

Screening for hypovitaminosis D: cost-effective or not?

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Abstract

Few topics have elicited more emotion than the issue of screening for vitamin D status and the discussion on the need for global supplementation with vitamin D metabolites. The importance of the problem is highlighted by the USPSTF posted draft research plan with the aim of making an update recommendations statement, possibly next year. Here, we discuss two different viewpoints on screening for vitamin D status: for and against. In the literature there are scientifically sound opinions supporting pro and cons positions. However, we believe that the best way to definitively elucidate this issue is the implementation of a randomized controlled trial evaluating clinical outcomes or harms in persons screened versus those not screened for vitamin D deficiency. The feasibility of such a trial is probably questionable owing to uncertainties still present concerning threshold for vitamin D sufficiency and end points (that is, for example, improved bone mineral density, reduced risk of falls and so on) to be reached.

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Introduction

Few topics have elicited more emotion than the topic of screening for vitamin D status and the discussion on the need for global supplementation with vitamin D metabolites. Whereas epidemiological data and data from preclinical models indicate a clear role for vitamin D deficiency in disease and for the potential to improve health by supplementing with vitamin D metabolites, evidence from randomized clinical trials remains disappointing beyond the prevention of rickets and osteomalacia (1).

Passionate discussions are also ongoing on the types of measures that are the most appropriate to determine vitamin D status and even on the most used measure, serum 25-hydroxyvitamin D₃, a consensus on reference values for sufficiency is lacking. A working group appointed by the Institutes of Medicine (IOM) has issued guidance on supplementation doses of vitamin D and has deducted levels of frank deficiency (<30 nmol/L),

insufficiency (30–50 nmol/L) and sufficiency (>50 nmol/L) on the basis of bone health parameters (2, 3). However, those who believe in a role for vitamin D beyond calcium and bone health, suggest that these levels do not apply to global health and higher cut-offs for sufficiency should be used (4). For example, to observe immune effects, levels well above 100 nmol/L need to be achieved (5). Here, we discuss two different viewpoints on screening for vitamin D status: for and against.

Screening for vitamin D status: FOR (Cook D, Mathieu C)

When asking ‘should there be a universal screening for vitamin D levels?’, this question generates different questions that deserve attention and that yield many different answers. It is obvious that universal screening,

in the meaning ‘screening all humans during their whole life’ is of course not desirable, but screening in an intelligent way, picking the right population and using the right tools is defensible.

1. Should we measure vitamin D status at all?

There is no doubt on the central role of the vitamin D system in bone and mineral metabolism, with hard evidence that vitamin D deficiency leads to rickets and osteomalacia (6). Supplementing these patients with vitamin D, in any form, will prevent and correct the abnormalities. In rare cases, rickets will be caused by genetic abnormalities and use of specific vitamin D metabolites will be needed (e.g. pseudo-vitamin D deficiency rickets, in people with mutations in CYP27B1, necessitating treatment with a 1 α -hydroxylated metabolite) (7). Thus, it is strange that the question on ‘should we screen for vitamin D deficiency’ is even asked in the context of a serious clinical or scientific discussion. Is it not in the same realm as ‘should we screen for hyperglycemia?’. Rickets and osteomalacia are proven diseases and whereas rickets has become rare in Western societies, it remains an important problem in many parts of the world, where nutrition is less balanced or frankly insufficient (8). Here of course, global substitution campaigns for vitamin D supplementation should be implemented and only when standard supplementation does not achieve clinical benefit, should vitamin D levels be measured (9).

Osteomalacia and other calcium and bone disorders due to vitamin D deficiency are however also on the rise in our societies, due to the changes in lifestyle, where people live more indoors and where nutritional imbalances are induced by medical intervention (e.g. bariatric surgery) (10). Societal changes have led to an increasing prevalence of vitamin D deficiency in children and adolescents, who have swapped their outdoor games for computer games. Another growing at-risk population are the frail elderly, in particular those living in an assisted living environment. Finally, more and more darker skinned people are living in areas with low sunlight exposure or in areas where climate is too harsh to be outdoors in the sun for long periods. These people are at great risk of becoming vitamin D deficient. In these groups, standard supplementation of vitamin D according to the guidelines of local authorities, based on the IOM guidelines, should be implemented (3). Of course, in these populations, also measuring the level of vitamin D, to evaluate whether the standard supplementation is sufficient is appropriate.

2. How should we measure vitamin D status?

Vitamin D is a fat soluble substance in some food sources, like fatty fish. However, most people get their vitamin D from self-synthesis in the skin under the influence of UVB light, through luminosity out of 7-dehydrocholesterol (11). This product is then hydroxylated, typically on the 25 position by CYP enzymes (e.g. CYP2R1, CYP2D11, CYP2D25, and CYP3A4). These enzymes are located throughout the body, but the majority of circulating 25-hydroxyvitamin D₃ is hydroxylated in the liver, in a dose dependent manner: the more vitamin D is synthesized in the skin or taken up from food sources, the more gets hydroxylated. This makes 25-hydroxyvitamin D₃ a good measure for overall vitamin D status, as it is directly correlated with the input. 25-Hydroxyvitamin D₃ is fat soluble and is linked to a carrier protein, vitamin D binding protein (DBP), for transport in the blood. To be active and bind with high affinity to the target receptor (a nuclear receptor, VDR, present in most tissues), a further hydroxylation needs to happen on the 1 α position, by CYP27B1. This enzyme is present in kidney, where its expression is tightly controlled by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D₃ itself (negative feedback). CYP27B1 (as many enzymes that can hydroxylate on the 25 position) is present in many other organs, like skin and immune cells (12). In some of these organs however, their expression is not controlled by calcium or bone signals, but by signals proper to the tissue (12). Degradation of 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ happens in many different ways, with the most typical pathway being a 24 hydroxylation, by the CYP24 enzyme, present in most cells. However, also other metabolization paths exist yielding an (still expanding) array of vitamin D metabolites of different abundance in blood (13). Debate exists on the role of the multitude of metabolites of vitamin D that can be detected by sensitive methods like LC–MS/MS as well as their usefulness for estimation of vitamin D sufficiency (14, 15).

To date the standard way of assessing vitamin D sufficiency is by measuring the circulating levels of 25-hydroxyvitamin D₃. This metabolite is present in the ng/mL or nmol/L range and can thus be measured using methods like radioimmunoassay, which are readily available in most commercial and clinical laboratories. A more precise assessment would be using LC–MS/MS, but this method is at present limited to more specialized laboratories. One can argue that in day to day clinical routine, having an estimate of 25-hydroxyvitamin D₃

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levels by the less sensitive techniques is good enough to evaluate adequacy or inadequacy of 25-hydroxyvitamin D₃ levels. A major problem is the use of cut-offs. Clinicians like a black and white situation, where a certain value indicates sufficiency and another insufficiency. However, in the case of 25-hydroxyvitamin D₃, as in the case of many biomarkers, there is a continuum and the cut-offs used for sufficiency and insufficiency are rather arbitrary (16). They have been chosen on the basis of data coming from a limited number of studies and observations and can thus be disputed. However, they can give the clinician a rough idea of the vitamin D status and are thus workable to guide in deciding on supplementation need or not (17).

Many argue that one should assess 1,25-dihydroxyvitamin D₃ levels to evaluate vitamin D sufficiency, as this is the active hormone actually binding to VDR. However, levels of 1,25-dihydroxyvitamin D₃ are harder to measure (pg/mL range) and require for accuracy LC-MS/MS, although again RIA kits are available that give an estimate. However, is there a rationale for measuring 1,25-dihydroxyvitamin D₃? Arguments pro are the fact that it is the active metabolite and that the renal conversion of 25-hydroxyvitamin D₃ to 1,25-dihydroxyvitamin D₃ by CYP27B1 under the influence of PTH is responsible for inducing the bone effects. Parathyroid, gut and bone are indeed primarily dependent on the circulating 1,25-dihydroxyvitamin D₃ form (18). However, evidence is accumulating that local conversion of 25-hydroxyvitamin D₃ into 1,25-dihydroxyvitamin D₃ in the target organs is essential also for calcium and bone metabolism, as it is absolutely the case for all the 'non-calcemic' effects attributed to the vitamin D system (19). In the immune system, it is clear that local conversion of vitamin D into the active metabolite in immune cells is happening under completely different control than the conversion for calcium and bone needs. In macrophages, 25-hydroxylases and CYP27B1 are present and in particular CYP27B1, responsible for the final hydroxylation step on the 1 α position, is not controlled by PTH, but by immune signals like inflammation (e.g. bacterial wall components like LPS) or inflammatory cytokines (e.g. IL1, IFN α). Thus, for immune purposes, mainly local levels of 1,25-dihydroxyvitamin D₃ matter, as well as circulating 25-hydroxyvitamin D₃, the substrate for the local conversion (20). Thus, in particular for the non-calcemic effects, 25-hydroxyvitamin D₃ remains an appropriate measure of vitamin D status.

What about the role of DBP, the transporter protein for 25-hydroxyvitamin D₃? It was originally

described as just a carrier molecule, but it has become clear that this protein itself determines in many tissues influx of 25-hydroxyvitamin D₃ into the cells, through its counterpart megalin or other proteins (21). This is the case in kidney, but the role of DBP and megalin remains unclear in other target organs like immune cells.

Finally, we have to recognize the gap in knowledge on the role of other metabolites of vitamin D in controlling vitamin D status. For example, 24,25-dihydroxyvitamin D₃ has long been considered just a degradation product, but independent actions of this (as other) metabolites have in the meantime been described and may also be important measures to complete the picture of vitamin D status (14).

3. Why not just supplement the whole population with vitamin D?

Epidemiological evidence for an association of vitamin D status with health in its broadest definition is overwhelming. Vitamin D deficiency is associated with impaired health and many diseases, like diabetes, complications of pregnancy or cancer (22, 23, 24). The question however is, whether the low vitamin D status is a marker for impaired health or a true contributor to disease. Till now we only have evidence for the former, as most well controlled intervention studies were not able to demonstrate clear benefit of vitamin D supplementation on outcomes (25, 26, 27).

Criticism of these studies can of course be that doses were too low, that the wrong vitamin D metabolite was used or that interventions started too late and did not last long enough. Still, these studies demonstrate that when doses are used that are in the range of those accepted by IOM as safe, and would thus be eligible for use in universal substitution strategies, no increase in health can be measured. Even when using somewhat higher doses, as in recent studies, no improvement in health could be seen. This poses a major problem for the 'substitute all' campaign, as low and safe doses do not improve health, but higher doses may induce side effects, like hypercalcemia or kidney stones. Granted, these complications are rare, but in case a whole population would be treated with high doses of vitamin D, these complications will emerge, causing harm and increasing health care cost higher than what screening for vitamin D deficiency in the first place costs, when used appropriately (see below).

4. Is targeted screening for vitamin D deficiency the way to go?

When discussing screening for vitamin D deficiency, we should take lessons from other fields, like type 2 diabetes: screen those at risk and advise the global population on healthy lifestyle, in diabetes this means exercise and healthy eating, in vitamin D the advice should be safe UV exposure and balanced nutrition, with oral supplements when UV exposure is insufficient or undesired and when nutritional sources scarce. This advice is warranted in the global population and will also benefit healthy individuals, as it will help keep them vitamin D sufficient and healthy. We have good guidance by IOM, translated to local guidelines in many countries, defining the average requirement (RDA) for people in different age groups, which will nearly always meet the needs of generally healthy people.

In diabetes, heated discussions are ongoing on how to screen (HbA1c, OGTT, fasting glycemia, random glycemia), but overall fasting glycemia does the job in most patients. As such, in vitamin D screening, 25-hydroxyvitamin D₃ levels measured with RIA will orient the clinician sufficiently and are an elegant way to assess vitamin D status in daily practice.

In diabetes, aggressive screening strategies are implemented in those at risk (obese, older people, familial history). As such, aggressive, broad screening strategies should be put in place for those at risk of vitamin D deficiency: people not getting UVB exposure (those living in assisted living facilities, those living in areas with prolonged periods of scarce sunlight or on the contrary those living in very hot areas avoiding sun, people wearing clothing providing full body coverage, adolescents), people with impaired vitamin D uptake (steatorrhea, bariatric surgery, other malabsorptive situations), people with unbalanced nutrition or higher nutrition needs (vegetarians, pregnancy), people taking medications that can alter vitamin D metabolism (such as anticonvulsants) and in particular people with risk factors for vitamin D deficiency, like presence of osteoporosis or osteomalacia. In these, measuring 25-hydroxyvitamin D₃ with a RIA method will give a sufficient idea of vitamin D status and can orient supplementation needs over and above general healthy living advice. For these people at risk, targeted vitamin D status assessment is appropriate and vitamin D supplementation at levels above the RDA will be necessary. Repeat measurements after 3–6 months will reveal sufficiency of supplementation dose or will urge the clinician to move to higher supplementation doses.

Screening for vitamin D status: AGAINST (Minisola S, Colangelo L, Cipriani C, Pepe J)

Screening for vitamin D deficiency should have the aim of identifying persons (either normal subjects or osteoporotic patients or people suffering from other diseases) with low vitamin D levels that theoretically could then take advantage of vitamin D supplementation (28). As a consequence of this theoretical screening program, we would expect an improvement in selected health outcomes (that is, for example, improved bone mineral density, reduced risk of falls and so on). Implicit in this, as well as in other screening programs, is that there are no harms as a consequence of this intervention and subsequent treatment (28, 29).

In the context of screening for vitamin D deficiency, there are a number of issues that preclude a fruitful outcome. First of all, it is important the definition of threshold for hypovitaminosis D (including both insufficiency and deficiency) (30). Indeed, even though there is universal agreement that individuals should not have 25(OH)D values less than 10 ng/mL (or 25 nmol/mL), there is an ongoing and never ending debate on what constitutes the threshold for sufficiency (i.e. 20 vs 30 ng/mL) (31, 32, 33, 34, 35). Another important point to consider is represented by the lack of randomized controlled trials that evaluated clinical outcomes or harms in persons screened versus those not screened for vitamin D deficiency (28). The issue of screening for vitamin D deficiency has been recently addressed by the U.S. Preventive Services Task Force (USPSTF) that systematically reviewed benefits and harms of vitamin D screening in asymptomatic adults (28). This committee found no direct evidence on effects of screening for vitamin D deficiency versus no screening on clinical outcomes. They also concluded that treatment of vitamin D deficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risk for falls but not risk for fractures. There are other societies or organizations that expressed reservations concerning universal screening owing to insufficient evidence. Among them are the American Academy of Family Physician or, for example, the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS) (36). The Endocrine society recommends screening for vitamin D deficiency in persons at risk (African Americans and Hispanic, pregnant and lactating women, older adults with a history of falls or non-traumatic fractures and patients with a number of diseases involving the skeleton). Some other body organizations, such as the National Academy of Medicine (formerly the

Institute of Medicine), did not issue formal guidelines on screening for vitamin D deficiency. The importance of vitamin D deficiency screening in adults has been recently once again re-emphasized by the USPSTF. Indeed, on October 25th, the USPSTF posted a draft research plan with the aim of making an update recommendations statement, possibly next year.

One could argue that there is a potential advantage in screening the population as a whole, represented by the correct identification of those individuals who would benefit by vitamin D supplementation. However, there are some points that should be considered in this context. The first one is represented by problems inherent with 25(OH)D assay, that is considered the best parameter reflecting vitamin D status. These are mainly related (but not limited) to differences in assay methods, to the role of bioavailable 25(OH)D versus the determination of the total amount, just to cite the most important (14).

We also have to keep in mind that, in case of screening, the large majority of the assays are not carried out in specialized or referral centers, which adhere to standardization programs, but in laboratories whose quality control may be suboptimal (14, 30). The second point that needs to be considered is represented by the well-known notion of pandemic proportions of hypovitaminosis D in the population of the world (4), especially in the elderly subjects (37). Therefore, the measurement of 25(OH)D assay might not be cost-effective, also considering that the price of the assay in some countries is at least ten times more than 1 year of supplementations (38). In addition to this, we should also consider that apart from the side effects reported with the utilization of mega doses of vitamin D (39, 40), there is no real harm with the daily, weekly or monthly doses prescribed in clinical practice (41).

Another potential advantage of screening could be represented by the establishment of baseline in those that need treatment. However, if this is the case, we favor measuring 25(OH)D in the post treatment period because this will increase adherence and will also be probably cost-effective from an economical point of view. This strategy is also supported by the variable responses reported using 'one size fits all' dose; this approach will not assure attaining a 25(OH)D level above any arbitrary cut point (42), unless the selected dose is very large (43, 44, 45). The American Geriatric Society reported data showing that only about half of the patients treated with 1000IU of vitamin D achieved the level of 30ng/mL (46). Furthermore, a recent retrospective study showed that 25(OH)D testing only benefits a small proportion of

patients in terms of achieving vitamin D sufficiency in the medium term (47).

Finally, there are currently a number of questionnaires that correctly predict serum 25(OH)D levels in the population as a whole as well as in specific subgroup, thus rendering universal screening not rewarding considering its cost (38, 48).

In conclusion, we believe that there is no need and no sufficient evidence to support screening for vitamin D status. It could be much more cost-effective to increase food fortifications with vitamin D and biofortification (49) and encourage vitamin D supplementation (50, 51, 52) and sensible sun exposure (53) for subjects living in countries in which such a lifestyle represents a unique opportunity, thus decreasing the cost of National Health Systems.

Conclusion

Screening vs non-screening for vitamin D insufficiency is one of the hot issues surrounding the field of vitamin D with scientifically sound opinions supporting the pro and cons positions. As previously stated, the importance of the problem is highlighted by the USPSTF posted draft research plan with the aim of making an update recommendations statement, possibly next year. The best way to definitively elucidate this issue is the implementation of a randomized controlled trial evaluating clinical outcomes or harms in persons screened versus those not screened for vitamin D deficiency. However, the feasibility of such a trial is questionable owing to uncertainties still present concerning threshold and end points to be reached.

Declaration of interest

Prof. S Minisola served as speaker for Abiogen, Bruno Farmaceutici, Diasorin, Eli Lilly, Italfarmaco and Shire. He also served in the advisory board of Abiogen, Kyowa Kirin, Pfizer and UCB. The other authors declare that they have no competing interests.

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