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High-dosage vitamin D supplements are unnecessary

PERSPECTIVES

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There is little evidence that disease can be prevented by administering high doses of vitamin D to persons with vitamin D status above 50 nmol/l. Overdoses may result in adverse health effects. We call for moderation in prescribing of vitamin D supplements for preventive purposes.

Illustration: Amanda Berglund

There is considerable research activity in the field of vitamin D and health. A search in PubMed as of January 2019 returns nearly 66 000 hits for 'vitamin D' and more than 5 000 hits for 'vitamin D supplementation'. According to figures from the Norwegian Prescription Database, the number of users of prescription-only vitamin D_3 supplements increased 85-fold in Norway over the six-year period from 2011 to 2017. In the same period, the sales of defined daily doses (20 µg) increased more than a hundredfold. In 2017, sales amounted to 39.5 million defined daily doses (1). In addition, sales of over-the-counter dietary supplements are high. High-dosage supplements that contain up to 80 µg vitamin D_3 per tablet are currently available on the Norwegian market. In contrast, according to the Nordic nutrition recommendations, the recommended daily intake of vitamin D for the general population amounts to 10 µg per day for children and adults and 20 µg per day for those 75 years and older (2).

Health outcomes

It is biologically plausible that vitamin D may help prevent a number of chronic diseases, such as cardiovascular disease, colon cancer and autoimmune diseases. This notion is supported by a number of observational studies (3). However, most randomised controlled trials have failed to show a consistent preventive effect of vitamin D supplements, with some exceptions (4): meta-

analyses and systematic reviews of randomised controlled trials provide some evidence that vitamin D has a preventive effect on falls and bone fractures. This effect has mainly been identified for supplementation with vitamin D and calcium in combination. There is insufficient evidence that vitamin D alone has a preventive effect.

A systematic Cochrane review updated in 2014 concluded that vitamin D supplements reduced total mortality by 6 %, but that these findings were insufficiently robust to serve as an argument for recommending vitamin D supplements (5). A recently published meta-analysis of 25 randomised controlled trials concluded that the risk of acute respiratory tract infections may be reduced by vitamin D supplements (6). The strongest effect was observed in those who had a clear vitamin D deficiency (Table 1) and who received daily or weekly supplements, rather than large bolus doses. There was considerable heterogeneity in the findings, and the absolute reduction in risk was minor at the population level.

Table 1

Commonly used threshold values for 25-hydroxyvitamin D measured in serum or plasma

25(OH)D in serum/plasma (nmol/l)	Description
< 12.5	Serious vitamin D deficiency
12.5–30	Vitamin D deficiency
30–50	Insufficient vitamin D status
≥ 50	Sufficient vitamin D status

Recent studies

Currently, a number of large-scale clinical trials that include several thousands of participants are underway (4). In these studies, participants are administered peroral vitamin D supplements in doses equivalent to 50 µg per day or more, but in varying dosage regimes. Their main objective is to investigate the preventive effect on cardiovascular disease, bone fractures or total mortality.

The results from the first large-scale trial with cancer as its primary endpoint showed no clear protective effect of vitamin D supplements (7). The study was undertaken in a healthy population who had a sufficient vitamin D status on average, and there were too few participants with low concentrations of 25-hydroxyvitamin D to study the effect in the case of clear vitamin D deficiency. In a study from New Zealand with more than 5 000 participants, a single dose of 5 000 µg vitamin D_3 was administered, followed by monthly doses of 2 500 µg vitamin D_3 (equivalent to an average daily intake of approximately 80 µg)

over a median period of 3.3 years. The supplement had no preventive effect on the primary endpoint of cardiovascular disease (8), nor on cancer (9), falls or fractures (10).

Results from the large-scale VITAL Study with more than 25 000 participants were recently published (11). No preventive effect was found with respect to the incidence of cardiovascular disease of a daily supplement of 50 µg vitamin D_3 over a median period of 5.3 years. There was, however, a tendency suggesting that vitamin D supplements could reduce cancer mortality.

Nutritional importance

Vitamin D can cure the deficiency-related conditions nutritional rickets and osteomalacia in children and adults respectively. If vitamin D supplements have a preventive effect on other conditions, these can be expected to be minor. Despite their impressive sample size, the new randomised controlled trials have insufficient statistical power to identify very small effects, because the studies are undertaken in populations with generally sufficient vitamin D status. According to the exclusion criteria listed in the clinical trials registries, the participants in several of the studies are permitted to take supplements in the order of 20 µg/day, including those in the control group.

Vitamin D is a nutrient of which everybody needs a minimum amount. Through diet and exposure to sunlight, all individuals will be supplied with some vitamin D, with day-to-day and seasonal variations. Insufficient and excessive intakes are both potentially harmful. However, the research focus on vitamin D has largely moved towards testing of health effects of vitamin D in pharmacological doses. Although new studies may enhance our knowledge about potentially preventive and possibly adverse health effects of supplements in high doses, they will contribute little to improving our knowledge about the nutritional importance of vitamin D for our health. An interpretation of the effects, or lack thereof, on the basis of the paradigm used in testing of medical drugs is not equally well suited for nutrients. Since a growing number of large-scale, well-designed studies cannot confirm any positive health effects of high doses of vitamin D supplements, the pendulum may now swing to the other extreme, where vitamin D is assumed to have no bearing on health. If future intervention studies are to provide genuinely new knowledge about the nutritional importance of vitamin D for our health, they will need to concentrate on populations that have a low vitamin D status and increase their intake through doses that are close to the recommended daily intake.

Adverse effects of overdosing

Adverse effects of high-dose supplements cannot be excluded. In some randomised trials in which very high doses of vitamin D were given annually (12, 13) or monthly (14), this caused an increased occurrence of falls and/or fractures.

Hypercalcaemia caused by excessive doses of vitamin D gives rise to symptoms in a number of organ systems, and may in serious cases be life-threatening with effects such as dehydration, renal affection, electrolyte imbalance and risk of cardiac arrhythmia and coma. Overdoses of vitamin D are often caused by manufacturing and labelling errors, while the general rise in sales and prescribing of high doses add to the risk (15, 16). In the summer of 2016, more than 100 children in Denmark were affected by hypercalcaemia caused by organic vitamin D drops that contained75 times more vitamin D than what was declared on the label (17).

What should we do?

There are indications that the potential health advantages of vitamin D supplements are restricted to those who suffer from vitamin D deficiency to begin with (18). Examples of such groups include immigrants with backgrounds from Asia, Africa and the Middle East, who in all studies that we are aware of have had a very low vitamin D status at the group level, consistent with risk of rickets and osteomalacia. This has also been shown in other European countries (19). The use of vitamin D supplements in doses corresponding to the recommended daily intake (10–20 µg) is sufficient to increase vitamin D status. This dose gives a greater increase in blood levels when the baseline values are low. A broad and moderate addition of vitamin D to commonly used foods such as dairy products and fats will also contribute. Although the total contribution from such vitamin D fortification will be small, it will have a significant impact for those who have the lowest baseline intake.

Over time, there has also been a considerable increase in measurements of 25-hydroxyvitamin D in blood samples (20). Mass screening for vitamin D is not required. We endorse the clinical recommendation from the Norwegian Association for Medical Biochemistry as part of the Norwegian Medical Association's campaign *Gjør kloke valg* [*Choosing Wisely*], which advises against requisitioning analyses of vitamin D in persons with no elevated risk of vitamin D deficiency (21).

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