Scandinavian Journal of Clinical & Laboratory Investigation, 2012; 72(Suppl 243): 129–135

ORIGINAL ARTICLE

When should we measure Vitamin D concentration in clinical practice?

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Abstract

The many recently published data on vitamin D have raised much interest in the medical community. One of the consequences has been a great increase in the prescription of vitamin D concentration measurements in clinical practice. It must be reminded that only the measurement of 25-hydroxyvitamin D (25(OH)D) concentration is indicated to evaluate vitamin D status. Furthermore, since vitamin D insufficiency is so common, since treatment is inexpensive and has a large safety margin, and since we already have much data suggesting that besides its classic effects on bone and mineral metabolism, vitamin D may potentially be helpful for the prevention/management of several diseases, perhaps should it be prescribed to everyone without prior testing? In our opinion, there are however groups of patients in whom estimation of vitamin D status is legitimate and may be recommended. This includes patients in whom a "reasonably" evidence-based target concentration (i.e., based on randomized clinical trials when possible) should be achieved and/or maintained such as patients with rickets/osteomalacia, osteoporosis, chronic kidney disease and kidney transplant recipients, malabsorption, primary hyperparathyroidism, granulomatous disease, and those receiving treatments potentially inducing bone loss. Other patients in whom vitamin D concentration may be measured are those with symptoms compatible with a severe vitamin D deficiency or excess persisting without explanation such as those with diffuse pain, or elderly individuals who fall, or those receiving treatments which modify vitamin D metabolism such as some anti-convulsants. Measurement of Vitamin D concentrations should also be part of any exploration of calcium/phosphorus metabolism which includes measurement of serum calcium, phosphate and PTH.

Key Words: *25-hydroxyvitamin D, osteoporosis, chronic kidney disease, vitamin D deficiency*

Abbreviation: *DRI: dietary recommended intake; RCT: randomized controlled trial; OV/BV: osteoid volume/bone volume*

Introduction

A considerable amount of recently published data on the proven or potential effects of vitamin D has raised much interest in the medical community. One of the consequences has been a great increase in the prescription of measurements of vitamin D concentration in serum or plasma. In France, for example, the prescription of measurement of 25-hydroxyvitamin D (25(OH)D) concentration has increased almost threefold between 2008 and 2010. As this measurement is reimbursed by the public health insurance (currently 17.55 Euros in France), it seems obvious to evaluate whether these prescriptions are justified or not. It must be emphasized that definitive recommendations on measureing vitamin D concentration or not in general practice must only be released by official Clinical Society such as the Endocrine Society, and, therefore, the following propositions only

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ISSN 0036-5513 print/ISSN 1502-7686 online
DOI: 10.3109/00365513.2012.682888

reflect our current opinion (which may change with the publication of new data) based on our own analysis of the literature, and our routine clinical practice.

General considerations

First of all it must be reminded that 25(OH)D concentration is the sole measurement indicated to evaluate the individual's vitamin D status

This is a consensus, even among groups that have released divergent recommendations on vitamin D [1,2]. The measurement of 1,25-dihydroxyvitamin D ($1,25OH_2D$) concentration, the most active vitamin D metabolite, must be limited to the diagnosis and management of rare disorders of phosphate and vitamin D metabolism, to the management of some patients with renal failure, and to the differential diagnosis of conditions presenting with hypercalcemia/hypercalciuria associated to low/low normal PTH levels. What is not consensual however is the 25(OH)D cut-off concentration below which vitamin D status may be considered as insufficient. For many vitamin D scientists, including the authors of the present article, the minimum 25(OH)D concentration should be 75 nmol/L [1,3–11], while the recent report by the IOM [2] indicated that a concentration of 50 nmol/L is largely sufficient and "covers the requirements of at least 97.5 % of the population". Anyway, even with the more conservative IOM cut-off of 50 nmol/L, insufficient vitamin D status is highly frequent. Indeed, approximately 50 % of the general European population has a 25(OH)D concentration below 50 nmol/L, and some groups of patients/subjects such as institutionalized persons, dark-skinned individuals or immigrants, are even very frequently severely deficient (25(OH)D concentration <25 nmol/L) as reviewed recently [12].

Administration of vitamin D as a dietary supplement may be considered without prior testing. The reasons may be summarized as low toxicity (even IOM considers up to 4,000 IU/day safe [2]), deficiency common in the general population and data suggesting benefits in prevention/management of several diseases e.g. colorectal cancer, some infectious diseases, cardiovascular diseases, and some auto-immune diseases. It is not up to us to give advice to the general population, but rather to the health authorities; if they become convinced that a prudent supplementation policy at national or regional level may give a favourable benefit-risk/cost ratio it is their prerogative. The objective would be to increase the 25(OH)D concentration to 50 nmol/L or more for most individuals (95 %?). As a consequence the mean 25(OH)D concentration of the population of most European countries would move from about 50 nmol/L to about 75 nmol/L. An intake of 600 IU/day, as proposed by the IOM group for adults up to 70 years would probably be insufficient, since according to a rule of thumb, 100 IU vitamin D will increase the 25(OH)D serum concentration by a mean 2 to 2.5 nmol/L, with a huge inter-individual variability [13]. Intake of 1,000 IU/day is probably a better choice as suggested by a recent systematic review and meta-regression analysis of the vitamin D intake-serum 25(OH)D relationship [13].

In the present paper we give our current opinion on which patients need vitamin D testing. Our message is to clinicians who, by definition, see patients, and to clinical chemists who may discuss with the clinicians about the relevance of measuring the 25(OH)D concentration in a given patient. We will separate the patients into two categories.

Patients in whom a "reasonably" evidence-based target concentration should be achieved and/or maintained

First, we must acknowledge that, although plentiful, the many evidences concerning the various potential extra-skeletal effects of vitamin D are mostly based on observational and mechanistic studies. Indeed, numerous prospective studies have shown that subjects in the highest quantile of 25(OH)D concentrations (usually >70–80 nmol/L) have a lower relative risk for many diseases than those in the lowest quantile (usually <30–40 nmol/L) [see for example 15–18]. However, the observational nature of these studies does not allow establishing a causal relationship between low vitamin D status and these diseases, and thus prevents defining clear clinical cut-off(s) to optimize these potential effects. We must mention a quite recent article co-signed by some of us (JCS, C P-D, GJ, EC) [11], which reported the opinion of a panel of 25 experts from various disciplines. In this paper, most authors recommended to measure the 25(OH)D serum concentration in general practice in a myriad of medical conditions including pregnant women, patients with cancers, auto-immune diseases, cardiovascular diseases, hypertension, diabetes. Two years after the submission of this article, we would not give the same advice concerning the need to test vitamin D in these patients. It must be remembered that most studies on which the reasoning of this article was based were published quite recently (2005 and after, see [15–18]), and that many clinicians started to measure 25(OH)D concentrations in their patients at this period and were discovering that vitamin D deficiency/insufficiency (even when defined by a 25(OH)D <50 nmol/L) is extremely frequent. Furthermore, while it became obvious for these colleagues that vitamin D had to be prescribed to most patients, the recommendations made by experts at this period [19–23] to prescribe higher (often 10 times higher) doses than the current DRI were questioned

by many. Indeed, what most doctors had learnt about vitamin D was that it prevents rickets on the one hand, and that it may be toxic on the other hand. They thus expressed the need to understand how the 25(OH)D serum concentration (as well as serum and urinary calcium concentrations) increases when they prescribe vitamin D at doses (much) higher than the DRI. Consequently, they requested an increased number of 25(OH)D concentration measurements. It has become clear that vitamin D intakes of 2,000 IU/day (and even more) are perfectly safe even if administered to subjects who have a spontaneous 25(OH)D concentration in the highest quartile of the general population (usually in the 70–90 nmol/L interval), assuming they have no granulomatous disease (sarcoidosis, tuberculosis…) or hypersensitivity to vitamin D due to a genetic defect [24]. We thus do not recommend a systematic evaluation of the vitamin D status any more in patients with (or at risk of) cardiovascular diseases, auto-immune diseases, cancers, infections, or in pregnant or lactating women. As indicated in the introduction, this opinion may change again according to newly published data (for example if one of the ongoing RCTs demonstrates that vitamin D supplementation improves one or several clinical outcomes if a given 25(OH)D concentration is achieved). In the interval, we propose to supplement these patients with vitamin D without prior testing (although we don't consider that measuring 25(OH)D concentration in some cancer, multiple sclerosis, HIV, or hypertensive patients is a "crime"). We acknowledge however that providing this kind of recommendations or suggestions that is based on published data and experience, and the situation of the physician who has to decide to measure or not to measure 25(OH)D concentration in a given patient, are two very different things. We are aware that in our countries (France and Belgium) at least, many doctors are still reluctant to prescribe vitamin D supplementation without knowing the vitamin D status of their patients. Similarly, some patients would not agree to take a vitamin D treatment if a vitamin D deficiency/insufficiency has not been evidenced by a low 25(OH)D concentration. For those doctors who will agree with our suggestion, the doses suggested by the Endocrine Society group as being the mean daily requirement are encouraged (for example 1,500–2,000 IU/day for adults – see Table III in [1]). It is probable that, with these doses, and due to an important inter-individual variability in the 25(OH)D response to a given vitamin D dose, not everybody will have a 25(OH)D concentration above 75 nmol/L, whereas a concentration of more than 50 nmol/L can be expected in most patients.

In our opinion, there are however groups of patients in whom measurements of vitamin D concentration are highly legitimate. The Endocrine Society group [1] proposes, and we fully agree, that vitamin D *deficiency* corresponds to 25(OH)D concentrations < 50 nmol/L, and *insufficiency* to concentrations of 50 to 75 nmol/L. In clinical practice, we want that our patients achieve a "sufficient" level; our target concentration is thus above 75 nmol/L. Like the Endocrine Society group, we acknowledge that this cut-off concentration is only "reasonably evidence-based" for the musculoskeletal health and mineral metabolism (prevention of rickets/osteomalacia, elevated PTH levels, osteoporotic fractures and falls in the elderly). Indeed, in the RCTs that shown positive effects of vitamin D on non-vertebral fractures [25] and falls [26], of subjects in the "vitamin D groups" had generally 25(OH)D concentrations of more than 75 nmol/L, whereas those in the "placebo groups" had concentrations in the 30–60 nmol/L interval. Consistent with these, bone biopsy data showed that histomorphometric signs of osteomalacia are not detected in subjects with a serum 25(OH)D concentration of more than 75 nmol/L whereas they are present, as defined by the most conservative threshold of the OV/BV ratio of 2 %, in approximately 10 % of those with a 25(OH)D concentration between 50 and 75 nmol/L [27]. Furthermore, Japanese patients with a basal 25(OH)D concentration of up to 70 nmol/L decreased their PTH concentration when they were given vitamin D (without calcium) [28], while the relationship between serum 25(OH)D and PTH concentrations in various populations indicated in some studies that the PTH concentration may increase when 25(OH)D is below 75–80 nmol/L. Due to uncertainty in 25(OH)D measurements (comparable to that of the measurement of other steroid hormones), a best estimate of 75 nmol/L allows for a uncertainty interval between 60 and 90 nmol/L [29]. Among patients in whom we propose to measure 25(OH)D, we include:

- Patients with rickets/osteomalacia.
- Patients with osteoporosis (with and without fracture). In these patients we recommend measuring 25(OH)D at diagnosis, as a part of a more extensive evaluation of possible secondary causes of low bone mass (including at least concentrations of serum calcium, phosphate, PTH, protein electrophoresis, blood cell count, CRP) [30]. If the 25(OH)D concentration is < 75 nmol/L it is proposed to prescribe vitamin D according to a "correction" protocol (examples to be found in [2,10,11,19]). After this first stage (aiming at increasing the 25(OH)D concentration to a value > 75 nmol/L) a "maintaining" treatment (aiming at maintaining the 25(OH)D concentration above 75 nmol/L) must be initiated (for example 1,500–2,000 IU/day or its equivalent given in weekly, monthly, or bi-monthly doses). We recommend to monitor the 25(OH)D concentration during this "maintaining" treatment (measure 25(OH)

D after 4–6 months in case of daily treatment, and, in case of intermittent treatment, after 6 months of treatment, just before a dose is given) and adapt the posology according to the measured value.

- Patients at risk of osteoporosis/bone loss because they receive specific treatments such as glucocorticoids chronically at a dose of 7 mg prednisone or more for any cause (see a recent review in [31]), analogs of GnRH for prostate cancer, or anti-aromatase therapy for breast cancer [32]. In these patients, 25(OH)D measurement may be done 4–6 months after a vitamin D treatment (1,500–2,000IU/day) is initiated to adapt the posology.

  - Patients at risk of osteoporosis/bone loss because they have a malabsorption syndrome (celiac disease, inflammatory bowel disease, cystic fibrosis, Crohn's disease…) in whom higher vitamin D doses are generally required. Similarly, 25(OH)D concentration measurement may be done 4–6 months after a vitamin D treatment (3,000–4,000 IU/day) is initiated to adapt the posology.
  - Patient who had bariatric Surgery, specially gastric bypass. Obese patients are usually vitamin D deficient but are not osteoporotic. However, after gastric bypass they have an accelerated bone loss. These patients cumulate two reasons for being vitamin D deficient: 1) even if they have lost 50 kg or more, they are usually still obese and store vitamin D in their fat mass, and 2) they have a malabsorption due to the surgical procedure. They usually need much higher vitamin D doses than the other patients [1].
  - Patients with chronic kidney disease (CKD) stage 3–5D and kidney transplant recipients. Measuring 25(OH)D concentrations in CKD patients and treating vitamin D deficiency/insufficiency as in the general population is a recommendation of the KDIGO guidelines [33]. This recommendation is in fact only a suggestion which is graded 2C. Secondary hyperparathyroidism is a hallmark of CKD, with several deleterious consequences. It must be underlined that until recently, nephrologists used to treat their patients with active vitamin D (analogs of calcitriol), not "mother" vitamin D, to control PTH secretion. Recent studies have shown that supplementation with cholecalciferol or ergocalciferol was able to decrease modestly but significantly PTH concentrations not only in non-dialyzed, but also in dialyzed and in transplant patients [34–37]. Furthermore, several prospective observational and non randomized interventional studies have linked vitamin D deficiency to increased mortality in CKD [38], accelerated GFR loss [39], and albuminuria [40]. Consequently supplementation with vitamin D is an increasing practice in CKD patients. We have shown that monthly supplementation with 100,000 IU vitamin D3 decreases PTH and is adequate to maintain the 25(OH)D concentration of most dialyzed [35] and kidney transplant patients [37] above 75 nmol/L, whereas 100,000 IU every two months failed to maintain this concentration in approximately one half of our kidney transplant recipients [37].
  - Patients with primary hyperparathyroidism (PHPT). These patients are often vitamin D deficient and osteoporotic, but they are also hypercalcemic. Treating hypercalcemic patients with a molecule that increases calcium absorption, and which may, when given at extremely large doses, cause hypercalcemia, hypercalciuria, and extra-skeletal calcifications was regarded with suspicion by most physicians. It was shown in 2005 that the administration of large doses of cholecalciferol to PHPT patients with a serum calcium concentration < 3 mmol/L did not increase serum calcium or phosphate, and decreased PTH significantly [41]. This was followed by similar published results (reviewed in [42]) so that the expert panel for the diagnosis/management of asymptomatic PHPT recommended to treat any PHPT patient with a 25(OH)D concentration < 50 nmol/L [43]with vitamin D. It is also recommended to supplement all PHPT patients with vitamin D (and calcium) once they have been surgically treated. This will allow an increase in bone mineral density and prevent symptomatic hypocalcemia due to "hungry bone syndrome" [42]. In our experience, 25(OH)D concentrations > 75 nmol/L (and sometimes more) are to be targeted after parathyroidectomy.
  - Patients with granulomatous disorders such as sarcoidosis or tuberculosis. In these patients it is prudent to target a 25(OH)D concentration around 50 nmol/L to avoid both hypercalcemia/hypercalciuria due to uncontrolled synthesis of calcitriol on the one side, and severe vitamin D deficiency, which is frequent in these patients because of the fear of inducing hypercalcemia, on the other side.
  - For the patients of the above category, adherence/observance to vitamin D supplementation will be a concern. It is thus not unrealistic to measure 25(OH)D at intervals in these patients. It is logical to measure 25(OH)D at its theoretical nadir, i.e. during the winter months if possible, and just before a dose is taken in case of intermittent dosage administered at intervals of one month or more.

Patients in whom a severe vitamin D deficiency or excess should be excluded without a special 25(OH)D concentration interval to be targeted

This includes patients in whom symptoms compatible with a severe vitamin deficiency (such as those with diffuse pain or elderly subjects who frequently fall), or with a vitamin D intoxication (such as those with extra-skeletal calcifications, nephrocalcinosis or recurrent renal stones) are present and persist without a clear explanation. Patients having a disease, such as hepatic failure, or receiving treatments that may modify vitamin D metabolism such as some anti-convulsants or ketokonazole can be included in this category. In these patients there is no special 25(OH)D concentration interval recommended although it is logical to consider 50–150 nmol/L as this would be unlikely be associated with these symptoms.

More generally, measurement of 25(OH)D concentration is recommended in any patients in whom an exploration of calcium/phosphate metabolism which includes a measurement of serum PTH is prescribed. Besides osteoporotic patients in whom the aim is to exclude a secondary cause of low bone mass and/or fractures, it should be prescribed in patients with renal lithiasis, chondrocalcinosis, and in case of persistence (without explanation) of symptoms of both hyper- or hypocalcemia. In such cases it is especially important to know the 25(OH) D concentration when a high PTH concentration is detected in patients with otherwise normal serum calcium and phosphate concentrations. The 25(OH) D concentration may help differentiating between a secondary hyperparathyroidism, and a so-called "normocalcemic" PHPT. This is now recognized as a separate and quite frequent entity, which probably necessitates the same treatment as hypercalcemic PHPT when osteoporosis, renal lithiasis or renal failure is present [44].

Conclusion

Growing interest for vitamin D and its proven or potential effects has induced a dramatic increase in the prescription of measuring vitamin D concentration in clinical practice. Although we consider that in many patients, these prescriptions are not justified, and that these patients should receive vitamin D without prior testing according to recent recommendations [1], we still continue to consider that estimating vitamin D status by measuring the 25(OH)D concentration is largely legitimate in several groups of patients. We insist on the fact that this article reflects our current opinion which may change depending on the publication of the results of several ongoing clinical trials.

Questions and Answers

R Lorenc, Poland

You mentioned that you have a very heavy reimbursement in France for 25(OH)D measurements. I would like to take issue with one of your points. You said that with glucocorticoid treatment, you need to measure 25(OH)D. I would advocate that in view of the deleterious effect of glucocorticoids on bone, we shouldn't wait for measurement and supplement immediately. What do you think?

JC Souberbielle

You are correct. Of course you should give vitamin D without testing in patients on glucocorticoids for whatever reason but after a few months of treatment you should measure vitamin D to ensure you are achieving concentrtaions in the required interval. It is different in patients with osteoporosis. Then you must know the 25(OH)D concentration at the beginning.

G Beastall, UK

You showed the enormous increase in the number of serum 25(OH)D measurements in France. I suspect the same is true in all our countries and it is not caused by the patients in whom you have advocated measurement. It is caused in my experience largely by the popular press and the media which are persuading people to have their vitamin D status checked because of its importance in protecting against a variety of conditions. It is a huge issue, often being driven by relatively weak science. People are demanding measurement of 25(OH)D concentrations through primary care physicians when they have a variety of non-specific symptoms. Is that primary care physician ever going to say 'No'?

JC Souberbielle

I think it is for the Health Authority to give recommendations. It is difficult; we give recommendations based on the literature, but when you are in your office with a patient, that is very different!

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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