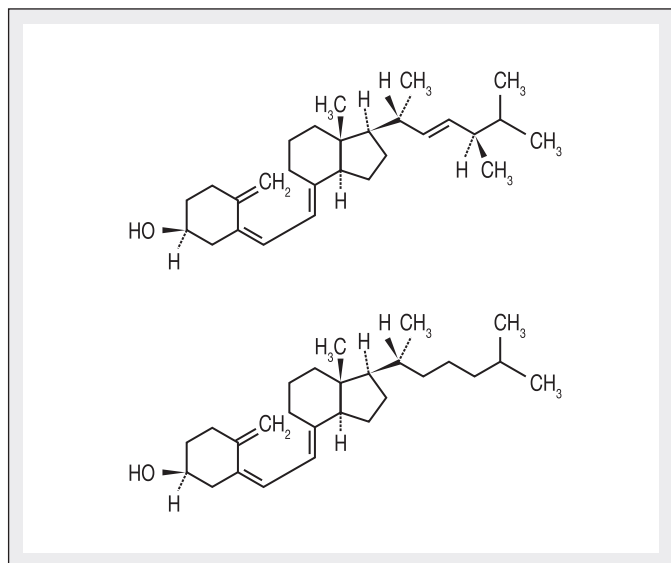


Fig. 1. Molecular structures of (upper) vitamin D2 (ergocalciferol) and (lower) vitamin D3 (cholecalciferol).

Either vitamin D2 or D3 can also be found in many pharmacological supplements but, whatever the source of the vitamin, it circulates in the bloodstream bound to a carrier protein, the vitamin D binding protein (DBP). In addition, VTD must be hydroxylated twice to produce the most biologically active form—1,25(OH)<sub>2</sub> vitamin D. The first step of hydroxylation, on the carbon in position 25, takes place in the liver to form 25-hydroxyvitamin D (25OHD). This step is poorly regulated: the more vitamin D synthesized or ingested, the greater the quantity of 25OHD formed, although some studies have shown a negative correlation between the increase in 25OHD and baseline plasma concentration. The half-life of 25OHD is approximately 3–4 weeks. The 25OHD–DBP complex enters the proximal renal tubule, where the second step of hydroxylation occurs on the carbon in position 1 by the enzyme 1- $\alpha$ -hydroxylase (CYP27B1), resulting in 1,25(OH)<sub>2</sub> vitamin D (calcitriol). This renal stage of hydroxylation is tightly regulated, and mainly stimulated by parathormone (PTH), hypophosphataemia and poor calcium intakes. The enzyme is down-regulated by fibroblast growth factor-23 (FGF-23), hyperphosphataemia and 1,25(OH)<sub>2</sub> vitamin D itself. The half-life of 1,25(OH)<sub>2</sub> vitamin D is approximately 4 h.

The best-known role of 1,25(OH)<sub>2</sub> vitamin D is to maintain phosphocalcic homeostasis by enhancing calcium and phosphorus uptake in the gut. This endocrine function is achieved by acting on a cytosolic receptor (the vitamin D receptor, or VDR), thus inducing the synthesis of different proteins, such as TRPV6, calbindin 9 and NPT2b. Severe VTD deficiency can cause rickets in children and osteomalacia in adults.

In addition to this endocrine function, VTD plays an important autocrine role. Indeed, most human cells express VDRs and possess 1- $\alpha$ -hydroxylase. The 25OHD penetrates these cells and is hydroxylated to produce 1,25(OH)<sub>2</sub> vitamin D, which remains localized to the cells and binds to the VDR. The 1,25(OH)<sub>2</sub> vitamin D–VDR complex penetrates into the nucleus of the cells and is combined with the retinoic-acid receptor (RXR). The RXR–VDR–1,25(OH)<sub>2</sub> vitamin D complex acts on various 'vitamin D responsive elements' (VDRE) that are close to the genes whose expression is thus activated or depressed, thereby modulating the synthesis of numerous proteins [1].

It is now believed that up to 3% of the human genome is directly or indirectly controlled by the VTD system [2]. In addition, more and more observational, experimental and also interventional studies have recently emerged to demonstrate the contribution of significant VTD supplementation to different health benefits. Of these so far, it is worth noting its positive effects on cancer [3], sarcopenia in the elderly [4], multiple sclerosis [5], hypertension [6], cardiovascular disease [7], congestive heart failure [8], lupus erythematosus [9], arthritis [10], type 1 diabetes [11] and various infectious diseases [12].

Although there is, as yet, no consensus to recommend a target range for serum 25OHD concentrations, the present report supports the suggestion that vitamin D insufficiency is defined by 25OHD levels less than 30 ng/mL (75 nmol/L),

as has already been proposed by several teams of experts [13–16].

## 2. Association of vitamin D and type 2 diabetes mellitus: in vitro and animal studies

Many different basic and animal studies have shown that VTD and calcium (Ca) are clearly involved in glycaemic homeostasis, and that altered Ca and VTD concentrations play a role in the development of diabetes. The relationship between vitamin D, Ca and insulin was elucidated in 1967, when Milner and Hales [17] showed that, in animals, Ca and magnesium (tightly regulated by the VTD system) were essential for insulin secretion. Also, having an inadequate VTD status may play a role in insulin resistance [18–21]: indeed, VTD has a direct effect on insulin action, as it stimulates the expression of the insulin receptor and, thus, enhances responsiveness for glucose transport [22]. Vitamin D also has indirect (Ca-mediated) effects on insulin action: Ca is tightly regulated, and intracellular  $\text{Ca}^{2+}$  concentrations must be kept within an extremely narrow range for the optimal action of insulin on different insulin-responsive tissues, such as skeletal muscle and fat tissue [23–25]. Changes in intracellular  $\text{Ca}^{2+}$  concentrations can lead to peripheral insulin resistance via impaired insulin signal transduction, with decreased glucose transporter-4 (GLUT4) activity [26]. Vitamin D also plays an active role in the functional regulation of the endocrine pancreas, as beta cells possess both VTD receptors [27] and 1-alpha-hydroxylase [28]. Furthermore, calbindin-D28k, a Ca-binding protein regulated by the VTD pathway, plays a role in the modulation of depolarization-stimulated insulin release (and, thus, controls the rate of insulin release via regulation of intracellular  $\text{Ca}^{2+}$  concentration) [29], and also protects beta cells against cytokine-mediated apoptosis and necrosis by inhibiting free radical formation [30]. Finally, different polymorphisms of the VDR have also been associated with T2DM, the metabolic syndrome, fasting plasma glucose and glucose intolerance [31–33].

## 3. Vitamin D and type 2 diabetes mellitus: epidemiology and observational studies

In 2009, the World Health Organization (WHO) estimated that 220 million people worldwide had diabetes. Vitamin D deficiency is another global problem, as it has been estimated that more than one billion people worldwide are vitamin D-deficient [1].

Seasonal variations of preprandial glucose, HbA1c concentration and glycaemic control have been demonstrated in T2DM patients, being higher in winter and lower in summer [34,35]. As winter is the season when sunshine (and vitamin D production) is reduced (with no skin vitamin D production in northern regions), these observations could be suggesting that these seasonal variations are linked to seasonal variations of vitamin D.

A cross-sectional survey of 5677 individuals in New Zealand concluded that serum concentrations of 25OHD were altered in patients with newly diagnosed T2DM and impaired glucose tolerance. The study also showed ethnic differences in vitamin

D among participants (with Maori and Pacific Islanders having lower levels than Europeans) [36].

Also, the Third National Health and Nutrition Examination Survey (NHANES III) [37] showed an inverse association between vitamin D status and diabetes in non-Hispanic whites and Mexican-Americans, but not in non-Hispanic blacks, again reflecting ethnic differences. [AU: please check ref numbers here; note ref 38 citation is missing in sequence. SW, editor] Pittas et al. [39] found statistically significant inverse associations between 25OHD concentrations and the prevalence of T2DM (odds ratio: 0.36, 95% CI: 0.16–0.80) on analyzing data from all studies reporting an association between 25OHD and diabetes prevalence, excluding data for non-Hispanic blacks [36,50,51]. Other cross-sectional or observational studies have been published on the topic, and their results generally—but not always—suggest an association between VTD status and/or Ca intake and T2DM risk. However, it is not reasonable to rely on these studies for a number of reasons, including: (1) lack of being adjusted for confounding factors (for example, body mass index, VTD and Ca status, physical activity and outdoor activity); (2) major differences in the populations studied (ethnicity, mean age, geographical location/latitude); and (3) wide range of pathologies present and different outcomes (such as newly diagnosed diabetics, glucose tolerance problems and insulin resistance).

Nevertheless, in the Nurses' Health Study, it appears that women with the highest intakes of Ca (greater than 1200 mg/day) and VTD (greater than 800 IU/day) had a 33% lower risk compared with those who had the lowest Ca (less than 600 mg/day) and VTD (less than 400 IU/day) intakes. It is also worth noting that, in that study, the combination of Ca and VTD appeared to be more effective than either high-dose Ca or VTD supplements alone [38].

Finally, it should be borne in mind that, while some studies have shown either a positive or no effect of VTD, no negative study of the topic has ever been published.

## 4. Vitamin D and type 2 diabetes mellitus: interventional studies

In evidence-based medicine, the level of evidence from interventional studies is much more important than that of observational or cross-sectional studies. In researching the use of significant VTD supplementation to achieve potential benefits in T2DM, different interventional studies have been conducted. However, these studies have major differences in design and outcomes. For this reason, the present report focuses only on those studies where 25OHD levels were determined. Indeed, it is difficult to draw any conclusions from studies where the most important determining factor was not evaluated. Also, only those studies where 'native' vitamin D3 or D2 was given to patients are included. In fact, it is not usually considered good practice to supplement patients with 1-hydroxylated or 1.25-dihydroxylated VTD as the first line of treatment.

Given these criteria, only one study of all those systematically and well reviewed, and including meta-analysis, by Pittas et al. on the role of vitamin D and Ca in T2DM (published in 2007)

Table 2  
Randomized controlled trials of the effect of vitamin D (VTD) and/or calcium (Ca) supplementation in type 2 diabetic (T2DM) patients.

First author, year [ref], location	Gender	Age (years, mean or range)	Study participants	25OHD conc and Ca intake at baseline	25OHD conc at study end; VTD assay	Interventional modalities	Main outcome	Comments and outcomes
Pittas, 2007 [40], New England, USA	M/F	71	Normal fasting glucose, $n = 222$ ; impaired fasting glucose, $n = 92$ ; non-diabetic, 100% white; BMI: 26.7 kg/m <sup>2</sup>	30 ng/mL; Ca: 750 mg/day	40 ng/mL; CPBA	D3 700 IU/day + Ca citrate 500 mg/day vs placebo; 3-year study	Normal group fasting glucose: no apparent effect; impaired fasting glucose group: no increase in plasma glucose and no insulin resistance (also seen in placebo group)	Somewhat higher 25OHD levels at baseline in these older patients
Avenell, 2009 [42], England and Scotland	M/F	77	RECORD trial: 5292 participants with recent osteoporotic fracture; 99% white, 8% diabetic; BMI: not reported, but mean weight was 65 kg, so BMI may have been around 26.7 kg/m <sup>2</sup>	15.2 ng/mL in 60 subjects; Ca: < 700 mg/day in 39%	24.8 ng/mL; HPLCD3	800 IU/day, Ca carbonate 1000 mg/day, both or placebo; follow-up: 24–62 months	No prevention of diabetes development or increase in need for diabetes medication	Doses too low to achieve 30 ng/mL
Tai, 2008 [41], Australia	M/F	55	33 VTD insufficient (< 20 ng/mL), with or without secondary hyperparathyroidism; no history of diabetes; BMI: 24.1 kg/m <sup>2</sup> ; 94% white	16 ng/mL; Ca: those who took supplements were allowed to go on (10 patients)	36 ng/mL; IDS RIA	75-g standard OGTT; Then 100,000 IU of D3 + 100,000 IU 2 weeks later; 2 weeks after second dose: new OGTT	In adults without diabetes, correction of VTD deficiency not associated with any effect on blood glucose or insulin metabolism; assessed by OGTT	Not a randomized controlled trial
Sugden, 2008 [43], Scotland	M/F	64	34 patients with T2DM; VTD insufficient (< 20 ng/mL); ? 100% white (not reported); BMI: 31.7 kg/m <sup>2</sup>	16.1 ng/mL; Ca: not reported	25.3 ng/mL (mean increase of 6.1 ng/mL vs placebo); IDS ELISA	Measure of endothelial function by flow-mediated vasodilatation of brachial artery; then 100,000 IU of D2 or placebo; 8 weeks later: re-evaluation of endothelial function	Improvement in brachial artery flow in VTD group by 2.3%, significant even after adjusting for blood pressure; VTD supplementation decreased blood pressure by 14 mmHg	Of interest, as endothelial function is powerful surrogate marker of cardiovascular risk; however, limited number of patients; as use of D2 reduces blood levels of 25OHD3, more significant results are to be expected with D3 supplementation; 30 ng/mL not achieved; very obese patients

Table 2 (Continued)

First author, year [ref], location	Gender	Age (years, mean or range)	Study participants	25OHD conc and Ca intake at baseline	25OHD conc at study end; VTD assay	Interventional modalities	Main outcome	Comments and outcomes
von Hurst, 2010 [47], New Zealand	F	23–68	81 insulin-resistant non-diabetic South Asian women living in Auckland (population at high risk of T2DM) with VTD insufficiency (< 20 ng/mL); BMI: 27.5 kg/m <sup>2</sup>	8.4 ng/mL; Ca: not reported	32 ng/mL (mean increase of 18.8 ng/mL vs placebo); DiaSorin RIA	Study of the insulin resistance (assessed as HOMA 1 and HOMA 2 models) after 4000 IU/day of D3 or placebo for 6 months	Significant improvements in insulin sensitivity, insulin resistance and fasting insulin decrease in VTD group; insulin resistance most improved when 25OHD levels were ≥ 32 ng/mL	Rare study where 32 ng/mL level was achieved; obese patients
Nagpal, 2009 [45], India	M	> 35 (mean between 42.4 and 45.0)	74 obese (waist circumference ≥ 78 cm) non-diabetic healthy Indian men; BMI: 26.7 kg/m <sup>2</sup>	14.6 ng/mL; Ca: not reported	28.6 ng/mL; DiaSorin RIA	75-g OGTT; Then, 120,000 IU of D3 × 3 (total: 460,000) at 2-week intervals or placebo; 42 days after baseline: new OGTT		
Jorde, 2009 [46], Norway	M/F	21–75	36 T2DM patients (> 1 year with disease) taking insulin and metformin with stable HbA1c (between 7.0–9.5%);? 100%white (not reported); BMI: 32.8 kg/m <sup>2</sup>	24 ng/mL; Ca: no data	47.3 ng/mL (mean delta of 23.3 ng/mL); Roche Elecsys D3	Blood sampling at baseline, then 40,000 IU/week of D3 or placebo for 6 months	No changes in HbA1c; no improvement in parameters of insulin secretion or resistance; no change in blood pressure	Limited number of patients (70% chance of finding a 0.5% significant difference in HbA1c); raised basal vitamin D levels (? due to Norwegian habit of taking cod liver oil; no washout prior to trial); 1 case of hypercalcaemia
Witham, 2010 [44], Scotland	M/F	> 18 (mean between 63.3 and 66.7)	58 T2DM patients with baseline 25OHD levels < 40 ng/mL and baseline mean systolic blood pressure above target range for T2DM; BMI: around 30 kg/m <sup>2</sup>	16–19 ng/mL; Ca: 12.4–16 mmol/day	25.2 ng/mL in group receiving 100,000 IU, 31.6 ng/mL in group receiving 200,000 IU; IDS ELISA	Blood sampling at baseline, then three groups: placebo; 100,000 IU of D3; and 200,000 IU of D3; endothelial function by measuring flow-mediated dilatation of brachial artery at 8 and 16 weeks as week as blood pressure	No change in endothelial function; diastolic (but not diastolic) blood pressure fell significantly between baseline and 8 weeks in both treated groups vs placebo; B-type natriuretic peptide levels fell significantly in 200,000 IU group vs placebo; no change in renin or aldosterone	No confirmation of results seen in [43] in similar population (but more patients here were taking statins or ACE inhibitors); benefit of supplementation on systolic blood pressure in these hypertensives

25OHD conc: 25-hydroxyvitamin D concentration; BMI: body mass index; CPBA: chloroperbenzoic acid; HPLC: high-performance liquid chromatography; RIA: radioimmunoassay; ELISA: enzyme-linked immunosorbent assay.

could be selected [39]. However, since that time, seven other studies have been published, and their results are summarized in Table 2.

In the first of these, Pittas et al. [40] showed that 700 IU/day of D3 and 500 mg/day of Ca citrate vs placebo prevented increases in plasma glucose and insulin resistance in patients with impaired fasting glucose. The treatment had no apparent effect on fasting glucose in non-glucose-impaired subjects, nor was any effect observed on blood glucose or insulin metabolism in non-diabetic subjects when their VTD levels were corrected [41].

In the large-scale Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, no prevention of the development of T2DM was observed with D3 at 800 IU/day alone or in combination with 1000 mg/day of calcium carbonate (CaCO<sub>3</sub>)—doses that proved insufficient to raise 25OHD levels to greater than 30 ng/mL [42]. However, the 8% of diabetic patients in the treated group had no increased need for medication during the course of the study.

Sugden et al. found that, in their initial studies, 100,000 IU of D2 improved endothelial function (assessed by flow-mediated vasodilatation of the brachial artery in response to hyperaemia and sublingual glyceryl trinitrate) in T2DM patients [43]. These results are of interest because endothelial function is a powerful surrogate marker of cardiovascular risk. However, they could not confirm their findings with either 100,000 or 200,000 IU of D3 [44] (generally thought to be more effective than D2 in raising and maintaining serum VTD levels, although this is still a subject of debate).

However, one interesting observation of the latter study was the reduction in systolic blood pressure in the treated groups, a change that was not observed in studies by Nagpal et al. [45] and Jorde and Figenschau [46]. The former dealt with obese, non-diabetic, healthy Indian men and showed postprandial improvement in insulin sensitivity. In the latter study, patients were overtly diabetic and had stable HbA1c levels that did not change after significant D3 supplementation (40,000 IU/week for 6 months, equivalent to a total of 1,040,000 IU). No improvement in parameters of either insulin secretion or insulin resistance [according to the homeostasis model assessment (HOMA) method] was observed in this Norwegian cohort, which was not the case of the study published by von Hurst et al. [47] of South Asian insulin-resistant non-diabetic women with VTD deficiency who underwent supplementation with 4000 IU/day of D3 for 6 months (total: 730,000 IU). The mean VTD level for this cohort was 32 ng/mL and, when serum values reached this threshold, an improvement in insulin resistance was observed.

## 5. Conclusion

At present, there is no doubt that a relationship between insufficient VTD and Ca status and T2DM exists. However, the number of interventional studies, and particularly of randomized controlled trials vs placebo, is limited. Moreover, the results observed in some of these studies have been contradictory (although no study has shown worsening of the pathology).

Nevertheless, although it may be that VTD supplementation does not prevent the emergence of diabetes in the healthy population, the potential benefits of its significant supplementation on the various parameters associated with the disease, such as hypertension, are important. VTD supplementation may also have different positive consequences, such as improvement in muscle performance that could lead to increased physical activity and weight loss and, thus, reduced insulin resistance.

Another observation worth noting from the various interventional studies is the method of administration and dosages used. Indeed, for better compliance, large yearly or monthly doses may be more advantageous, but may also have negative outcomes. Indeed, when Taylor and Wise [48] treated three T2DM patients with one intramuscular dose of 300,000 IU of D3, they saw an increase in insulin resistance. Jorde and Figenschau [46] found no significant improvements in the parameters they were studying (which was unexpected, given the results obtained in other interventional studies) but, instead, saw a hypercalcaemic event in one subject. It should also be borne in mind that the protocol followed in that study was intensive (40,000 IU/week for 6 months). Although it is generally agreed that native VTD is not toxic at the doses used in clinical practice (there is a factor of 1000 between therapeutic and toxic doses), a U-shape curve may still be seen, as was recently reported by Sanders et al. [49] who, on supplementing older women with yearly high doses (500,000 IU) of vitamin D3, unexpectedly found a greater risk of falls.

Furthermore, it should be remembered that all these studies were performed for only a short period of time compared with a lifetime of treatment for chronic diseases such as T2DM. Indeed, it is not reasonable to extrapolate the conclusions of a 6-week trial to the rest of a patient's life.

The medical community is still awaiting more evidence, particularly regarding the prevention of T2DM and improvement of the disease with significant VTD supplementation. Nevertheless, so far, the evidence is sufficient to suggest that T2DM patients should aim to maintain VTD levels greater than 30 ng/mL over the course of a year.

## Conflict of interest statement

None to declare.

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