Review

Sources of vitamin D for humans

Evgen Benedik[1,2]

[1] Division of Paediatrics, University Medical Centre Ljubljana, Slovenia
[2] Biotechnical Faculty, University of Ljubljana, Slovenia

Abstract: Both vitamin D insufficiency and deficiency are now well-documented worldwide in relation to human health, and this has raised interest in vitamin D research. The aim of this article is therefore to review the literature on sources of vitamin D. It can be endogenously synthesised under ultraviolet B radiation in the skin, or ingested through dietary supplements and dietary sources, which include food of animal and plant origin, as well as fortified foods. Vitamin D is mainly found in two forms, D_3 (cholecalciferol) and D_2 (ergocalciferol). In addition to the D_3 and D_2 forms of vitamin D, 25-hydroxy vitamin D also contributes significantly to dietary vitamin D intake. It is found in many animal-derived products. Fortified food can contain D_3 or D_2 forms or vitamin D metabolite 25-hydroxy vitamin D. Not many foods are a rich source (> 4 μg/100 g) of vitamin D (D represents D_3 and/or D_2), e.g., many but not all fish (5–25 μg/100 g), mushrooms (21.1–58.7 μg/100 g), Reindeer lichen (87 μg/100 g) and fish liver oils (250 μg/100 g). Other dietary sources are cheese, beef liver and eggs (1.3–2.9 μg/100 g), dark chocolate (4 μg/100 g), as well as fortified foods (milk, yoghurt, fat spreads, orange juice, breakfast grains, plant-based beverages). Since an adequate intake of vitamin D (15 μg/day set by the European Food Safety Authority) is hard to achieve through diet alone, dietary supplements of vitamin D are usually recommended. This review summarizes current knowledge about different sources of vitamin D for humans.

Keywords: Vitamin D, dietary sources, dietary supplements, fortified food

Introduction

Vitamin D generally encompasses two molecules: cholecalciferol (vitamin D_3; sourced from skin exposure to ultraviolet B radiation (UVB, usually sunlight) on its precursor, 7-dehydrocholesterol, in skin and mainly food of animal origin) and ergocalciferol (vitamin D_2; sourced from food of plant origin) [1].

In humans, it has been roughly estimated that UVB induced production of vitamin D_3 in the skin accounts for about 80% of vitamin D supply, whereas dietary intake usually plays only a minor role [2]. It was believed that the endogenous synthesis of vitamin D_3 in countries closer to the equator that have sunny climates was sufficient to meet daily requirements [1]; however, unexpectedly, production in these regions is still not sufficient [3–5]. The effectiveness of current sunlight exposure guidelines among various populations should therefore be reassessed [6]. It should be in accordance with World Health Organization (WHO) recommendations, which suggest avoiding outdoor activities between 10 a.m. and 4 p.m. to prevent overexposure to UVB radiation and its harmful effects on the skin, eyes and immune system and increased risk of skin cancer [7].

A number of factors govern the absorption efficiency of vitamin D (D represents D_3 and/or D_2 unless stated otherwise) in the human gastrointestinal tract, such as the complexity of the food matrix (the amount and type of fatty acids, dietary fibre and its interaction of other fat soluble compounds with vitamin D, as well as host-associated factors (age, disease, surgery, obesity, genetic variation etc.) [8]. Vitamin D_2 and vitamin D_3 share similar steps in the metabolism described in detail elsewhere [8, 9]. Briefly, vitamin D is absorbed via chylomicrons. Absorption from dietary sources in humans is between 55 to 99% [10]. Once in the circulation, it is converted to 25-hydroxy vitamin D (25(OH)D or calcidiol, the sum of both $25(OH)D_2$ and $25(OH)D_3$), with a reported half-life of 2–3 weeks. It is synthesised primarily in the liver, although other tissues have this enzymatic activity as well. The final hydroxylation of the reabsorbed, intracellular 25(OH)D occurs mainly in the kidneys but also in some other important target tissues such as the immune system. 25(OH)D is a substrate for tissue activation to form the biologically active form of vitamin D, 1,25-dihydroxy vitamin D ($1,25(OH)_2D$ or calcitriol) with a half-life of a few hours. $1,25(OH)_2D$ then acts through intracrine, autocrine and paracrine effects. Finally, $1,25(OH)_2D$ stimulates its own destruction, to metabolise 25(OH)D and $1,25(OH)_2D$ into water-soluble inactive forms. Renal activation to form $1,25(OH)_2D$ is affected by many hormones (e.g., parathyroid hormone) and metabolites (e.g., calcium and phosphate) [11]. Activation of vitamin D in non-renal target tissues or cells (e.g., macrophages) is regulated mainly by the 25(OH)D concentration [12].

Furthermore, vitamin D plays an important role in epigenetics and gene regulation. Bound to its intracellular receptor, $1,25(OH)_2D$ is able to regulate many target genes, with beneficial effects on human health [14]. Hypovitaminosis D increases the incidence and severity of several age-related

common diseases, such as oxidative stress-associated metabolic disorders. These include obesity, insulin resistance, type 2 diabetes, hypertension, pregnancy complications (small for gestational age, preterm birth, detrimental effect on offspring bone and teeth development, and risk of infectious diseases), memory disorders, osteoporosis, autoimmune diseases, certain cancers, and systemic inflammatory diseases [13]. New understandings of vitamin D-related advances in metabolomics, transcriptomics, epigenetics, in relation to its ability to control oxidative stress in conjunction with micronutrients, vitamins and antioxidants, following normalization of serum 25(OH)D and tissue $1,25(OH)_2D$ concentrations, are likely to promise better cost-effective clinical outcomes in humans. Furthermore, in a cell, $1,25(OH)_2D$ can also act through its non-genomic effects by initiating multiple signalling pathways via binding to a membrane receptor. These result in immediate responses in the target cells (e.g., bone, teeth, brain, parathyroid, muscle, kidney cells). Some of the widely studied responses include calcium uptake from the intestine, insulin secretion by β-cells of the islets of pancreas and others [13].

Serum 25(OH)D concentration is a robust and reliable marker of vitamin D status and has been used by numerous agencies in the establishment of vitamin D dietary requirements. It has also been used for population surveillance of vitamin D deficiency or inadequacy. The Endocrine Society has established ranges of serum 25(OH)D concentration indicating vitamin D deficiency (< 20 ng/ml or < 50 nmol/l), insufficiency (20–30 ng/ml or 50–75 nmol/l) and target concentration for optimal vitamin D effects (30–50 ng/ml or 75–125 nmol/l) [14].

Optimal serum 25(OH)D concentration has pleiotropic functions; it optimizes bone health through the maintenance of the calcium and phosphorus balance, muscle function, cardiovascular system, immune system, inhibits cancerogenesis, positively alters the gut microbiota, and many other functions as described above [15].

The main risk factors that have a strong negative impact on the endogenous synthesis of vitamin D and consequently lead to deficiency are: 1) geographical (latitude above/below 40° during winter time), 2) socio-cultural (clothing, strong sunscreen protection factor, poor nutritional and dietary habits, e.g., poorly planned vegan diet, indoor activities that have replaced outdoor activities, e.g., working in office, gym workout, long working hours, migrants from Africa and Asia in western countries), religious (veiled clothing) and 3) physiological (skin pigmentation, age, obesity, chronic diseases, genetic abnormalities) [16, 17]. Furthermore, many drugs affect how vitamin D is metabolised and can therefore modify an individual's vitamin D requirements. Classes of drugs that have the potential to alter the serum 25(OH)D concentration are discussed elsewhere [18].

Vitamin D insufficiency and deficiency are linked with various negative health outcomes and are now well-documented worldwide [19, 20], including Europe [21, 22]. Oral vitamin D drugs are the treatment of choice in treating both vitamin D insufficiency and deficiency. However, the amount of vitamin D drugs required to treat the deficiency depends largely on the degree of the deficiency and the previously discussed risk factors [21]. The main purpose of this review is to discuss potential dietary sources, fortified food and dietary supplements of vitamin D for human nutrition. Medicinal uses of vitamin D are therefore not covered here but can be found in most textbooks of medicine and any pharmaceutical formulary [21].

As mentioned, dietary intake generally accounts for a very small amount of total vitamin D supply, but it is nevertheless an important source [23]. It is estimated that the daily dietary intake of vitamin D, assessed mainly with the use of a standardised food frequency questionnaire and/or 24 h-recall methodology, in many European populations is well below 10 μg/day [24]. The mean intake of vitamin D for all age groups in Northern Europe varies between 3 and 14 μg/day, in Western Europe between 1.5 and 5 μg/day, in Southern Europe between 1 and 3 μg/day, in Eastern Europe between 2 and 5 μg/day and in the Middle East between 1 and 4 μg/day [22]. Furthermore, low serum 25(OH)D concentration has also been observed in non-Western immigrants in European countries, in comparison with the indigenous paler-skinned people [22].

Since the intake of vitamin D from the diet is inadequate and when endogenous synthesis is insufficient, dietary supplementation is strongly recommended for all age groups, especially during winter time above/below 40° latitude [25, 26]. The European Food Safety Authority (EFSA) has set an adequate intake for vitamin D for infants aged 7–11 months at 10 μg/day (400 IU/day), and for children aged 1–17 years and adults, including pregnant and lactating women, at 15 μg/day (600 IU/day) [27]. Other international institutions also have similar recommendations, which are summarized elsewhere [28, 29].

When vitamin D is supplemented, caution should be exercised because of possible toxicity of excessive oral vitamin D intake, especially by ingestion of extremely high doses of vitamin D for a prolonged period [8]. To avoid overdosing, EFSA has set tolerable upper intake levels for vitamin D intake. For adults (including pregnant and lactating women and adolescents aged 11–17 years) it is set at 100 μg/day (4000 IU/day), for children aged 1–10 years at 50 μg/day (2000 IU/day), for infants aged 6–12 months at 35 μg/day (1.400 IU/day), and for infants aged up to 6 months at 25 μg/day (1000 IU/day) [30, 31]. However, serum concentrations of 25(OH)D above 150 ng/ml or 325 nmol/l may result in vitamin D intoxication and are

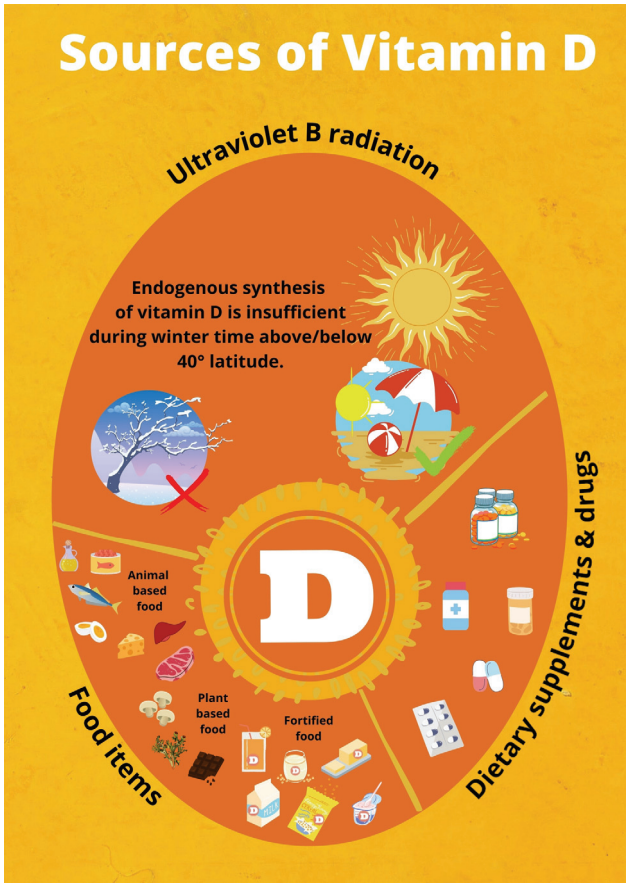

Figure 1. Main sources of vitamin D (made possible with Canva® www.canva.com).

associated with hypercalcemia, hypercalciuria and mineral deposits in soft tissues [32, 33]. Interestingly, there is no risk of vitamin D toxicity from prolonged exposure to UVB radiation because the skin destroys excess vitamin D [34]. Data from the scientific literature about sources of vitamin D are shown in Figure 1.

Dietary sources of vitamin D

Vitamin D_3, vitamin D_2, 25-hydroxycholecalciferol (25(OH)D_3 or calcifediol) and 25-hydroxy ergocalciferol (25(OH)D_2 or ercalcidiol) constitute the vitamin D and its metabolites content in food. As said before, vitamin D_3 and 25(OH)D_3 are mainly found in food of animal origin and vitamin D_2 and 25(OH)D_2 in food of plant origin and yeast. In general, the vitamin D content in food depends on the food's fat content, the fodder the animals have been fed, and the food's exposure to UVB light [35]. Dietary sources of vitamin D generally account for a very small amount of the total vitamin D supply [36]. Very few foods are a rich source of vitamin D or 25(OH)D_3 and 25(OH)D_2 and such foods are usually seldom consumed. The majority of vitamin D intake is therefore achieved with foods that are poorer in vitamin D but are consumed more regularly and in higher quantities [23, 24].

The flesh of some fish (such as wild trout, wild pacific salmon, wild tuna and wild mackerel) and fish liver oils are among the best dietary sources of vitamin D (vitamin D_3) [23]. It is important to know the origin of our food since the vitamin D content depends on it. The vitamin D_3 content is usually higher in wild, rather than farmed animals. Many factors can cause considerable differences in the vitamin D_3 content in animal food. Animal feed is thought to be a primary factor causing the variation seen between species and also among individuals within species. Supplementation of feed with vitamin D_3 (and/or 25(OH)D_3) can increase the vitamin D content in the animals' tissues, just as diet influences the serum 25(OH)D concentration in humans. For the majority of animals, vitamin D_3 content is positively associated with overall fat content, but in fish, the two are not correlated. A significant content of vitamin D_3 has been found in some fish having a low-fat content (e.g., halibut) [38]. Another important factor influencing the vitamin D content in food is UVB exposure. Higher concentrations of vitamin D were detected in foods from animals exposed to more sunlight or UVB light [23]. For example, farmed salmon has only about 25% of the vitamin D_3 content of wild salmon [37]. Similarly, egg yolk vitamin D_3 content depends largely on the content of vitamin D in the hens' feed and on the type of farming. The content of vitamin D_3 in the egg yolk of free-range farmed hens can be 3.5 times higher than that of those battery farmed [38]. Interestingly, Reindeer lichen, mushrooms (wild penny bun, wild golden chanterelle, Maitake), yeast, dark chocolate, cocoa and some other plants (waxy leaf nightshade, tomato plant), are also good sources of vitamin D (vitamin D_2) (Table 1) [39–43]. Mushrooms and yeasts are treated with UVB light to induce the conversion of ergosterol into vitamin D_2. Although the content of vitamin D_2 in UVB-exposed mushrooms may decrease with storage and cooking, if they are consumed before the "best-before" date, the vitamin D_2 content is likely to remain above 10 µg/100 g fresh weight, which is higher than the content in most vitamin D-containing foods [42]. Worldwide mushroom consumption has increased markedly in the past four decades, and mushrooms have the potential to be the only non-animal, unfortified food source of vitamin D that can provide a substantial amount of vitamin D_2 in a single portion [42]. The EFSA and American Food and Drug Administration have therefore approved UVB-treated mushroom powder as a food additive for use as a source of vitamin D_2 in food products [44, 45].

Apart from the D_3 and D_2 forms of vitamin D, 25(OH)D_3 also contributes significantly to dietary vitamin D intake. It is found in many animal-derived products, such as animal

Table 1. Selected dietary sources of vitamin D (μg and IU/100 g)

Food items	μg/100g	IU/100g
Fish oil		
Cod liver oil	250	10000
Fishes (raw)		
Carp	25	1000
Eel	20	800
Salmon		
Farmed [46]	6	240
Wild caught [46]	25	1000
Mackerel	16	640
Trout	15	600
Sole	15	600
White fish	12	480
Caviar	12	480
Sardines	11	440
Swordfish	10	400
Oysters	8	320
Tuna	5	200
Meat and meat products		
Beef liver	1.7	68
Chicken liver	1.3	52
Veal steak	0.4	16
Eggs		
Yolk	5.6	224
Hens' eggs, fresh or boiled	2.9	116
Milk and milk products		
Milk powder	20	800
Cheese (45.0% milk fat)	1.3	52
Butter	1.2	48
Yoghurt (3.5% milk fat)	<0.1	<4
Milk (3.5% milk fat)	<0.1	<4
Human milk	<0.1	<4
Plant-based sources		
Reindeer lichen [39]	87	3480
Mushrooms		
Wild penny bun [42]	58.7	2348
Maitake	30	1200
Wild golden chanterelle [42]	21.1	844
Margarine (fortified)	7.5	300
Dark chocolate (min. 60% cocoa) [41]	4.0	160
Cocoa powder (20% fat) [41]	1.6	64
Soy drink (fortified)	0.8	32
Waxy leaf nightshade [40]	0.2	8
Tomato plant [40]	<0.1	<4
Rice drink	<0.1	<4

IU: International Units. Sources: Open Platform for Clinical Nutrition (OPEN, http://opkp.si/en).

fats (0.7 μg/100 g), animal muscle (0.3–1.0 μg/100 g), organ meats (kidney, liver) (0.5 μg/100 g) and eggs (0.4 μg/100 g) but is rarely included in vitamin D food composition data [35, 37].

These data suggest that the food composition database (FCDB) of vitamin D content, especially for foods that have been traditionally recommended as good sources of naturally occurring vitamin D, is out-of-date and needs to be re-evaluated and updated [46, 47]. A compilation of the vitamin D content of various food groups based on FCDB by the web-based application Open Platform for Clinical Nutrition (OPEN, http://opkp.si/en) is provided in Table 1. OPEN is aimed at meal planning, but it is also designed to calculate recipes and nutrient intakes for individuals or groups. It can apply any FCDB complying with EuroFIR procedures, which facilitates access to and exchange of comparable, high quality food composition data for industry, regulators and researchers across Europe [48]. Since each country has nationally specific cuisines and its inhabitants consume specific dishes and foods, some of which may be fortified with vitamin D, it is best to use national FCDB. Examples of publicly available FCDB that can also be used for consideration of vitamin D content are FoodData Central (https://fdc.nal.usda.gov/), Canadian Nutrient File (https://food-nutrition.canada.ca/cnf-fce/) and various EuroFIR databases (https://www.eurofir.org/food-information/food-composition-databases/). However, FCDB is often incomplete or lacking compositional data on the vitamin D content in certain foods/dishes, which may result in an apparently lower dietary intake of vitamin D [49]. Nevertheless, computer or web-based applications for dietary intake assessment of vitamin D, as well as other macro- and micronutrients of a patient or the general population, are useful tools [48].

Food fortified with vitamin D

Fortification is the process of supplementing food with required nutrients for their health benefits and in order to prevent diseases, as defined by the Codex General Principles [50]. Vitamin D_2 and vitamin D_3 can be added to foods. Fortification with 25(OH)D_3 would appear to have advantages over vitamin D_2 and D_3, since it is known to be more rapidly effective for correcting deficiency [51]. Being costly, it is unlikely to replace vitamin D_3/D_2 for use in food fortification [22]. Animal based foods, such as milk and dairy products, are typically fortified with vitamin D_3, and many plant based foods, such as plant based drinks, are commonly fortified with vitamin D_2 [23]. In general, food can be enriched with vitamin D by simply adding vitamin D to it (i.e., traditional vitamin D food fortification) or by practicing so-called "bio-addition". Bio-addition of vitamin D, which is also called "biofortification," refers to various methods of increasing the vitamin D content in food without direct exogenous addition of this compound [42, 52].

The addition of vitamin D in conjunction with calcium is common in a number of foods, including milk (usually low-fat milk), yoghurt, fat spreads (such as margarine), orange juice, breakfast grains, plant based drinks (such as beverages made from soy, almond, or oats), certain baby foods, milk formulas, enteral nutrition and others [50]. Vitamin D in conjunction with calcium promotes calcium absorption and is therefore essential for optimal musculoskeletal health, mineralization of osteoid tissue formation and the maintenance of muscle function [53, 54]. On the other hand, there is some concern that calcium supplements (but not food sources) could be harmful [55].

Considering the lack of natural vitamin D rich foods, some countries, particularly high latitude countries, have developed national programmes of fortifying certain foods with vitamin D to prevent deficiency. Fortified foods provide most of the dietary vitamin D source in the United States, Canada [56] and some Nordic countries [22, 57].

Milk products are systematically, either mandatorily or voluntarily, fortified with vitamin D only in Finland, Norway, Sweden, Canada and the United States [57, 58]. In other countries, such as the United Kingdom, Ireland, Spain and Australia, several vitamin D fortified dairy products are available but they do not have formal public health fortification or supplementation policies [58]. In countries in which vitamin D fortification policies are strongly applied, the contribution of milk to total vitamin D intake is higher than in countries without fortification policies [58]. The consumption of vitamin D fortified milk has been positively associated with the serum 25(OH)D concentration in humans [58], without a specific effect of local vitamin D fortification policies. Even with relatively low milk consumption, a correlation between milk consumption and serum 25(OH)D concentration was determined [59].

Vitamin D food fortification has been shown to be a valid way of increasing vitamin D dietary intake. Furthermore, vitamin D fortified milk affects both vitamin D intake and serum 25(OH)D concentration in the elderly, in adults and in children [58, 60, 61].

On the other hand, fortification of dairy products may not be the only strategy. Considering the different food habits among different populations, wider vitamin D fortification of several products rather than a limited range of foods being fortified has been suggested [62]. In many countries in which a fortification programme is not currently applied, the hypothesis of systematic vitamin D food fortification has been considered, and simulation studies have recently been performed [63]. A well-designed, well-managed monitoring and evaluation system is essential for ensuring the success and sustainability of any food fortification programme, since only regular monitoring can ensure the adequacy of vitamin D fortification [64].

Results show that food fortification may be more efficient at increasing or maintaining serum 25(OH)D concentrations rather than depending on self-supplementation [61]. In addition, because the minority of the population uses vitamin D supplements regularly and vitamin D intake from some but not all fish may be inconsistent or non-existent, vitamin D food-fortification efforts are warranted [65, 66].

Improving vitamin D intake through food fortification will not only lead to improved health outcomes, but will benefit the economy directly, by reducing healthcare costs associated with vitamin D related diseases and indirectly through improved quality of life and longer independent living time [60, 67]. The WHO and the Food and Agriculture Organization of the United Nations (FAO) have therefore indicated that food fortification has potentially the widest and most sustainable impact and is generally considered to be more cost-effective than other intervention approaches [64].

However, because multiple studies in populations at locations above/below 40° latitude have shown insufficient or deficient baseline serum 25(OH)D concentrations, vitamin D food fortification may be important for many countries regardless of latitude [61, 68]. To help elucidate this, vitamin D food fortification and supplementation trials have continued at different latitudes around the world [61].

Dietary supplements of vitamin D

In recent years, dietary supplements containing vitamin D have become more common and are more frequently consumed. There are even increasing numbers of vitamin D formulations on the global market, due to reported vitamin D insufficiency and deficiency [33]. The form of vitamin D used in supplement products can be vitamin D_3, vitamin D_2 or 25(OH)D_3 and can be administered orally in solid form, such as tablets or capsules or as liquid preparations such as oral drops or spray. There is a debate about the efficiency of different supplementation formulations containing vitamin D (starch-adsorbed vitamin D, oil-based oral spray and water-based oral spray). However, a recently published paper in this field showed no difference in efficiency among formulations of vitamin D [69]. Furthermore, there is no difference in efficacy and safety of daily, weekly and monthly administrations of the daily equivalent of 1000 IU of vitamin D [70].

Briefly, vitamin D_3 is mainly pharmaceutically produced by irradiation of 7-dehydrocholesterol from lanolin and the chemical conversion of cholesterol, whereas vitamin D_2 is manufactured using UVB irradiation of ergosterol in mushroom and yeast [53]. All forms (vitamin D_3, vitamin D_2 or

25(OH)D_3) raise serum 25(OH)D concentrations but most evidence indicates that vitamin D_3 increases it to a greater extent and maintains these higher concentrations longer than vitamin D_2 [71]. Vitamin D_2 as a form of exogenous vitamin D supplementation is used extensively in the United States, although its therapeutic use in Europe is virtually non-existent [72]. Furthermore, studies suggested that 25(OH)D_3 supplementation can raise serum 25(OH)D concentrations even more efficiently, since it acts more rapidly [51]. However, vitamin D_3 and 25(OH)D_3 cannot be therapeutically compared µg to µg, nor can an accurate calculation be made of the biological potency in IUs contained in 1 µg of 25(OH)D_3. If patients needing vitamin D supplementation are to be given an exact and controlled amount of IU, in compliance with the recommendations of the most relevant clinical guidelines for the management of vitamin D deficiency, vitamin D_3 therefore still appears to be the most reasonable option. However, 25(OH)D_3 is being increasingly used clinically, although its usage is limited to specific patients, since it is quite expensive [72].

It would appear from informal observations of the marketplace that manufacturers are increasing the vitamin D content of their products. Traditionally, many marketed dietary supplements have contained 400 IU per daily dose, but doses in supplements have been increasing. Vitamin D can now be found in multi-vitamin/multi-mineral formulations, as well as in a single supplement in a range of dosage levels, including 1000 to 5000 IU of vitamin D_3 per dose or even up to 50000 IU of vitamin D_2 per dose [73].

Dietary supplements are available in a variety of over-the-counter preparations. They do not require strict regulation and show a large variation in the percentage label claims of vitamin D [74, 75]. Drugs, prescription formulations, which are more strictly regulated, give content values within standard acceptance ranges [74]. There is therefore a great need for tighter regulations when it comes to dietary supplements, which should be similar to those for drugs, to ensure that the actual content of vitamin D in supplements complies with their label claims, to prevent potential toxicity [74].

However, given the insufficient endogenous synthesis of vitamin D, an adequate intake is hard to achieve through diet alone, even when fortified, so dietary supplements with vitamin D are nevertheless still strongly recommended [75].

Conclusion

Vitamin D (D represents D_3 and/or D_2) is known to have a pleiotropic function in human health. It is produced endogenously during exposure to UVB but is also found in some food items, such as some but not all fish, eggs, fortified food products and dietary supplements. When the intake of vitamin D from the diet is inadequate and when endogenous synthesis is insufficient, dietary supplementation is strongly recommended for all age groups, especially during wintertime above/below 40° latitude. However, available data on the serum 25(OH)D concentration in populations worldwide indicates vitamin D insufficiencies, as well as deficiencies. Approaches to improve the serum 25(OH)D concentration in the population include increasing the intake of natural vitamin D containing food, food fortification, vitamin D supplements and increasing solar UVB exposure. There is therefore a need for strategies implemented through national food legislation to decrease overall deficiencies of vitamin D in the population. Since increasing solar UVB exposure can be harmful, natural dietary sources of vitamin D are usually insufficient and since supplement intake positively correlates with a healthier lifestyle and higher socio-economic status, food fortification seems to be the best potential strategy for addressing the vitamin D deficiency identified by the WHO/FAO.

References

1. Nair R, Maseeh A. Vitamin D: The “sunshine” vitamin. J Pharmacol Pharmacother. 2012;3(2):118–26. https://doi.org/10.4103/0976-500X.95506
2. Kučan R, Soltirovska Šalamon A, Andronikov D, Benedik E. Dietary sources of vitamin D, vitamin D supplementation, and its bio-viability. Cent Eur J Paediatr. 2018;14(2):115–22.
3. Mendes MM, Hart KH, Botelho PB, Lanham-New SA. Vitamin D status in the tropics: Is sunlight exposure the main determinant? Nutr Bull. 2018;43(4):428–34. https://doi.org/10.1111/nbu.12349
4. Maldonado G, Paredes C, Guerrero R, Ríos C. Determination of vitamin D status in a population of ecuadorian subjects. Sci World J. 2017.
5. Kagotho E, Omuse G, Okinda N, Ojwang P. Vitamin D status in healthy black African adults at a tertiary hospital in Nairobi, Kenya: A cross sectional study. BMC Endocr Disord. 2018;18(1):1–7. https://doi.org/10.1186/s12902-018-0296-5
6. Lee YM, Kim SA, Lee DH. Can current recommendations on sun exposure sufficiently increase serum vitamin D level? One-month randomized clinical trial. J Korean Med Sci. 2020;35(8):e50. https://doi.org/10.3346/jkms.2020.35.e50
7. World Health Organization. World Health Organization Sun Protection Available from: http://www.who.int/uv/sun_protection/en/
8. Maurya VK, Aggarwal M. Factors influencing the absorption of vitamin D in GIT: an overview. J Food Sci Technol. 2017;54(12):3753–65.
9. Silva MC, Furlanetto TW. Intestinal absorption of vitamin D: a systematic review. Nutr Rev. 2018;76(1):60–76. https://doi.org/10.1093/nutrit/nux034
10. Reboul E. Intestinal absorption of vitamin D: from the meal to the enterocyte. Food Funct. 2015;6(2):356–62. https://doi.org/10.1039/c4fo00579a
11. Ramasamy I, Vitamin D. Metabolism and guidelines for vitamin D supplementation. Clin Biochem Rev. 2020;41(3):103–26.

12. Chun RF, Shieh A, Gottlieb C, Yacoubian V, Wang J, Hewison M, et al. Vitamin D binding protein and the biological activity of vitamin D. Front Endocrinol (Lausanne). 2019;10:718.
13. Sirajudeen S, Shah I, A Al Menhali. A narrative role of vitamin D and its receptor: with current evidence on the gastric tissues. Int J Mol Sci. 2019;20(15):3832. https://doi.org/10.3390/ijms20153832
14. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30. https://doi.org/10.1210/jc.2011-0385
15. Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. Am Heart J. 2020;12(2097):1–28.
16. World Health Organization. WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Vitamin D supplements during pregnancy. 2020. Available from: https://www.who.int/publications/i/item/9789240008120
17. Darling AL. Vitamin D deficiency in western dwelling South Asian populations: an unrecognised epidemic. Proceedings of the Nutrition Society. 2020;79(3):259–71.
18. Wakeman M, A literature review of the potential impact of medication on vitamin D status. Risk Manag Healthc Policy. 2021;14:3357–81. Available from: https://www.dovepress.com/a-literature-review-of-the-potential-impact-of-medication-on-vitamin-d-peer-reviewed-fulltext-article-RMHP
19. Hribar M, Hristov H, Gregorič M, Blaznik U, Zaletel K, Oblak A, et al. Nutrihealth study: seasonal variation in vitamin D status among the slovenian adult and elderly population. Nutrients. 2020;12(6):1838. Available from: https://www.mdpi.com/2072-6643/12/6/1838
20. van Schoor N, Lips P. Global overview of vitamin D status. Endocrinol Metab Clin North Am. 2017;46(4):845–70.
21. Soltirovska Šalamon AS, Benedik E, Bratanič B, Velkavrh M, Rogelj I, Fidler Mis N, et al. Vitamin D status and its determinants in healthy slovenian pregnant women. Ann Nutr Metab. 2015;67(2):96–103.
22. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: A position statement of the European Calcified Tissue Society. Eur J Endocrinol. 2019;180(4):P23–54. https://doi.org/10.1530/EJE-18-0736
23. Roseland JM, Phillips KM, Patterson KY, Pehrsson PR, Taylor CL. Vitamin D in foods: an evolution of knowledge. In Vitamin D, 4th ed. Elsevier Inc; 2017. p. 41–77.
24. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull. 2014;39(4):322–50.
25. Edis Z, Bloukh SH. Vitamin D deficiency – main factors affecting the serum 25-hydroxyvitamin D ([25(Oh)D]) status and treatment options. Int J Res. 2016;3(01):197–211.
26. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74:1498–513. https://doi.org/10.1038/s41430-020-0558-y
27. Bresson JL, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, et al. Dietary reference values for vitamin D. EFSA J. 2016;14(10):4547. Available from: www.efsa.europa.eu/efsajournal
28. Bender DV, Kelečić DL, Barišić A, Karas I, Domislović V, Oroz V, et al. Review of recommendations for supplementation of vitamin D in children and adolescents. Cent Eur J Paediatr. 2018;14(2):123–9. Available from: http://cejpaediatrics.com/index.php/cejp/article/view/316
29. Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: A narrative review of current evidence. Endocr Connect. 2019;8(2):R27–43. https://doi.org/10.1530/EC-18-0432
30. Bresson J, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst K, et al. Scientific opinion on dietary reference values for vitamin D EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). EFSA J. 2016;179:1–179. Available from: www.efsa.europa.eu/efsajournal
31. Hart A, Maxim L, Siegrist M, Von Goetz N, Cruz C, Merten C, et al. Draft document for public consultation on draft guidance on communication of uncertainty in scientific assessments. European Food Safety Authority. 2018;25:1–70.
32. Chauhan K, Shahrokhi M, Huecker MR. Vitamin D. In: StatPearls. StatPearls Publishing. 2021.
33. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited? Aging Clin Exp Res. 2021;33(1):19–24. https://doi.org/10.1007/s40520-020-01678-x
34. Kulie T, Groff A, Redmer J, Hounshell J, Schrager S. Vitamin D: an evidence-based review. J Am Board Fam Med. 2009;22(6):698–706. https://doi.org/10.3122/jabfm.2009.06.090037
35. Jakobsen J, Christensen T. Natural vitamin D in food: to what degree does 25-hydroxyvitamin D contribute to the vitamin D activity in food? JBMR Plus. 2021;5(1):e10453. https://doi.org/10.1002/jbm4.10453
36. Dixon KM, Mason RS. Vitamin D. Int J Biochem Cell Biol. 2009;41(5):982–5.
37. Jakobsen J, Smith C, Bysted A, Cashman KD. Vitamin D in wild and farmed atlantic salmon (salmo salar) – What do we know? Nutrients. 2019;11(5):982. https://doi.org/10.3390/nu11050982
38. Kühn J, Schutkowski A, Kluge H, Hirche F, Stangl GI. Free-range farming: A natural alternative to produce vitamin D-enriched eggs. Nutrition. 2014;30(4):481–4.
39. Göring H. Vitamin D in nature: a product of synthesis and/or degradation of cell membrane components. Biochem. 2018;83(11):1350–7.
40. Black LJ, Lucas RM, Sherriff JL, Björn LO, Bornman JF. In pursuit of vitamin D in plants. Nutrients. 2017;9(2):1–9.
41. Kühn J, Schröter A, Hartmann BM, Stangl GI. Cocoa and chocolate are sources of vitamin D_2. Food Chem. 2018;269:318–20.
42. Cardwell G, Bornman JF, James AP, Black LJ. A review of mushrooms as a potential source of dietary vitamin D. Nutrients. 2018;10(10):1–11.
43. Wu JY, Siu KC, Geng P. Bioactive ingredients and medicinal values of grifola frondosa (Maitake). Foods. 2021;10(1):95.
44. US Food and Drug Administration. Food additives permitted for direct addition to food for human consumption; vitamin D_2 mushroom powder. Fed Regist. 2020;85:41916–20. Available from: https://www.federalregister.gov/documents/2020/07/13/2020-13822/food-additives-permitted-for-direct-addition-to-food-for-human-consumption-vitamin-d2
45. Turck D, Castenmiller J, de Henauw S, Hirsch-Ernst K, Kearney J, Maciuk A, et al. Safety of vitamin D2 mushroom powder as a novel food pursuant to Regulation (EU) 2015/2283. EFSA J. 2020;18(1):5948. https://doi.org/10.2903/j.efsa.2020.5948
46. Lu Z, Chen TC, Zhang A, Persons KS, Kohn N, Berkowitz R, et al. An evaluation of the vitamin D3 content in fish: is the vitamin D content adequate to satisfy the dietary requirement for vitamin D? J Steroid Biochem Mol Biol. 2007;103(3–5):642–4.
47. De Roos B, Sneddon AA, Sprague M, Horgan GW, Brouwer IA. The potential impact of compositional changes in farmed fish on its health-giving properties: Is it time to reconsider current dietary recommendations? Public Health Nutr. 2017;20(11):2042–2049. https://doi.org/10.1017/S1368980017000696

48. Koroušić Seljak B, Stibilj V, Pograjc L, Mis NF, Benedik E. Food composition databases for effective quality nutritional care. Food Chem. 2013;140(3):553–61. https://doi.org/10.1016/j.foodchem.2013.02.061
49. Benedik E, Seljak BK, Hribar M, Rogelj I, Bratanič B, Orel R, et al. Comparison of a web-based dietary assessment tool with software for the evaluation of dietary records. Slov J Public Heal. 2015;54(2):91–7.
50. El Khatib S, Abou Shahine M. Nutritional considerations of vitamin D deficiency and strategies of food fortification. In: Vitamin D deficiency. IntechOpen; 2020.
51. Guo J, Lovegrove JA, Givens DI. 25(OH)D3-enriched or fortified foods are more efficient at tackling inadequate vitamin D status than vitamin D3. Proc Nutr Soc. 2018;77(3):282–91. https://doi.org/10.1017/S0029665117004062
52. Cashman KD. Vitamin D: dietary requirements and food fortification as a means of helping achieve adequate vitamin D status. J Steroid Biochem Mol Biol. 2015;148:19–26. https://doi.org/10.1016/j.jsbmb.2015.01.023
53. Holick MF. Medical progress: Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81. https://doi.org/10.1056/NEJMra070553
54. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, Clarke R. Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. JAMA Netw Open. 2019;2(12):e1917789. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6991219/
55. Heravi AS, Michos ED. Vitamin D and calcium supplements: helpful, harmful, or neutral for cardiovascular risk? Methodist Debakey Cardiovasc J. 2019;15(3):207–213. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6822648/
56. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr. 2004;80(6 Suppl):1710S–6S.
57. Itkonen ST, Andersen R, Björk AK, Brugård Konde Å, Eneroth H, Erkkola M, et al. Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. Scand J Public Health. 2020. https://doi.org/10.1177/1403494819896878
58. Itkonen ST, Erkkola M, Lamberg-Allardt CJE. Vitamin D fortification of fluid milk products and their contribution to vitamin D intake and vitamin D status in observational studies – a review. Nutrients. 2018;10(8):1054. https://doi.org/10.3390/nu10081054
59. Vatanparast H, Calvo MS, Green TJ, Whiting SJ. Despite mandatory fortification of staple foods, vitamin D intakes of Canadian children and adults are inadequate. J Steroid Biochem Mol Biol. 2010;121(1–2):301–3. https://doi.org/10.1016/j.jsbmb.2010.03.079
60. Al Khalifah R, Al Khalifah R, Alsheikh R, Alnasser Y, Alnasser Y, Alnasser Y, et al. The impact of vitamin D food fortification and health outcomes in children: A systematic review and meta-regression. Syst Rev. 2020;9:144. https://doi.org/10.1186/s13643-020-01360-3
61. Brett NR, Gharibeh N, Weiler HA. Effect of vitamin D supplementation, food fortification, or bolus injection on vitamin D status in children aged 2–18 years: A meta-analysis. Adv Nutr. 2018;9(4):454–64. https://doi.org/10.1093/advances/nmy012
62. Cashman KD, Kiely M. Tackling inadequate vitamin D intakes within the population: fortification of dairy products with vitamin D may not be enough. Endocrine. 2016;51(1):38–46.
63. Pilz S, März W, Cashman KD, Kiely ME, Whiting SJ, Holick MF, et al. Rationale and plan for vitamin D food fortification: A review and guidance paper. Front Endocrinol. 2018;9:373.
64. Allen L, de Benoist B, Dary O, Hurrell R, editors. (2006) Guidelines on food fortification with micronutrients. World Health Organization, Food and Agricultural Organization of the United Nations; 2006. Available from: https://www.who.int/publications/i/item/9241594012
65. Davies PS, Bates CJ, Cole TJ, Prentice A, Clarke PC. Vitamin D: seasonal and regional differences in preschool children in Great Britain. Eur J Clin Nutr. 1999;53(3):195–8. https://doi.org/10.1038/sj.ejcn.1600697
66. Moore C, Murphy MM, Keast DR, Holick MF. Vitamin D intake in the United States. J Am Diet Assoc. 2004;104(6):980–3.
67. Aguiar M, Andronis L, Pallan M, Högler W, Frew E. The economic case for prevention of population vitamin D deficiency: a modelling study using data from England and Wales. Eur J Clin Nutr. 2020;74(5):825–33. https://doi.org/10.1038/s41430-019-0486-x
68. Buttriss JL, Lanham-New SA. Is a vitamin D fortification strategy needed? Nutr Bull. 2020;45(2):115–22. https://doi.org/10.1111/nbu.12430
69. Žmitek K, Hribar M, Hristov H, Pravst I. Efficiency of vitamin D supplementation in healthy adults is associated with body mass index and baseline serum 25-hydroxyvitamin D level. Nutrients. 2020;12(5):1268. https://doi.org/10.3390/nu12051268
70. Takács I, Tóth BE, Szekeres L, Szabó B, Bakos B, Lakatos P. Randomized clinical trial to comparing efficacy of daily, weekly and monthly administration of vitamin D3. Endocrine. 2017;55(1):60–5. https://doi.org/10.1007/s12020-016-1137-9
71. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr. 2012;95(6):1357–64. https://doi.org/10.3945/ajcn.111.031070
72. Henríquez MS, de Romero MJGT. Cholecalciferol or calcifediol in the management of vitamin D deficiency. Nutrients. 2020;12(6):1617. https://doi.org/10.3390/nu12061617
73. Institute of Medicine. DRI Dietary reference intakes: Calcium, Vitamin D. Washington, DC: The National Academies Press; 2011.
74. Garg S, Sabri D, Kanji J, Rakkar PS, Lee Y, Svirskis D. Evaluation of vitamin D medicines and dietary supplements. J Nutr Health Aging. 2013;17(2):2–5.
75. Žmitek K, Krušič S, Pravst I. An approach to investigate content-related quality of nutraceuticals used by slovenian consumers: A case study with folate and vitamin d supplements. Foods. 2021;10(4):845.
76. Mulligan GB, Licata A. Taking vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. J Bone Miner Res. 2010;25(4):928–30. https://doi.org/10.1002/jbmr.67

History
Received April 29, 2021
Accepted September 21, 2021
Published online October 18, 2021

Acknowledgement
I would like to thank Ms. Neža Lipovec for her help with the preparation of the manuscript.

Conflict of interest
The author declares that there are no conflicts of interest.

Funding
The work was financially supported by the Slovenian Research Agency (P3-0395: Nutrition and Public Health).

Assistant Professor Evgen Benedik, PhD
Division of Paediatrics
University Medical Centre Ljubljana
Bohoričeva 20
1000 Ljubljana, Slovenia
evgen.benedik@kclj.si