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SHORT COMMUNICATION

How Can We Increase the Clinical Benefits of Vitamin D Supplementation in Adult People with Multiple Sclerosis?

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Vitamin D (VD) supplementation in adult people with multiple sclerosis (MS) remains most of the time suboptimal, linked to outdated prescription rules mainly based on good bone health. In MS, the physician should ensure that people have a normal serum 25-hydroxyvitamin D level for the maintenance of an effective immune system. Here, we highlight the pitfalls classically encountered in the prescription of Vitamin D in this population and propose a simple algorithm for optimal supplementation.

Key words: Vitamin D, multiple sclerosis, Vitamin D supplementation

INTRODUCTION

Vitamin D (VD) was long thought to be required solely for the maintenance of phosphorus–calcium homeostasis and bone mineralization.[1] In fact, VD is now known to be involved in many other physiological processes. The compounds notably have an important role in the pathogenesis of multiple sclerosis (MS), through its effects on the regulation of the immune response.[2] A growing body of evidence indicates that VD deficiency (defined as a serum 25-hydroxyvitamin D (25[OH]D) level below 20 ng/ml) and VD insufficiency (also referred to as "subclinical VD deficiency," with a serum 25[OH]D level between 20 and 30 ng/ml) are not only environmental risk factors that contribute to the risk of developing MS but are also associated with an elevated relapse rate and a greater lesion burden on MRI.[3-5] Despite contradictory findings on the prognosis of people with MS (e.g., the recently published results of the Vitamin D to Ameliorate Multiple Sclerosis study[6]), it is commonly accepted that VD supplementation remains necessary in this population for the prevention of infectious diseases in general and viral diseases in particular.[7] In most countries, however, a predominant focus on bone health means that (i) the recommended dietary intakes of VD are ridiculously low and (ii) no guidelines on VD supplementation for people with MS are available. Furthermore, VD supplementation suffers from preconceived beliefs and ideas that result in obsolete prescriptions (i.e., at odds with recent data on this topic). Here, we highlight the pitfalls classically encountered in the prescription of VD in adult MS and propose a simple algorithm for optimal supplementation.

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EVALUATION OF VITAMIN D STATUS AND ESTIMATION OF THE APPROPRIATE DOSE LEVEL

The first issue is the patient's VD status, which is generally evaluated by assaying the serum 25(OH)D level. However, the robustness of this marker is still subject to debate because 25(OH)D is not the biologically active form of VD [Figure 1].[8] There is also debate in the literature with regard to an adequate or optimal serum Vitamin D level. Although most guidelines (based on bone health) agree on a value ≥30 ng/ml, it appears that at least 40 ng/ml may be more appropriate in patients with MS because a plateau effect on clinical relapses has been observed at levels above 44 ng/ml.[9]

THE DURATION OF VITAMIN D SUPPLEMENTATION AND THE RECOMMENDED DIETARY INTAKE

Although prophylactic doses of VD are typically recommended during the cold months of the year, VD

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deficiency is pandemic (i.e., year-round) in many countries. Neither the synthesis of VD in the skin nor a normal diet is a reliable source for repletion of VD deficiency or insufficiency, and so, long-term supplementation with VD is preferable. As mentioned above, the recommended dietary allowance of VD is ridiculously low because of toxicity concerns. However, it is noteworthy that doses of up to 10,000 IU/day are considered to be safe – except for patients with (or at risk of) hypercalcemia, such as those with granulomatous diseases.[10] Nevertheless, the tolerable upper intake level of 10,000 UI/day is not intended as a target intake, but a risk for harm once intakes surpass this level, and should therefore only be proposed for short periods in the context of profound hypovitaminosis D.[11]

RISK FACTORS FOR POOR VITAMIN D STATUS

In addition to MS, a number of other diseases, risk factors, and predisposing conditions are associated with poor VD status.[12] These include endocrine and metabolic disorders (such

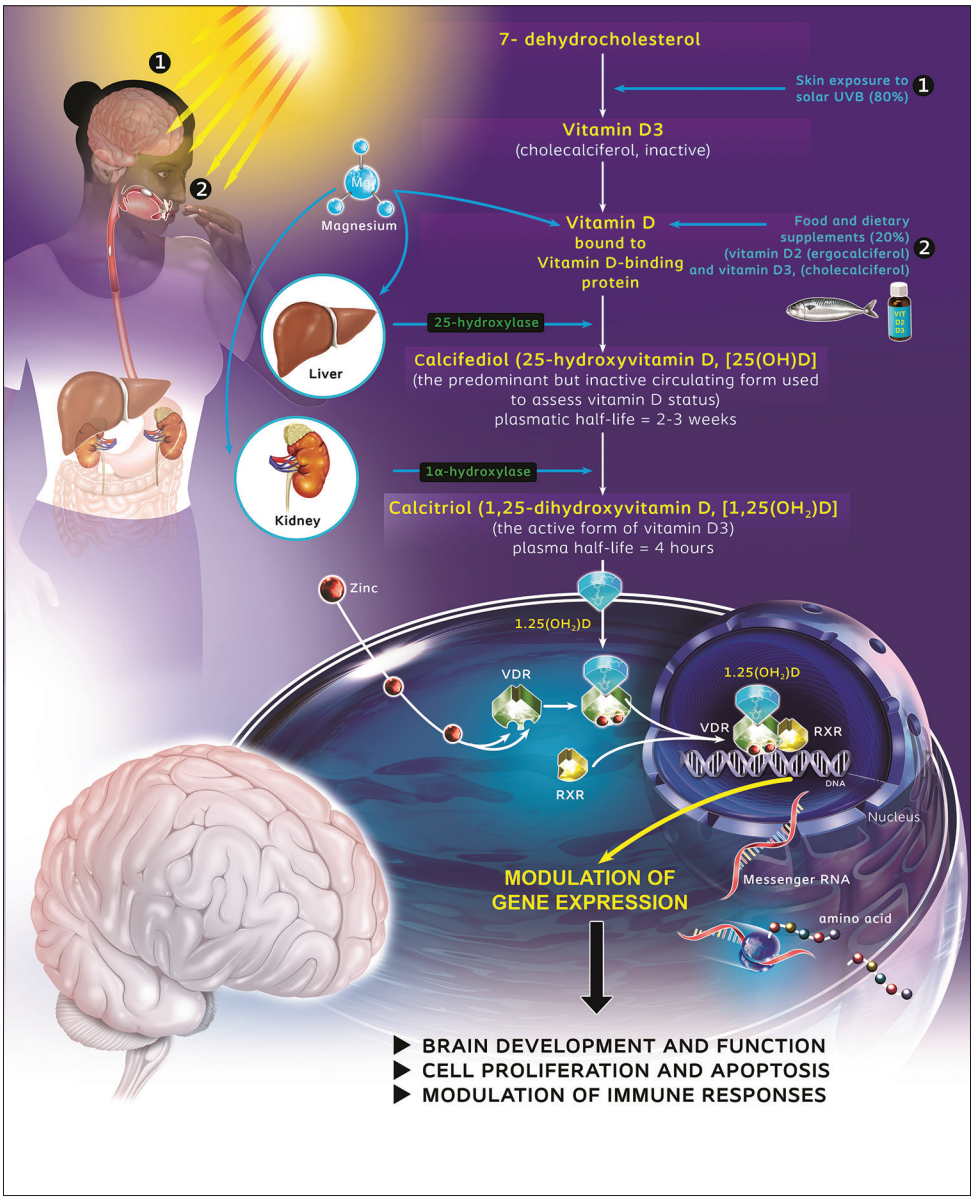

Figure 1: A schematic depiction of Vitamin D (VD)'s metabolism and immunomodulatory actions in the brain. The VD-binding protein's activity is magnesium dependent; similarly, the various conversions of VD from its inactive (storage) form to an active form (in the liver and then the kidney) depend on the bioavailability of magnesium. Likewise, an optimal zinc status is required for the maintenance of sufficient VD receptor activity. Any improvement in VD status will significantly improve the modulation of gene expression in a wide variety of biological pathway and will thus strengthen the immune system

as diabetes mellitus, obesity, and metabolic syndrome), pregnancy (due to a greater physiological demand for VD), malabsorption syndromes (such as inflammatory bowel diseases), systemic connective tissue diseases, nutritional habits (e.g., veganism), long-term medication use (especially antiepileptic medications), and mental illnesses (such as depression) – all of which are more prevalent in people with MS than in the general population. According to the latest clinical studies on this topic, the VD dose should be increased in people presenting several risk factors (particularly obesity and malabsorption syndromes).[13] Furthermore, in the presence of these risk factors, regular dosing of Vitamin D seems justified to avoid problems of both under- and overtreatment.

VITAMIN D COFACTORS

It is important to note that the role of certain nutrients in VD activation and function has been neglected or underestimated. In particular, magnesium and zinc appear to be essential for activating VD's functions in bone health and immunity activity.[14,15] Magnesium is required for the synthesis of the active form of VD [Figure 1]. Likewise, zinc is essential for many biological processes (including immune functions), and an optimal zinc status is necessary for the maintenance of Vitamin D receptor activity [Figure 1]. It is important to bear in mind that plasma magnesium and zinc concentrations can be measured but are not necessarily representative of the body's total magnesium and zinc content. Furthermore, it is estimated that almost 80% of the population in modern societies has a deficiency of magnesium and zinc because of (i) removal of the metals during food processing, (ii) changes in soil conditions, and (iii) changes in dietary habits. Thus, considering that hypermagnesemia induced by magnesium supplements is possible but extremely rare (it mostly occurs in persons having excessive magnesium intake and/or advanced chronic kidney disease) and zinc toxicity is also a rare condition, a systematic but moderate supplementation in magnesium and zinc seems necessary in adult MS population.[16]

PHARMACEUTICAL FORMULATION AND METHOD OF ADMINISTRATION

VD supplements are available in various formulations, such as capsules, tablets, gummies, drops, and oils. All these pharmaceutical formulations appear to be equally effective, although drops usefully contain fewer controversial additives. In fact, certain VD supplements (notably capsules) contain butylhydroxytoluene (BHT), a synthetic antioxidant used to increase shelf life. BHT is considered to be a carcinogen and an endocrine disruptor. It appears that some laboratories have removed BHT from their formulation, although other controversial substances (such as the synthetic food sweetener – saccharin) remain. In this context, a complete review of the safety profiles of the various available formulations of Vitamin D offered in Europe and the United States, or even in other parts of the world, would be legitimate, as it would strengthen the argument for specific recommendations for Vitamin D supplementation methods. Furthermore, it was recently demonstrated that daily VD supplementation at a lower dose is clearly preferable to monthly or even three-monthly VD supplementation at a supraphysiological dose, i.e., the most common currently prescribed method of administration.

SUGGESTED GUIDELINES FOR VITAMIN D SUPPLEMENTATION IN PEOPLE WITH MULTIPLE SCLEROSIS

Although most European guidelines recommend population-wide VD supplementation regardless of the serum 25(OH)D level, it makes sense for people with MS to have their serum assayed for 25(OH) D and calcium. These baseline values will (i) provide information on the severity of the VD deficiency, (ii) indicate whether or not the serum calcium level is normal, and (iii) help the physician and the patient to make better decisions regarding VD supplementation. In France, a serum 25OH-D assay typically costs around 11 EUR but is not reimbursed; the six indications reimbursed do not include supplementation in MS.

As mentioned above, a 25(OH)D level between 40 and 60 ng/ml would be optimal in patients with MS, although it lacks robust longitudinal studies that definitively link these specific serum levels to improved clinical outcomes in MS and provides sufficient VD for the body's systems as a whole and not just for the bones. A higher serum 25(OH)D level (between 60 and 100 ng/ml) might be even more favorable for the prevention of infections in particular.[7]

On the basis of the clinical data in the literature and the few empirical guidelines issued by neurological associations,[1,17-19] the prescription of "therapeutic" doses of VD (between 6000 and 10,000 IU/day) and "prophylactic" doses of VD (between 2000 and 4000 IU/day) should be calculated as a function of the initial VD status [Figure 2]. A checkup assay at 3 months will then enable the daily dose level to be adjusted (if necessary) for long-term maintenance of appropriate VD status [Figure 2]. It is noteworthy that for at-risk patients (particularly obese individuals, pregnant women, and people taking antiepileptic medications), the VD dose level should be increased to 10,000 IU/day, i.e., the maximum dose considered to be safe for the majority of people.

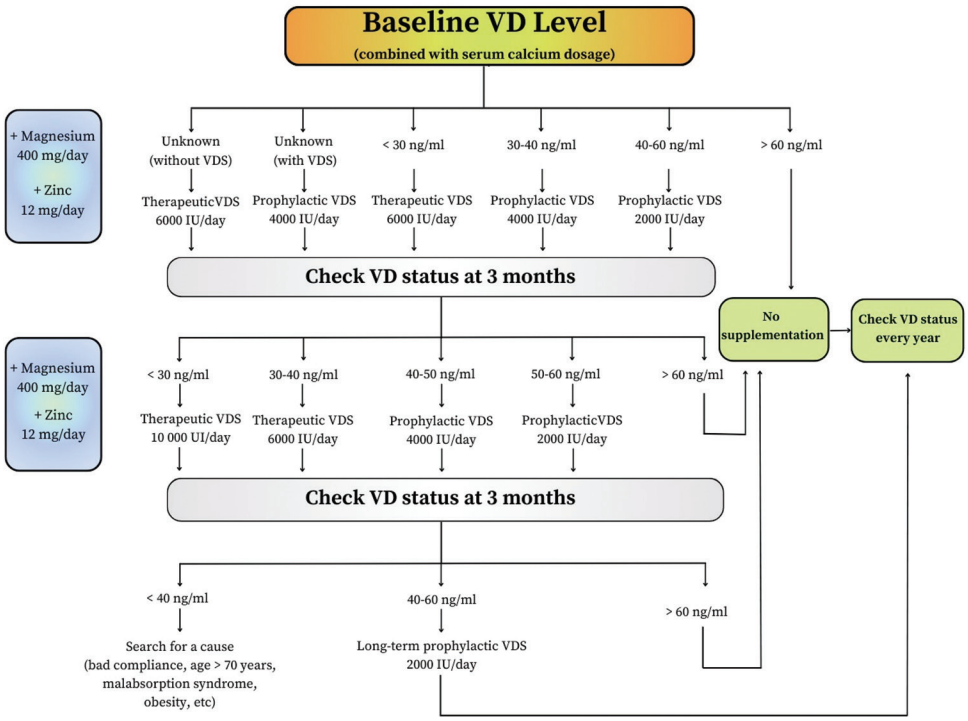

Figure 2: A compact algorithm for Vitamin D (VD) assay and supplementation in adults with multiple sclerosis (MS). People with MS should have a serum VD assay before starting supplementation – although in my experience, almost all nonsupplemented people have a serum VD level below 30 ng/ml (i.e., VD insufficiency). Year-round VD supplementation must maintain the serum VD level (measured annually) at between 40 and 60 ng/ml

Magnesium and zinc supplements must also be coprescribed with VD, to ensure sufficient activation. The recommended daily allowance of magnesium for adults is 300–400 mg, with a higher value still during pregnancy. The recommended daily allowance of zinc for adults is 8–12 mg; similarly, pregnant and breastfeeding women need larger amounts than the general population. If VD deficiency or insufficiency persists despite supplementation, the cause must be sought [Figure 2].

CONCLUSIONS

Although the use of VD supplementation to modify the clinical and radiological course of MS is still subject to debate, the physician should ensure that adult people with MS have a normal serum 25(OH)D level for the maintenance of an effective immune system. Ideally, the patient's baseline serum 25(OH)D level should be assayed before the prescription and then monitored regularly so that the daily dose level can be adjusted to the severity of the deficiency.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Bugnicourt JM, upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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