Consensus on the Prevention of Vitamin D Deficiency

Subjects: Nutrition & Dietetics

Contributor: INGVARS RASA , Pawel Pludowski , , Mihail Boyanov , Camelia Diaconu , Tatiana Mokhort , Nadiia Zherdova , Stefan Pilz

Vitamin D is crucial for musculoskeletal health, as it plays an important role in the regulation of bone and mineral metabolism, and it can prevent and cure nutritional rickets and osteomalacia. In addition, vitamin D receptor (VDR) expression in almost all human cells suggests, or even documents, a more widespread role of vitamin D for overall health, a notion that is supported by several experimental and epidemiological studies. While there still exist knowledge gaps and controversy regarding potential extra-skeletal effects of vitamin D, there is a wide consensus that the high worldwide prevalence of vitamin D deficiency is of concern and requires actions to improve this situation.

vitamin D recommendations guidelines osteoporosis

1. Introduction

Vitamin D is crucial for musculoskeletal health, as it plays an important role in the regulation of bone and mineral metabolism, and it can prevent and cure nutritional rickets and osteomalacia [1][2]. In addition, vitamin D receptor (VDR) expression in almost all human cells suggests, or even documents, a more widespread role of vitamin D for overall health, a notion that is supported by several experimental and epidemiological studies [1][3][4][5][6][7][8]. While there still exist knowledge gaps and controversy regarding potential extra-skeletal effects of vitamin D, there is a wide consensus that the high worldwide prevalence of vitamin D deficiency is of concern and requires actions to improve this situation [2][7][9]. Addressing this issue has to consider the unique metabolism of vitamin D, which is mainly synthesized in the skin stimulated by ultraviolet-B (UV-B) exposure, whereas nutrition is usually only a minor source of vitamin D [10]. Vitamin D from all different sources is metabolized to 25-hydroxyvitamin D (25(OH)D, calcifediol) in the liver, which is the main circulating vitamin D metabolite that is determined to assess vitamin D status. Further hydroxylation of 25(OH)D in the kidneys or certain extra-renal tissues results in the formation of 1,25-dihydroxyvitamin D (1,25(OH)2D, also called calcitriol), which exerts endocrine, autocrine, and paracrine effects as a steroid hormone [10]. Heterogeneous recommendations, regarding several issues in the practical management of vitamin D deficiency, represent a challenge for clinicians and health authorities on how to deal with this public health problem [11][12][13][14][15][16][17][18][19][20][21][22]. In this context, systematic evaluations of current vitamin D guidelines did, not only, observe a great heterogeneity of the recommendations, but it also reported a low quality score regarding the methodological processes for the majority of these vitamin D guidelines [17][18]. **Table 1**

and **Table 2** provide an overview of selected guideline recommendations, with a focus on Central and Eastern European countries, for prevention and treatment of vitamin D deficiency, respectively.

Table 1. Selected guideline recommendations for prevention of vitamin D deficiency in adults with a focus on Central and Eastern European countries, published since 2010.

Authority and/or Country or Region (Year)	Target Population	Age (Years)	Oral Vitamin D (IU)	Reference
Endocrine Society (2011) USA	General population	19–70	600–2000/day	Holick et al. [14]
		>70	800–2000/day	
	Pregnant and lactating women		600–2000/day	
	Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications		2–3 times more	
DACH (2012) Germany/Austria/Switzerland	General population	>18	800/day	DGE [23]
EVIDAS (2013) Central Europe	General population	>18	800–2000/day	Płudowski et al. [21]
	Obese individuals and elderly		1600–4000/day	
	Prevention of pregnancy and fetal development complications	>16	1500–2000/day	
	Night workers and dark skin pigmentation		1000–2000/day	
EFSA (2016) Europe	General population	>18	600/day	EFSA [24]
Russia (2016)	General population	>18	800–1000/day	Pigarova et al. [25]
	Pregnant women		800–2000/day	
Poland (2018)	General population	19–75	800–2000/day	Rusińska, Płudowski et al. [26]

Authority and/or Country or Region (Year)	Target Population	Age (Years)	Oral Vitamin D (IU)	Reference
	Obese individuals	19–75	1600–4000/day	
	General population	>75	2000–4000/day	
	Obese individuals	>75	4000–8000/day	
	Pregnant and lactating women		2000/day	
Belarus (2013)	General population	>18	800–2000/day	Rudenko [27]
Hungary (2012)	General population	>18	1500–2000/day	Takács et al. [22]
	Pregnant and lactating women		1500–2000/day	
Bulgaria (2019)	General population	>19	600–2000/day	Borisova et al. [28]
	Pregnant and lactating women		600–2000/day	
	Patients on anticonvulsants, glucocorticoids, antifungals		2–3 times more	
Slovakia (2013)	Postmenopausal osteoporosis	>50	800–	Payer et al.

focus on

Authority and/or Country or Region (Year)	Target Population	Oral Vitamin D for Treatment (IU)	Treatment Duration	25(OH)D Target Concentration nmol/L (ng/mL)	Oral Vitamin D for Maintenance (IU)	Reference
Endocrine Society (2011) USA	General population	50,000/week or 6000/day	8 weeks	75 (30)	1500–2000/day	Holick et al. [14]
	Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications	2–3 times more; at least 6000–10,000/day			3000–6000/day	
EVIDAS (2013) Central Europe	General population	50,000/week or 7000–10,000/day	4–12 weeks	75–125 (30–50)	a maintenance dose may be instituted	Płudowski et al. [21]

Authority and/or Country or Region (Year)	Target Population	Oral Vitamin D for Treatment (IU)	Treatment Duration	25(OH)D Target Concentration nmol/L (ng/mL)	Oral Vitamin D for Maintenance (IU)	Reference
Italy (2018)	General population	50,000/week or 5000/day	8 weeks	>75 (>30)	50,000 IU twice per month or 1500–2000 IU/day	Cesareo et al. [30]
Russia (2016)	General population	25(OH)D < 50 nmol/L (<20 ng/mL):		>75 (>30)	1000–2000/day or 6000–14,000/week	Pigarova et al. [25]
		50,000/week or	8 weeks			
		200,000/month or	2 months			
		150,000/month or	3 months			
		6000–8000/day	8 weeks			
		25(OH)D < 75 nmol/L (30 ng/mL):				
		50,000/week or	4 weeks			
		200,000 or	single dose			
		150,000 or	single dose			
		6000–8000/day	4 weeks			
Poland (2018)	General population	6000/day	12 weeks or until a 25(OH)D concentration of 75 nmol/L (30 ng/mL) is reached	>75–125 (>30–50)	maintenance dose i.e., a prophylactic dose recommended for the general population (see **Table 1**)	Rusińska, Płudowski et al. [26]

Authority and/or Country or Region (Year)	Target Population	Oral Vitamin D for Treatment (IU)	Treatment Duration	25(OH)D Target Concentration nmol/L (ng/mL)	Oral Vitamin D for Maintenance (IU)	Reference
Belarus (2013)	General population	25(OH)D < 25 nmol/L (<10 ng/mL): 2000 to 10,000/day	4–12 weeks	75–200 (30–80)	800–2000 IU/day	Rudenko [27]
		25(OH)D 25–50 nmol/L (10–20 ng/mL): 800 to 4000/day	1 year			
Hungary (2012)	General population	50,000/week or	4–8 weeks	75 (30)	1500–2000/day	Takács et al. [22] [31]
		30,000/week or	6–12 weeks			
		2000/day	12 weeks			
Bulgaria (2019)	General population [9][32][33][34][35]	To maintain bone health: 1000–2000/day	-	[9] 50 (20)	maintenance dose i.e., a prophylactic dose [32] recommended for the general population (see **Table 1**)	Borisova et al. [28]
		For extra–skeletal effects: 2000–4000/day	-	75–110 (30–44)		

ata from
ol/L) are
ween the
25(OH)D
ions are,
itamin D
ve to be
forts and

3. Screening of Vitamin D Deficiency in Adults

No published study evaluated the effects of a screening program for vitamin D deficiency in the general population, so the evidence is insufficient to balance the benefits and harms of such a screening [36][37]. Accordingly, it can be stressed that it is currently not justified to recommend a general screening for vitamin D deficiency by measuring 25(OH)D concentrations in the whole general population. Nevertheless, considering that certain groups of individuals or patients are particularly prone to vitamin D deficiency and/or may particularly benefit from vitamin D treatment, it can be suggested, in line with the Endocrine Society, that 25(OH)D measurements should be considered in these groups [14].

Total serum 25(OH)D concentration, i.e., the sum of 25(OH)D_3 and 25(OH)D_2, is the accepted marker for the assessment of vitamin D status, as it best reflects vitamin D supply by all different sources, i.e., endogenous vitamin D synthesis in the skin, diet, supplements, and mobilization from tissue stores. Previous reports on a relatively high inter-assay and inter-laboratory variability of 25(OH)D measurements underscore the need for assay

standardization and laboratory quality assurance [38][39]. In patients with vitamin D deficiency and certain related health issues, e.g., bone diseases, it should be considered to measure additional laboratory parameters, including serum calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), creatinine (to calculate the estimated glomerular filtration rate), and magnesium, as these laboratory markers may be useful to guide further diagnostics and treatment of these patients. Measurements of, e.g., serum calcium and creatinine are, however, also advised in patients with 25(OH)D concentrations above 100 ng/mL (250 nmol/L), as vitamin D oversupply/toxicity may lead to hypercalciuria, followed by hypercalcemia, potential acute kidney disease, and vascular calcification. Hypercalcemia does, however, usually not occur at 25(OH)D concentrations below 150 ng/mL (375 nmol/L) [40]. There are hardly any contraindications to correct vitamin D deficiency by vitamin D supplementation (e.g., kidney stones are *per se* no contraindication) except of rare conditions with an increased sensitivity to vitamin D treatment, such as inherited 24-hydroxylase-deficiency [41]. This is a rare genetic disorder in which catabolism of vitamin D metabolites is impaired, leading to hypercalcemia, low PTH concentrations, and relatively high serum 25(OH)D concentrations along with an increased risk of nephrolithiasis [41]. If such a disease is suspected, the measurement of 24,25-dihydroxyvitamin D, in a specialized laboratory, aids in the diagnosis as a high ratio of 25(OH)D to 24,25-dihydroxyvitamin D suggests this disease that is further confirmed by genetic analyses [41].

Classification of vitamin D status and its terminology, according to 25(OH)D concentration, remains a controversial issue in the scientific literature [7][16][21]. Being aware that it is an individual continuum from vitamin D deficiency to a sufficient and optimal vitamin D status, as well as to vitamin D toxicity, it can be suggested that a classification system. It should be kept in mind that such a general classification of vitamin D status cannot take into account variations in the individual sensitivity to vitamin D effects that may be due to genetic polymorphisms, epigenetic or nutritional factors (e.g., magnesium status), as well as co-morbidities or medications [42][43][44][45][46].

4. Prevention of Vitamin D Deficiency in Adults

Most nutritional vitamin D guidelines conclude that vitamin D requirements are met for the vast majority (i.e., 97.5%) of the population when achieving a target 25(OH)D concentration of at least 20 ng/mL (50 nmol/L) [11][12]. Recommended dietary reference intakes for vitamin D usually range from 600 to 800 international units (IU) (40 IU are equal to 1 µg) per day and should ensure a sufficient vitamin D status under conditions of minimal-to-no sunlight exposure [11][12][13][16][47][48]. These vitamin D intake doses were calculated according to meta-regression analyses of so called “winter RCTs” to estimate the dose-response curve of vitamin D intakes and achieved serum 25(OH)D concentrations without relevant endogenous vitamin D synthesis in the skin [11]. It is a major limitation of most nutritional vitamin D guidelines that they performed meta-regression analyses based on aggregate data because such an approach does not adequately capture between person variability in the treatment response [47][48]. Using individual participant data instead of aggregate data for meta-regression analyses, as a superior methodological approach, results in significantly higher vitamin D intakes to achieve certain target 25(OH)D concentrations [47][48]. Individual participant data meta-regression analyses and single RCTs suggest that an overall vitamin D intake of about 1000 IU of vitamin D per day is required to maintain 25(OH)D concentrations of, at least,

20 ng/mL (50 nmol/L) in 97.5% of the population [48][49]. Therefore, a vitamin D supplement dose of at least 800 IU per day is recommended when targeting a sufficient vitamin D status, i.e., a 25(OH)D concentration of at least 20 ng/mL (50 nmol/L). Of course, it can be improved and maintained vitamin D status by consuming natural or fortified food sources, but vitamin D intake by diet is usually in the range of about 100 to 200 IU per day in the general population [31][50].

In detail, a vitamin D supplementation dose of 800 to 2000 IU per day is recommend for adults who want to ensure a sufficient vitamin D status, with up to 4000 IU per day for certain groups, particularly for patients with obesity and malabsorption syndromes, as well as for individuals with a dark skin pigmentation (see **Table 3**). The relatively wide dose ranges for vitamin D account for various differences in the dose-response relationship for a given supplemental vitamin D dose and the achieved 25(OH)D concentration with higher dose requirements with increasing body weight and vice versa [51][52][53][54][55][56][57][58]. If a clinician is asked by a random individual which vitamin D dose is safe and very likely avoids vitamin D deficiency, a dose of 800 to 1000 IU per day should fulfill these criteria for the vast majority, even if individual characteristics, including the 25(OH)D status, is unknown. It should, however, also be noted that a few health authorities and experts consider a 25(OH)D concentration, of at least 10–12 ng/mL (25 to 30 nmol/L), as a reasonable treatment target that can be achieved by supplementation of 400 IU of vitamin D per day [11][13][16][47].

Daily, weekly, or monthly vitamin D supplementation, at equivalent doses, lead to similar increases in 25(OH)D serum concentrations, when measured after 2 to 3 months [59][60][61]. Adherence may be better with intermittent vitamin D dosing, but there are also concerns that high intermittent vitamin D doses may be less beneficial or might even be harmful in certain settings [61][62][63]. In view of the available evidence from clinical vitamin D trials and some pathophysiological considerations (e.g., altered vitamin D metabolism with high intermittent vitamin D doses), a daily vitamin D dosing schedule should rather be preferred, but when exceedingly high intermittent vitamin D doses are avoided, a weekly or monthly dosing schedule can also be applied [60][61]. The panel members could not reach a clear consensus on a clear cut-off for exceedingly high vitamin D doses, but single doses above about 50,000 IU of vitamin D should rather be avoided. Due to superior evidence regarding clinical benefits and dose-response, the vitamin D3 (cholecalciferol) is preferred over vitamin D2 (ergocalciferol) for the prevention of vitamin D deficiency [45][64].

Table 3. Statement regarding prevention of vitamin D deficiency in adults.

Consensus Statement	Consensus Voting Scale	Level of Agreement
In healthy adults without other risk factors, a supplementation of 800–2000 IU/day, for those who want to achieve a targeted/measured 25(OH)D concentration, should be considered during wintertime (mainly November-April) due to insufficient endogenous dermal vitamin D synthesis and depending on the body weight.	9 (strongly agree)	30%
Due to decreased skin synthesis in elderly (>65 years), a supplementation of 800–2000 IU/day is recommended throughout the year.	8	20%
In hospitalized/institutionalized individuals, a supplementation of 800–2000	7 (agree)	50%

Consensus Statement	Consensus Voting Scale	Level of Agreement
IU/day is recommended throughout the year. Women planning a pregnancy should start or maintain the vitamin D supplementation as recommended for healthy adults without other risk factors (800–2000 IU/day). The vitamin D supplementation should be continued throughout pregnancy and lactation. In certain patients/individuals or conditions 2–3 times higher vitamin D dosages, without using vitamin D doses above the UL of 4000 IU/day, are recommended for prevention compared to healthy adults without other risk factors: Malabsorption (e.g., cystic fibrosis, inflammatory bowel diseases, bariatric surgery, radiation enteritis) Obesity (BMI ≥ 30 kg/m^2) Dark skin pigmentation As vitamin D metabolites are stored in fat and other tissues and gradually released into the blood circulation, a daily or weekly or monthly supplementation regimen is equally effective and safe, if monthly doses are not exceedingly high, for the prevention of vitamin D deficiency. A tailored approach for vitamin D administration, involving the patients' preferences of the supplementation regimen (daily, weekly, monthly) might enhance the adherence to preventive vitamin D supplementation. For the prevention of vitamin D deficiency, the supplementation of oral cholecalciferol (vitamin D3) is recommended.	6 5 (neutral) 4 3 (disagree) 2 1 (strongly disagree)	0% 0% 0% 0% 0% 0%
Overall agreement 100%, consensus endorsed		

References

1. Bouillon, R.; Marcocci, C.; Carmeliet, G.; Bikle, D.; White, J.H.; Dawson-Hughes, B.; Lips, P.; Munns, C.F.; Lazaretti-Castro, M.; Giustina, A.; et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr. Rev. 2019, 40, 1109–1151.
2. Pilz, S.; Zittermann, A.; Trummer, C.; Theiler-Schwetz, V.; Lerchbaum, E.; Keppel, M.H.; Grubler, M.R.; Marz, W.; Pandis, M. Vitamin D testing and treatment: A narrative review of current evidence. Endocr. Connect. 2019, 8, R27–R43.
3. Maretzke, F.; Bechthold, A.; Egert, S.; Ernst, J.B.; Melo van Lent, D.; Pilz, S.; Reichrath, J.; Stangl, G.I.; Stehle, P.; Volkert, D.; et al. Role of Vitamin D in Preventing and Treating Selected Extraskeletal Diseases—An Umbrella Review. Nutrients 2020, 12, 969.
4. Zittermann, A.; Trummer, C.; Theiler-Schwetz, V.; Lerchbaum, E.; Marz, W.; Pilz, S. Vitamin D and Cardiovascular Disease: An Updated Narrative Review. Int. J. Mol. Sci. 2021, 22, 2896.
5. Bouillon, R.; Manousaki, D.; Rosen, C.; Trajanoska, K.; Rivadeneira, F.; Richards, J.B. The health effects of vitamin D supplementation: Evidence from human studies. Nat. Rev. Endocrinol. 2021, 18, 96–110.
6. Pilz, S.; Zittermann, A.; Obeid, R.; Hahn, A.; Pludowski, P.; Trummer, C.; Lerchbaum, E.; Perez-Lopez, F.R.; Karras, S.N.; Marz, W. The Role of Vitamin D in Fertility and during Pregnancy and Lactation: A Review of Clinical Data. Int. J. Environ. Res. Public Health 2018, 15, 2241.

7. Holick, M.F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev. Endocr. Metab. Disord. 2017, 18, 153–165.
8. Gaksch, M.; Jorde, R.; Grimnes, G.; Joakimsen, R.; Schirmer, H.; Wilsgaard, T.; Mathiesen, E.B.; Njolstad, I.; Lochen, M.L.; Marz, W.; et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PLoS ONE 2017, 12, e0170791.
9. Cashman, K.D.; Dowling, K.G.; Skrabakova, Z.; Gonzalez-Gross, M.; Valtuena, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Molgaard, C.; et al. Vitamin D deficiency in Europe: Pandemic? Am. J. Clin. Nutr. 2016, 103, 1033–1044.
10. Saponaro, F.; Saba, A.; Zucchi, R. An Update on Vitamin D Metabolism. Int. J Mol. Sci. 2020, 21, 6573.
11. Pilz, S.; Trummer, C.; Pandis, M.; Schwetz, V.; Aberer, F.; Grubler, M.; Verheyen, N.; Tomaschitz, A.; Marz, W. Vitamin D: Current Guidelines and Future Outlook. Anticancer Res. 2018, 38, 1145–1151.
12. Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J. Clin. Endocrinol. Metab. 2011, 96, 53–58.
13. Buttriss, J.L.; Lanham-New, S.A.; Steenson, S.; Levy, L.; Swan, G.E.; Darling, A.L.; Cashman, K.D.; Allen, R.E.; Durrant, L.R.; Smith, C.P.; et al. Implementation strategies for improving vitamin D status and increasing vitamin D intake in the UK: Current controversies and future perspectives: Proceedings of the 2nd Rank Prize Funds Forum on vitamin D. Br. J. Nutr. 2021, 1–21.
14. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 2011, 96, 1911–1930.
15. Giustina, A.; Bouillon, R.; Binkley, N.; Sempos, C.; Adler, R.A.; Bollerslev, J.; Dawson-Hughes, B.; Ebeling, P.R.; Feldman, D.; Heijboer, A.; et al. Controversies in Vitamin D: A Statement from the Third International Conference. JBMR Plus 2020, 4, e10417.
16. Bouillon, R. Comparative analysis of nutritional guidelines for vitamin D. Nat. Rev. Endocrinol. 2017, 13, 466–479.
17. Fraile Navarro, D.; Lopez Garcia-Franco, A.; Nino de Guzman, E.; Rabassa, M.; Zamanillo Campos, R.; Pardo-Hernandez, H.; Ricci-Cabello, I.; Canelo-Aybar, C.; Meneses-Echavez, J.F.; Yepes-Nunez, J.J.; et al. Vitamin D recommendations in clinical guidelines: A systematic review, quality evaluation and analysis of potential predictors. Int. J. Clin. Pract. 2021, 75, e14805.

18. Dai, Z.; McKenzie, J.E.; McDonald, S.; Baram, L.; Page, M.J.; Allman-Farinelli, M.; Raubenheimer, D.; Bero, L.A. Assessment of the Methods Used to Develop Vitamin D and Calcium Recommendations—A Systematic Review of Bone Health Guidelines. Nutrients 2021, 13, 2423.
19. Rosen, C.J.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; Kovacs, C.S.; et al. IOM committee members respond to Endocrine Society vitamin D guideline. J. Clin. Endocrinol. Metab. 2012, 97, 1146–1152.
20. Pludowski, P.; Holick, M.F.; Grant, W.B.; Konstantynowicz, J.; Mascarenhas, M.R.; Haq, A.; Povoroznyuk, V.; Balatska, N.; Barbosa, A.P.; Karonova, T.; et al. Vitamin D supplementation guidelines. J. Steroid Biochem. Mol. Biol. 2018, 175, 125–135.
21. Pludowski, P.; Karczmarewicz, E.; Bayer, M.; Carter, G.; Chlebna-Sokol, D.; Czech-Kowalska, J.; Debski, R.; Decsi, T.; Dobrzanska, A.; Franek, E.; et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe—Recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol. Pol. 2013, 64, 319–327.
22. Takacs, I.; Benko, I.; Toldy, E.; Wikonkal, N.; Szekeres, L.; Bodolay, E.; Kiss, E.; Jambrik, Z.; Szabo, B.; Merkely, B.; et al. Hungarian consensus regarding the role of vitamin D in the prevention and treatment of diseases. Orv. Hetil. 2012, 153 (Suppl. 2), 5–26.
23. German Nutrition Society (DGE). New reference values for vitamin D. Ann. Nutr. Metab. 2012, 60, 241–246.
24. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies). Scientific opinion on dietary reference values for vitamin D. EFSA J. 2016, 14, 4547.
25. Pigarova, E.A.; Rozhinskaya, L.Y.; Belaya, J.E.; Dzeranova, L.K.; Karonova, T.L.; Ilyin, A.V.; Melnichenko, G.A.; Dedov, I.I. Russian Association of Endocrinologists recommendations for diagnosis, treatment and prevention of vitamin D deficiency in adults. Probl. Endocrinol. 2016, 62, 60–84. (In Russian)
26. Rusinska, A.; Pludowski, P.; Walczak, M.; Borszewska-Kornacka, M.K.; Bossowski, A.; Chlebna-Sokol, D.; Czech-Kowalska, J.; Dobrzanska, A.; Franek, E.; Helwich, E.; et al. Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel with Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 Update. Front. Endocrinol. 2018, 9, 246.
27. Rudenko, E. National Regulation about Methods of Diagnosis, Prevention and Differentiated Treatment of Vitamin D Deficiency; Ministry of Health of the Republic of Belarus: Minsk, Belarus, 2013.

28. Borissova, A.-M.; Boyanov, M.A.; Popivanov, P.R.; Kolarov, Z.; Petranova, T.P.; Shinkov, A.D. Recommendation for Diagnosis, Prevention and Treatment of Vitamin D Deficiency; Bulgarian Society of Endocrinology: Sofia, Bulgaria, 2019.
29. Payer, J.; Killinger, Z.; Jackuliak, P.; Kužma, M. Postmenopausal osteoporosis: Standard diagnostic and therapeutic practice. Clin. Osteol. 2018, 23, 18–27.
30. Cesareo, R.; Attanasio, R.; Caputo, M.; Castello, R.; Chiodini, I.; Falchetti, A.; Guglielmi, R.; Papini, E.; Santonati, A.; Scillitani, A.; et al. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. Nutrients 2018, 10, 546.
31. Cashman, K.D. Global differences in vitamin D status and dietary intake: A review of the data. Endocr. Connect. 2022, 11, e210282.
32. Lips, P.; Cashman, K.D.; Lamberg-Allardt, C.; Bischoff-Ferrari, H.A.; Obermayer-Pietsch, B.; Bianchi, M.L.; Stepan, J.; El-Hajj Fuleihan, G.; Bouillon, R. 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, P23–P54.
33. Płudowski, P.; Ducki, C.; Konstantynowicz, J.; Jaworski, M. Vitamin D status in Poland. Pol. Arch. Med. Wewn. 2016, 126, 530–539.
34. Avdeeva, V.A.; Suplotova, L.A.; Pigarova, E.A.; Rozhinskaya, L.Y.; Troshina, E.A. Vitamin D deficiency in Russia: The first results of a registered, non-interventional study of the frequency of vitamin D deficiency and insufficiency in various geographic regions of the country. Probl. Endokrinol. 2021, 67, 84–92.
35. Nikolova, M.G.; Boyanov, M.A.; Tsakova, A.D. Correlations of Serum Vitamin D with Metabolic Parameters in Adult Outpatients with Different Degrees of Overweight/Obesity Coming from an Urban Community. Acta Endocrinol. 2018, 14, 375–383.
36. Burnett-Bowie, S.M.; Cappola, A.R. The USPSTF 2021 Recommendations on Screening for Asymptomatic Vitamin D Deficiency in Adults: The Challenge for Clinicians Continues. JAMA 2021, 325, 1401–1402.
37. US Preventive Services Task Force; Krist, A.H.; Davidson, K.W.; Mangione, C.M.; Cabana, M.; Caughey, A.B.; Davis, E.M.; Donahue, K.E.; Doubeni, C.A.; Epling, J.W., Jr.; et al. Screening for Vitamin D Deficiency in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2021, 325, 1436–1442.
38. Macova, L.; Bicikova, M. Vitamin D: Current Challenges between the Laboratory and Clinical Practice. Nutrients 2021, 13, 1758.
39. Binkley, N.; Dawson-Hughes, B.; Durazo-Arvizu, R.; Thamm, M.; Tian, L.; Merkel, J.M.; Jones, J.C.; Carter, G.D.; Sempos, C.T. Vitamin D measurement standardization: The way out of the

chaos. J. Steroid Biochem. Mol. Biol. 2017, 173, 117–121.

40. Marcinowska-Suchowierska, E.; Kupisz-Urbanska, M.; Lukaszkiewicz, J.; Pludowski, P.; Jones, G. Vitamin D Toxicity—A Clinical Perspective. Front. Endocrinol. 2018, 9, 550.
41. Cappellani, D.; Brancatella, A.; Morganti, R.; Borsari, S.; Baldinotti, F.; Caligo, M.A.; Kaufmann, M.; Jones, G.; Marcocci, C.; Cetani, F. Hypercalcemia due to CYP24A1 mutations: A systematic descriptive review. Eur. J. Endocrinol. 2021, 186, 137–149.
42. Carlberg, C. Vitamin D: A Micronutrient Regulating Genes. Curr. Pharm. Des. 2019, 25, 1740–1746.
43. Hanel, A.; Neme, A.; Malinen, M.; Hamalainen, E.; Malmberg, H.R.; Etheve, S.; Tuomainen, T.P.; Virtanen, J.K.; Bendik, I.; Carlberg, C. Common and personal target genes of the micronutrient vitamin D in primary immune cells from human peripheral blood. Sci. Rep. 2020, 10, 21051.
44. Krasniqi, E.; Boshnjaku, A.; Wagner, K.H.; Wessner, B. Association between Polymorphisms in Vitamin D Pathway-Related Genes, Vitamin D Status, Muscle Mass and Function: A Systematic Review. Nutrients 2021, 13, 3109.
45. Bilezikian, J.P.; Formenti, A.M.; Adler, R.A.; Binkley, N.; Bouillon, R.; Lazaretti-Castro, M.; Marcocci, C.; Napoli, N.; Rizzoli, R.; Giustina, A. Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? Rev. Endocr. Metab. Disord. 2021, 22, 1201–1218.
46. Kupisz-Urbanska, M.; Pludowski, P.; Marcinowska-Suchowierska, E. Vitamin D Deficiency in Older Patients—Problems of Sarcopenia, Drug Interactions, Management in Deficiency. Nutrients 2021, 13, 1247.
47. Cashman, K.D. Vitamin D Requirements for the Future-Lessons Learned and Charting a Path Forward. Nutrients 2018, 10, 533.
48. Cashman, K.D.; Ritz, C.; Kiely, M.; Odin, C. Improved Dietary Guidelines for Vitamin D: Application of Individual Participant Data (IPD)-Level Meta-Regression Analyses. Nutrients 2017, 9, 469.
49. Pilz, S.; Hahn, A.; Schon, C.; Wilhelm, M.; Obeid, R. Effect of Two Different Multimicronutrient Supplements on Vitamin D Status in Women of Childbearing Age: A Randomized Trial. Nutrients 2017, 9, 30.
50. Calvo, M.S.; Whiting, S.J. Public health strategies to overcome barriers to optimal vitamin D status in populations with special needs. J. Nutr. 2006, 136, 1135–1139.
51. Mo, M.; Wang, S.; Chen, Z.; Muyiduli, X.; Wang, S.; Shen, Y.; Shao, B.; Li, M.; Chen, D.; Chen, Z.; et al. A systematic review and meta-analysis of the response of serum 25-hydroxyvitamin D concentration to vitamin D supplementation from RCTs from around the globe. Eur. J. Clin. Nutr. 2019, 73, 816–834.

52. Bacha, D.S.; Rahme, M.; Al-Shaar, L.; Baddoura, R.; Halaby, G.; Singh, R.J.; Mahfoud, Z.R.; Habib, R.; Arabi, A.; El-Hajj Fuleihan, G. Vitamin D3 Dose Requirement That Raises 25-Hydroxyvitamin D to Desirable Level in Overweight and Obese Elderly. J. Clin. Endocrinol. Metab. 2021, 106, e3644–e3654.
53. Zittermann, A.; Ernst, J.B.; Gummert, J.F.; Borgermann, J. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: A systematic review. Eur. J. Nutr. 2014, 53, 367–374.
54. Autier, P.; Gandini, S.; Mullie, P. A systematic review: Influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. J. Clin. Endocrinol. Metab. 2012, 97, 2606–2613.
55. Cashman, K.D.; Ritz, C.; Adebayo, F.A.; Dowling, K.G.; Itkonen, S.T.; Ohman, T.; Skaffari, E.; Saarnio, E.M.; Kiely, M.; Lamberg-Allardt, C. Differences in the dietary requirement for vitamin D among Caucasian and East African women at Northern latitude. Eur. J. Nutr. 2019, 58, 2281–2291.
56. Cashman, K.D.; Kiely, M.E.; Andersen, R.; Gronborg, I.M.; Tetens, I.; Tripkovic, L.; Lanham-New, S.A.; Lamberg-Allardt, C.; Adebayo, F.A.; Gallagher, J.C.; et al. Individual participant data (IPD)-level meta-analysis of randomised controlled trials to estimate the vitamin D dietary requirements in dark-skinned individuals resident at high latitude. Eur. J. Nutr. 2021, 61, 1015–1034.
57. Mazahery, H.; von Hurst, P.R. Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. Nutrients 2015, 7, 5111–5142.
58. Ramasamy, I. Vitamin D Metabolism and Guidelines for Vitamin D Supplementation. Clin. Biochem. Rev. 2020, 41, 103–126.
59. Ish-Shalom, S.; Segal, E.; Salganik, T.; Raz, B.; Bromberg, I.L.; Vieth, R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J. Clin. Endocrinol. Metab. 2008, 93, 3430–3435.
60. Takacs, I.; Toth, B.E.; Szekeres, L.; Szabo, B.; Bakos, B.; Lakatos, P. Randomized clinical trial to comparing efficacy of daily, weekly and monthly administration of vitamin D3. Endocrine 2017, 55, 60–65.
61. Mazess, R.B.; Bischoff-Ferrari, H.A.; Dawson-Hughes, B. Vitamin D: Bolus Is Bogus—A Narrative Review. JBMR Plus 2021, 5, e10567.
62. Jorde, R.; Grimnes, G. Serum cholecalciferol may be a better marker of vitamin D status than 25-hydroxyvitamin D. Med. Hypotheses 2018, 111, 61–65.
63. Rothen, J.P.; Rutishauser, J.; Walter, P.N.; Hersberger, K.E.; Arnet, I. Oral intermittent vitamin D substitution: Influence of pharmaceutical form and dosage frequency on medication adherence: A randomized clinical trial. BMC Pharmacol. Toxicol. 2020, 21, 51.

64. Tripkovic, L.; Lambert, H.; Hart, K.; Smith, C.P.; Bucca, G.; Penson, S.; Chope, G.; Hypponen, E.; Berry, J.; Vieth, R.; 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, 1357–1364.