

Widespread vitamin D insufficiency: A new challenge for primary prevention, with particular reference to multiple sclerosis

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■ Points essentiels

La carence en vitamine D est très répandue : un nouveau défi pour la prévention primaire avec référence particulière à la sclérose en plaques

Au cours des dix dernières années, nos connaissances sur la vitamine D ont été révolutionnées sur deux points principaux.

Tout d'abord, cette vitamine est non seulement essentielle pour le métabolisme osseux et celui du calcium, mais elle a aussi une action hormonale primordiale via son métabolite actif (le calcitriol) et la présence de récepteurs spécifiques dans presque tous les organes. Les diverses actions des effets « non classiques » de la vitamine D – c'est-à-dire anti-inflammatoires, immunomodulatrices, antiprolifératives ou comme neurotransmetteur – pourraient avoir des effets protecteurs et préventifs dans une grande variété de maladies, telles que les pathologies auto-immunes, le cancer, les infections et les maladies cardiovasculaires.

Deuxièmement, les besoins quotidiens en vitamine D ont été redéfinis à la suite de multiples études métaboliques et pathologiques récentes. Ils sont environ dix fois plus élevés que ce qui était considéré comme suffisant il y a encore

■ Key points

In the past 10 years, our knowledge of vitamin D has been revolutionized on two main points. Firstly, this vitamin is not only crucial for bone and calcium metabolism but also exerts major hormonal actions via its active metabolite (calcitriol) and specific receptors in almost all organs. The diverse non-classical actions of vitamin D—i.e. anti-inflammatory, immunomodulatory, antiproliferative and as a neurotransmitter—could have protective and preventive effects for a wide variety of pathologies, such as autoimmune diseases, cancer, infections and cardiovascular affections.

Secondly, daily **vitamin D requirements have been redefined** thanks to many recent metabolic and pathological studies and are about 10 times higher than the amount considered sufficient until a few years ago. The fact that sunshine is the essential natural source of vitamin D and is limited in temperate and Nordic countries, coupled with the fact that modern lifestyle increasingly removes people from exposure to the sun, could explain why a great majority of the general population in these countries are in a state of **vitamin D insufficiency**.

A lack of vitamin D can therefore also be observed in all pathologies but it may play a pathogenic role only in some of them. The incrimination of hypovitaminosis D as a risk factor is

quelques années. Le fait que le soleil soit la source naturelle essentielle de vitamine D et que cette source soit limitée dans les pays tempérés et nordiques, couplé avec le fait que la vie moderne réduit de plus en plus l'exposition au soleil, pourrait expliquer pourquoi une grande majorité de la population générale de ces pays est en hypovitaminose D permanente. Une carence en vitamine D peut aussi être observée dans toutes les maladies, mais elle ne semble jouer un rôle pathogénique que dans certaines d'entre elles. Le rôle de l'hypovitaminose D comme facteur de risque d'une maladie donnée paraît être une hypothèse raisonnable lorsque types d'études ayant utilisé avec des approches différentes ont permis de conclure de façon concordante que la vitamine D était vraisemblablement impliquée dans le processus pathologique de cette maladie. Dans la sclérose en plaques, prise ici comme exemple, il existe un rationnel substantiel – basé sur des résultats expérimentaux, épidémiologiques, génétiques et immunologiques – en faveur de l'implication de la vitamine D, qui constituerait un des facteurs de risque de la maladie parmi d'autres.

Les éventuels effets curatifs de la vitamine D qui existeraient, en plus d'une action préventive, sont actuellement évalués, mais ils n'ont pas encore été démontrés dans la plupart de ces pathologies. Toutefois, ces deux questions semblent être clairement distinctes et peuvent impliquer des mécanismes différents.

En conclusion, puisque l'insuffisance en vitamine D existe chez la plupart des gens habitant les pays de moyenne ou haute latitude, puisque la supplémentation en vitamine D pourrait avoir de multiples actions préventives, puisqu'elle est à la fois peu coûteuse et sûre et, s'agissant d'une vitamine-hormone, cette supplémentation paraît obligatoire d'un point de vue médical général, une telle supplémentation devrait donc être médicalement organisée sans plus tarder afin de traiter tous les sujets actuellement en manque, qu'ils soient patients ou « normaux ».

a reasonable assumption when several different research approaches used in a given pathology have consistently concluded that vitamin D is likely involved in that pathology. In **multiple sclerosis**, taken here as a prime example, there is a substantial rationale for vitamin D involvement, based on the findings of different experimental, epidemiological, genetic and immunological studies.

Possible curative effects of vitamin D, in addition to a preventive action, are currently being tested but have not yet been demonstrated in most pathologies. However, these two questions appear to be clearly distinct and may involve notably different mechanisms.

Lastly, since vitamin D insufficiency exists in most people living in mid- or high-latitude countries, vitamin D could exert multiple major preventive actions, simple supplementation is both safe and inexpensive and, for a vitamin-hormone, supplementation seems obligatory from a general preventive medical point of view alone, it follows that **vitamin D supplementation should be organized in these countries to treat all those currently in a state of insufficiency, patients and 'normal' subjects alike, without further delay.**

The action of vitamin D in calcium homeostasis and in prevention of rickets has been known about for 80 years. However, the past 10 years have seen an exponential increase in scientific publications on this vitamin, involving almost all fields of medicine [1,2]. In particular, we will emphasize two major points that have recently upset classical thinking on vitamin D, the first being qualitative, related to the multiple effects of this vitamin which exert not only on bone but also on almost all organs and in several major types of pathologies, the second being quantitative and concerning estimated requirements for this vitamin, which have increased ten-fold in the last

few years. We will then review the numerous factors that currently contribute to a widespread and almost generalized hypovitaminosis D and take the example of a serious chronic affection for which this lack appears to be deleterious, namely multiple sclerosis (MS). Lastly, we will look at the immediate practical clinical implications that emerge from this new knowledge.

Multiplicity of actions of vitamin D

Vitamin D is synthesized in the skin (D3) from a steroid precursor thanks to ultraviolet (UVB) radiation and is also available in dietary form (D2 or D3). It is transformed in the

liver into 25(OH)D, which is representative of the overall vitamin D store in the body and is the metabolite measured to evaluate vitamin D status [2]. Lastly, 25(OH)D is transformed in the kidney, under parathyroid hormone control, into 1,25(OH)₂D (calcitriol). Calcitriol is the active metabolite, which binds to specific vitamin D receptors (VDR) and produces a genuine hormonal activity. The VDR are not only present in bone, intestine and kidney, which are the classical target tissues of vitamin D, but also in skin, gonads, liver, pancreas, breast, cardiovascular system, lungs, brain, circulating immunity cells such as macrophages, monocytes and activated lymphocyte T and B cells, etc. [2]. These tissues and cells possess the enzymatic machinery required to transform circulating 25(OH)D into calcitriol, which binds to the VDR and exerts autocrine/paracrine effects within cells in numerous organs [3]. It should be noted that transport of vitamin D and its metabolites in the serum by a binding protein, the successive transformations of these different metabolites as well as the VDR are under the control of multiple genetic factors [4–6], which cannot be detailed here but could account for a part of the well-known interactions existing between genetics and the environment in many pathologies. Besides its classical actions on bone and calcium metabolism, vitamin D (via its daughter hormone, i.e. calcitriol) has anti-inflammatory, immunomodulatory, antiproliferative and neurotransmitter effects, which involve some autoimmune diseases—such as MS, diabetes (type I), haemorrhagic rectocolitis, rheumatoid arthritis, etc.—several cancers (in particular colorectal cancer, and likely also breast and ovarian cancer, etc.), infections in general, cardiovascular pathology, and some general symptoms such as falls and muscle weakness [1,2,7–13]. This list, which is already extensive and diverse, is not exhaustive since ongoing studies will likely add other specific pathologies in the very near future. Thus, the multiplicity of effects and target organs of vitamin D and consequently of the pathologies involved constitutes a first and recent revolution in our knowledge of this vitamin.

New estimate of vitamin D requirement

The physiological limits of the 25(OH)D serum level have been revised in the last few years thanks on the one hand to metabolic studies correlating the 25(OH)D serum level to parathyroid hormone activity and to calcium absorption in the gut, and on the other hand to pathological studies analyzing this serum level in relation to bone demineralisation and pathological fractures: for the great majority of authors, normality is currently between 75 and 250 nmol/L (30 and 100 ng/mL) [3,7–20]. However, for all the extra-bone, non-classical effects of vitamin D, numerous association studies have recently suggested that the protective action of this vitamin could not be fully effective before at least 100 nmol/L (40 ng/mL) [1,9,13,14,19]. Conversely, a lower limit remaining at 50 nmol/L (20 ng/mL) would effectively

prevent rickets in infants and noticeably reduce fracture risks and falls in the elderly [21,22], in itself a laudable result but inadequate in view of all that we have recently learnt about the other multiple actions of vitamin D [20]. Concerning the physiological upper limit, commonly defined as 250 nmol/L (100 ng/mL), it appears to be well below the possibly toxic zone, which could be located beyond 375 nmol/L (150 ng/mL) [23], but well above the level of 125 nmol/L which has rather empirically been determined in a recent American report [22] ignoring a number of recent, scientifically valid, epidemiological studies in normal subjects [20]. Furthermore, the daily vitamin D requirement has recently been redefined from the new norms generally accepted for the optimal 25(OH)D serum level. To reach a 25(OH)D serum level of at least 75 nmol/L (30 ng/mL), a total daily intake of 1000 to 4000 IU of vitamin D (according to individuals, but on average 2000 IU) is required, which is about ten times higher than the figure that, until a few years ago, was estimated sufficient, but is still markedly lower than the possibly toxic dosage (located beyond 10,000 IU/d) [24–26]. This represents a second, quantitative revolution in our knowledge of vitamin D.

Factors contributing to hypovitaminosis D

In parallel with these two main types of improvements in our knowledge, physiological, geographical, historical and epidemiological studies have given us a clearer understanding of the multiple factors contributing to hypovitaminosis D [27]. The dietary intake of vitamin D is marginal (less than 100 IU/d) and even food naturally rich in vitamin D (mainly oil fish) or artificially fortified allows one to reach, at most, a few hundred of IU/d, which remains markedly below the daily requirement. Sunshine, therefore, remains the principal natural source of vitamin D, providing 80–90% of the requirement. Exposing half of the body to the sun in summer can provide 10,000–20,000 IU in less than half an hour, but this supply disappears within a few weeks. Although sunshine is of course sufficient in tropical or subtropical regions all year round, it is insufficient for at least 6 months of the year in all countries located beyond the 40th parallels, North or South, because the sun at its zenith is then seasonally too low for vitamin D synthesis by UVB: this mainly concerns Canada, the northern half of the USA, almost all of Europe (the 40th parallel passing through the middle of Spain), the countries of the former USSR, and, in the southern hemisphere, New Zealand, Tasmania and Patagonia, altogether representing about one billion people and 15% of the world's population [28]. It should also be noted that the half-life of 25(OH)D is a few weeks and that of calcitriol a few hours: consequently, the stock of vitamin D can only be regularly replenished in the tropics. Moreover, vitamin D synthesis by UVB is only possible for a few hours a day, either side of midday, when the sun is high enough in the sky. However, this is precisely the period of the day that dermatologists have for

many years been advising us to limit exposure to the sun, for excellent dermatological reasons [29]. Lastly, the elderly are less able to synthesize vitamin D than young people, dark skin is five to six times less efficient at synthesizing vitamin D than light skin, obesity and smoking are particular risk factors for vitamin D insufficiency and requirements are increased in pregnancy [27]. Thus, one may readily understand why many 'normal' subjects may be in a state of chronic vitamin D insufficiency: because of the latitude of the country where they live, their lifestyle (e.g. if, for whatever reason, they do not expose themselves to the sun or if they avoid outdoor activities during the most efficient hours for UVB), their clothing habits (with too little exposure of the skin) or a continuous use of sun-blocks, or if they are dark skinned, markedly overweight, heavy smokers, elderly or pregnant, with, of course, the possibility that several of these common risk factors have a cumulative effect.

Historical points on vitamin D

From a historical point of view, after the first migrations of *Homo erectus* from East Africa to northern regions about one million years ago, the ancestors of inhabitants of mid- or high-latitude countries had sufficient time to evolve and adapt in a Darwinian sense to limited sunshine, thanks mainly to a lightening of the skin, which is particularly efficient at synthesizing vitamin D with relatively small amounts of UVB [30,31]. Even so, light skins still have to be exposed to sunshine in order to synthesize vitamin D. The industrial revolution, which took place in the second half of the 19th century in what are now the developed countries, was likely another decisive turn in the history of vitamin D and humanity, resulting within only a few generations in a marked loss of the benefits acquired after a very long adaptation to small amounts of sunshine [32,33]. A drastic and rapid decline (on a historical scale) in average vitamin D serum level probably occurred when large numbers of the population in these countries left an essentially rural way of life—in which they were almost constantly exposed to nature, the climate and sunshine—to colonize towns and live and work indoors [15]. Nowadays, paediatricians in temperate and Nordic countries systematically supplement infants with vitamin D to prevent rickets and geriatricians do likewise with the elderly to prevent falls and pathological fractures. Curiously, large epidemiological studies involving older children, adolescents and young and middle-aged adults were performed only a few years ago in temperate countries such as the USA, Canada, the UK, France, Germany, Spain, Russia, New Zealand, Israel, etc.: all have shown, with a lower limit of 75 nmol/L for the optimal vitamin D serum level, that a chronic insufficiency exists in about 70% of people in these countries in summer and 90% in winter [10,27]. Even if one considers that only a vitamin D serum level lower than 50 nmol/L is actually abnormal [21,22], almost 50% of those people would still be in a state of insufficiency [27].

Consequently, in recent years there have been increasing calls for a near systematic vitamin D supplementation of the general population in these countries, at least in winter [7,9,15,34–36]. Furthermore, financial projections based on the current data from association studies suggest that systematic vitamin D supplementation in these countries could markedly decrease the prevalence of a number of currently frequent, serious affections in different medical fields and that this could lead to savings in the order of tens of billions of Euros a year in countries such as Germany and France [28,37,38]. Nevertheless, irrespective of the actual amount, such savings could only be expected in the long term. In summary, it took almost a century to understand that rickets observed in infants in industrial Northern countries was due to vitamin D deficiency, and it has taken almost another century to realize that in fact all age groups in these countries suffer from a lack of vitamin D.

Need for a rationale using different research approaches to incriminate hypovitaminosis D in pathology

There is currently a broad consensus that hypovitaminosis D is widespread in temperate and Nordic countries and, to a lesser degree, in the rest of the world [39], where the benefits and drawbacks of a 'modern' way of life have also largely penetrated. However, one should remain very cautious before assuming that a lack of vitamin D may be one of the risk factors for a given disease. Indeed, since vitamin D insufficiency is already widespread in the normal population, it will necessarily also be observed, if it is looked for, in all pathologies, without exception. At this point we should stress that, contrary to normal practice when seeking to validate a scientific medical demonstration, the use of control groups made up of 'normal' subjects makes little sense in the special case of vitamin D since every 'normal' subject may also potentially be in a state of insufficiency: so, patients and normal subjects usually have analogous low vitamin D serum levels and the differences at times observed between them often in fact reflect the presence of associated or confounding factors acting to the detriment of patients (disability, lifestyle, etc.). Consequently, before hypovitaminosis D can be incriminated as a possible risk factor for a given pathology, it would appear necessary that a rationale made of several types of research approaches exists in the same pathology, for example, based on experimental, epidemiological, genetic, metabolic, immunological studies. This appears to be the case in the extra-neurological pathologies cited above. In neurology, only MS possesses, at least for the time being, such a substantial rationale, and the first publications on vitamin D in Parkinson's disease [40] and Alzheimer's disease [41], albeit promising, do not yet appear to be sufficient grounds to claim that hypovitaminosis D also contributes to the cause of these diseases.

Hypovitaminosis D in multiple sclerosis

Hypovitaminosis D exists in MS and is often profound. However, it should be taken into account, particularly in advanced forms of the disease, that confounding or associated factors may contribute to this insufficiency, e.g. a limited exposure to the sun because of hypersensitivity to heat (Uthoff phenomenon) and/or disability, restraining outdoor activities [27]. Nevertheless, in the early stages of MS, including in clinically isolated syndrome, recent retrospective and prospective association studies found inverse correlations between 25(OH)D serum level and the relapse rate, which is much more suggestive that vitamin D plays a specific protective role in MS, at least at the beginning of the disease [42,43]. Moreover, in MS, there are also major experimental, immunological, genetic and epidemiological arguments suggesting a role of vitamin D in a non-ambiguous way [27]. Vitamin D has a preventive and curative effect in experimental allergic encephalomyelitis, which is the best experimental model of MS. In immunology, the activity of macrophages and activated lymphocytes (B and T cells) is clearly influenced by calcitriol [44] and vitamin D increases the number of regulatory T lymphocytes in healthy subjects [45]. In several recent studies performed in MS patients, it was shown that vitamin D favourably modulated cytokines, CD4+, CD8+ and regulatory T cells *in vitro* or *in vivo* [46–53] by a mechanism close to that of interferon β , which thus places the possible role of this vitamin at the core of the disease pathophysiology. These immunomodulatory mechanisms could be common to the other autoimmune diseases possibly involved in vitamin D insufficiency. In genetics, multiple recent studies in MS patients have shown that the genetic regulation of VDR [5,6] and vitamin D binding protein (transporting this vitamin and its metabolites in the plasma) [54] could influence the risk of MS. From an epidemiological point of view, it has long been known that latitude influences MS prevalence, at the world level or at the scale of continents, and even in relatively small countries such as France or New Zealand [27,55]. More recently, it has been shown that strong links exist between exposure to the sun in the general population and MS risk [56] and between vitamin D status and MS risk [27]. Therefore, a causality chain is now highly likely between high latitude, lack of sunshine, poor vitamin D status and an increased risk for MS. Vitamin D does in fact appear to be the best candidate for the ultimate link in this chain since it is located precisely at the interface between the organism, in which it permanently circulates, and the environment, which obviously influences it. A parallel specific immunosuppressive role of UVB, i.e. without involving any vitamin D mechanism, is possible [57] but is currently based on very few data in animals and humans and, in any case, does not rule out the vitamin D pathway and role, for which numerous experimental and clinical results already exist independently of UVB [27]. Accordingly, the multiplicity of research approaches as-

sessing a role of hypovitaminosis D in MS and the concordance of the results of all these studies have already provided a high level of evidence in favour of the involvement of vitamin D in this disease [27,58].

Multiplicity of risk factors in multiple sclerosis

However, the risk factors for MS are multiple and cannot be reduced to hypovitaminosis D alone. Genetic factors, in particular some HLA groups, play a major role and there are in the environment, in addition to hypovitaminosis D, other risk factors that play a significant role, such as past infection with the Epstein-Barr virus and smoking [59]. The disease could be triggered by a combination of several risk factors and the existence of potentiation has already been shown, both between genetics and the environment and between several environmental risk factors [27,60–62]. Thus, the relative role of hypovitaminosis D appears limited within the realm of all risk factors for MS, accounting for a significant effect at the scale of a population but not for the whole range of individual situations, in which the different genetic and environmental risk factors may interact in a very variable way. These interactions between genetics and the environment likely also exist in the other affections in which hypovitaminosis D is possibly involved. One of the current major avenues of research in MS is to determine the precise mechanisms of interactions between the different identified risk factors.

Treatment with vitamin D

Another avenue of research is to test a possible neurological curative effect of vitamin D in MS patients, in particular at the early stages of the disease, which are commonly sensitive to anti-inflammatory and immunomodulatory therapeutic effects. In MS as in most affections possibly involving vitamin D, limited phase II trials using this vitamin have already provided some favourable results, but reliable phase III data have not yet been reported. Be that as it may, in these different affections a clear distinction should be made between a possible curative action of vitamin D, which largely remains to be evidenced using randomized controlled trials (RCTs), and a preventive effect of this vitamin before the start of the disease, which has already epidemiologically been strongly suggested by numerous association studies, even if the precise epochs during which vitamin D is crucial in this protection also generally remain to be determined. For example, in MS, several epochs may be important for the vitamin D protective role: before conception, i.e. in the environmental past of parents (epigenetics), during pregnancy of the mother, at birth, during infancy, childhood, adolescence, or later, i.e. just before the beginning of the disease [27,58,63]. Thus, the protective effects of vitamin D could be important all through

the past preceding the clinical start of the disease, and it may be that the mechanisms ensuring these protective effects are noticeably different in nature from those involved in the possible curative actions of this vitamin after the clinical onset of the disease. Finally, while awaiting the results of phase III trials using vitamin D, which may still require some years, it appears wise from a general preventive point of view to supplement with this vitamin all patients in whom an insufficiency has been evidenced by a serum titration, in particular if they have particular aggravating factors for such insufficiency (advanced age, disability, dark skin, avoidance of the sun, clothing habits, obesity, smoking, pregnancy, etc.) [64]. The practical modalities of prescription and survey of vitamin D supplementation are relatively simple and will not be reviewed here [64]. However, preventive implications also concern normal subjects (see below).

Concluding remarks

Major practical clinical measures could emerge as a result of new information about vitamin D.

There no longer appears to be any doubt about the physiological reality of the recently revised norms of the optimal 25(OH)D serum level (75–250 nmol/L) and therefore about the daily requirement for vitamin D (1000–4000 IU/d): many reliable metabolic and pathological studies have shown that the new norms are well-founded, and they may even be increased slightly more in the near future to take fully into account the extra-bone requirements.

There is no longer any justification for believing that the proportion of subjects in a state of vitamin D insufficiency is only marginal, since such insufficiency already exists in the majority of the general population of temperate and Nordic countries, whatever the lower limit finally adopted for the optimal serum level (between 50 and 100 nmol/L), and this lack is also more or less massively (according to this lower level) observed in patients, whatever their age and pathology: numerous recent epidemiological and clinical studies have demonstrated this reality which can no longer be ignored.

There is no longer any justification for refraining from prescribing vitamin D supplementation for patients with a given pathology, in whom a lack of vitamin D has been evidenced, on the pretext that it has not yet been formally demonstrated that the vitamin plays a preventive and/or a curative role in that pathology, since the hormonal and preventive effects of vitamin D far exceed a single organ or pathology. Indeed, there can be no justification for continuing to wait for the outcome of yet more studies when there is already a considerable body of concordant data from different medical fields, which were obtained using different methodological approaches and have already provided a globally high level of evidence: in particular, for the prevention of osteoporosis, pathological fractures, some autoimmune diseases (including MS and diabetes), some can-

cers (e.g. colorectal cancer), infections in general and cardiovascular pathology, to cite only what is already well-established. Nevertheless, it is true that much work remains before we can elucidate the precise mechanisms involving vitamin D in the prevention of these different pathologies and before we can ascertain (using RCTs) whether specific curative effects of this vitamin also exist in some of them [22,65].

There is no longer any excuse for refraining from vitamin D supplementation because of a fear of 'intoxication' if one has the simple aim of bringing the vitamin D serum level to within the currently accepted norms and if one respects the very rare contraindications, which are essentially the granulomatous diseases [66]: the risk of side effects is then almost nil, as already demonstrated, with a large safety margin before a possible toxic serum level could be reached.

There can be no genuine arguments over the financial cost of a near generalized vitamin D supplementation, which appears to be very inexpensive compared to the potentially gigantic savings to be made from prevention of many serious and currently frequent diseases.

Lastly, there is no point in waiting for official recommendations from the health authorities, since the medicine in this case already appears to be a century late. Moreover, correcting a vitamin insufficiency does not require official authorization since it is an elementary medical duty: indeed, failure to do so could even soon be seen as negligence.

All things considered, the time has clearly come to supplement all those in a state of vitamin D insufficiency, i.e. both patients and 'normal' subjects, as some pioneers have been recommending for several years. This is certainly a huge programme, involving the whole of the medical establishment, which should organize it. However, if it can be set up, the time will come, perhaps in 10 or 20 years, when its benefits will be observed. Even though these benefits will not be felt immediately and their exact extent is still uncertain, medicine and health could eventually gain a great deal from such prevention and they have almost nothing to lose by it. However, before undertaking primary prevention with vitamin D, it is up to every physician to form his or her own opinion on the matter, ignoring the few discordant recommendations—which always exist in medicine—and rather weighing the considerable body of convergent positive results supporting the multiple actions of vitamin D in human health. Concerning the latter results, it should be recognized that a large quantity of them have been obtained in a short time, which may naturally delay a common awareness of the problem. However, time is also short and will not come again for patients and 'normal' subjects currently in a state of insufficiency. They are many.

Conflict of interest : none

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