

MINI REVIEW

Optimizing Vitamin D Levels: Bridging the Gap Between Theory and Practice for Optimal Health in Switzerland

Brida Caviezel¹, Laura Szczypior², Eleni Sourla¹, Titus Baston³, Anja Kuzmitski², Kathrin Peschke¹, Issa Rasheed Fetian^{3,4a}, Lukas Villiger¹

¹ Praxis Dr Villiger and DiaMon Institute, Baden-Dättwil, Switzerland, ² Institut für Arbeitsmedizin, Baden, Switzerland, ³ Hausarztpraxis, Brugg, Switzerland, ⁴ University of Basel, Basel, Switzerland

Keywords: Vitamin D deficiency, primary care, serum vitamin D levels, patient outcomes, nutrient management

<https://doi.org/10.36000/hbT.2024.15.001>

healthbook TIMES Das Schweizer Ärztejournal Journal Des Médecins Suisses

Vol. 15, Issue 4, 2024

Optimizing vitamin D levels poses a significant challenge in healthcare, characterized by varying guidelines, recent changes in testing coverage and widespread vitamin D deficiency. In Switzerland, where 59% of primary care patients have insufficient vitamin D levels and 12% are deficient, the complexity is heightened by the discontinuation of health insurance coverage for vitamin D testing without risk factors, as of July 1, 2022. This article explores the multifaceted landscape of vitamin D management, addressing the intricacies of testing, supplementation and guideline implementation. Through an analysis of the current guidelines and the pathophysiology of vitamin D, we aim to equip clinicians with the insights needed to navigate these complexities, optimize patient care and improve outcomes.

PEER REVIEWED ARTICLE

Dr Joël Capraro, Kantonsspital, Aarau, Endokrinologie, Diabetologie und Metabolismus

Dr Stefan Zechmann, Stoffwechselzentrum, St. Gallen, friendlyDocs AG

Received on November 19, 2024; accepted after peer review on December 20, 2024; published online on December 23, 2024.

Introduction

The quest for optimal vitamin D levels represents a complex challenge in healthcare, marked by numerous uncertainties and intricacies, with varying guidelines and recommendations for different populations.¹ Clinicians and patients are confronted with a complex landscape of vitamin D management, shaped by varying guidelines and recent changes in testing coverage.² This situation necessitates careful consideration of several factors: identifying

^a Corresponding author:
Issa Rasheed Fetian, MD
HAP MZ Brugg, Hausarztpraxis
Fröhlichstrasse 5
5200 Brugg
Switzerland
Email: issa.fetian@gmail.com

which individuals should be tested for vitamin D deficiency, assessing the associated costs of testing, determining the circumstances under which testing is warranted and recognizing when supplementation becomes essential.³

In Switzerland, as in many regions around the world, optimizing vitamin D levels remains a challenging and ambiguous task.⁴ The Swiss Federal Office of Public Health (BAG) defines vitamin D deficiency as serum levels falling below 20 ng/mL (50 nmol/L), with severe deficiency characterized by levels below 10 ng/mL (25 nmol/L). Despite these clear thresholds, the global prevalence of vitamin D deficiency is alarmingly high, affecting around 1 billion individuals, with 50% of the population not meeting the recommended levels.⁵ In Switzerland, the issue is particularly severe: 59% of primary care patients show insufficient vitamin D levels and 12% are classified as deficient.⁶ Adding to the complexity, since July 1, 2022, basic health insurance in Switzerland no longer covers vitamin D testing for individuals without identified risk factors.⁷

Amid the complexities of data interpretation and implementation, the challenge of reconciling diverse and sometimes conflicting recommendations from professional societies becomes increasingly evident as translating guidelines into effective strategies for optimizing vitamin D levels demands a nuanced approach that is carefully tailored to individual patient needs; thus, this article seeks to navigate these complexities by providing an in-depth analysis of the current state of vitamin D optimization. Through a comprehensive synthesis of existing guidelines, an in-depth examination of the pathophysiology of vitamin D biosynthesis and deficiency and an evaluation of real-world case studies, we seek to clarify the prevailing uncertainties. Our goal is to equip clinicians with the knowledge and tools necessary to navigate the complexities of vitamin D optimization, thereby enhancing informed decision-making and improving patient outcomes.

Physiology of vitamin D

Within the human body, vitamin D, encompassing both ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃), undergoes conversion into the primary circulating forms of 25-hydroxyvitamin D (25-OH-D₂ or 25-OH-D₃), also referred to as calcitriol. These forms can subsequently transform into biologically active metabolites, namely 1,25-dihydroxyergocalciferol (1,25-OH-2D₂) or 1,25-dihydroxycholecalciferol (1,25-OH-2D₃), recognized as calcitriol.⁸

In the skin, under the influence of UV-B radiation, provitamin D₂ and provitamin D₃ are synthesized from ergosterol and 7-dehydrocholesterol, respectively. Following the cleavage of the B-ring of these molecules, thermal isomerization takes place.⁹

Moreover, vitamin D is not solely reliant on sunlight; it can also be sourced from a variety of delectable foods.^{10,11} Delve into the depths of the ocean with a bounty of fish options, harness the benefits of fish oil's nutritional goodness and explore the nourishment offered by select cuts of meat.¹² Embrace the creamy textures of dairy products and enrich your diet with the wholesome goodness of mushrooms, soy and fortified cereals.¹³ With such a diverse array of options, maintaining adequate vitamin D levels becomes not just a necessity but a culinary journey worth savoring.¹⁴

Vitamin D is transported into the bloodstream where it binds to the vitamin D-binding protein (VDBP), synthesized in the liver.^{15,16} Additionally, irrespective of its source — whether derived from dietary intake or synthesized in the skin — it undergoes predominantly hepatic hydroxylation mediated by the enzyme CYP2R1, resulting in the formation of 25-hydroxycholecalciferol (25-OH-vitamin D3 or calcitriol). Subsequently, it is released back into circulation bound to VDBP.¹⁷

Calcitriol is the active form of vitamin D3, which regulates the calcium and phosphate balance in the body, enhancing their absorption and utilization.¹⁸ Under the influence of the enzyme CYP27B1, calcitriol is primarily converted into its active form, calcitriol (1,25-OH-2D3 or 1 α ,25-dihydroxyvitamin D3), in the kidney by the enzyme 1 α -hydroxylase.¹⁹ This process is primarily stimulated by parathyroid hormone (PTH) and inhibited by calcium, phosphate and fibroblast growth factor (FGF 23).²⁰ Calcitriol is the biologically active hormone.²¹ In the bloodstream, vitamin D is primarily bound to VDBP or albumin; very little circulates freely.²²

Functions of vitamin D

The vitamin D receptor (VDR) for 1,25-OH-2D belongs to the steroid receptor family and is present in nearly all human cells.²³ It is a transcription factor that regulates gene expression and influences the activity of genes responsible for the biological effects of vitamin D.²⁴ Vitamin D plays an essential role in calcium absorption in the small intestine.²⁵

The calcitriol-VDR complex stimulates the transcription of the calcium channels TRPV5 and TRPV6 in intestinal cells, enabling calcium to be absorbed into the cells along a steep electrochemical gradient through the brush border membrane.²⁶ Subsequently, calcium is transported within the cell with the help of calbindin, whose expression is also induced by calcitriol.²⁷ The calcium is then transported through the cell and released into the bloodstream either via CaATPase or the sodium/calcium exchanger protein (NCX1) and in this process, CaATPase is also induced by 1,25-OH-2D.²⁸

Similar mechanisms lead to calcium reabsorption in the distal tubule of the kidney. The proteins involved are homologous to TRPV5 and calbindin, but not identical.²⁹

The situation in the bone tissue is less clear-cut, as the vitamin D receptor (VDR) is also present in osteoblasts, cells responsible for bone formation; calcitriol promotes the differentiation of osteoblasts and regulates proteins such as collagen, alkaline phosphatase and osteocalcin, which are essential for bone development, while also inducing RANKL, a membrane-bound protein in osteoblasts that stimulates the formation and activation of osteoclasts, indicating that vitamin D regulates both bone formation and resorption.³⁰

The full range of vitamin D functions is not yet completely understood. Nonetheless, clinical studies suggest a broader spectrum of effects, demonstrating potential benefits in conditions such as coronary heart disease (CHD), cerebrovascular events, arterial hypertension, infections, autoimmune disorders and skin diseases.³¹

Vitamin D deficiency

The BAG defines vitamin D deficiency as serum levels falling below 20 ng/mL (50 nmol/L), with severe deficiency characterized by levels below 10 ng/mL (25 nmol/L).⁵ The clinical symptoms of long-term vitamin D deficiency manifest as rickets in children and osteomalacia in adults. Both conditions stem from impaired bone mineralization, which results from inefficient absorption of calcium and phosphate from the diet. In the absence of adequate vitamin D, only about 10–15% of calcium and approximately 60% of phosphate are absorbed.³²

Rickets is characterized by skeletal changes (e.g., deformities, growth disturbances), radiological alterations (e.g., reduced mineralization, deformities) and elevated alkaline phosphatase levels.³³ Depending on the severity and duration of vitamin D deficiency, initial hypocalcaemia progresses to normo-calcemia and hypophosphatemia due to increased PTH secretion, eventually leading to combined hypocalcaemia and hypophosphatemia when calcium can no longer be released from the bones.³⁴

Osteomalacia is characterized by increased bone resorption and suppression of new bone mineralization.³⁵ Despite the under mineralization of the bone, serum calcium concentration often remains within the normal range due to the regulation by PTH.³⁶ The clinical symptoms of vitamin D deficiency in adults are less pronounced than in children and can include diffuse muscle and bone pain, as well as specific fractures (such as femoral neck fractures and stress fractures).³⁷ Muscle pain and weakness (myopathy), which occur alongside skeletal symptoms in older adults, can lead to impaired physical performance, an increased risk of falls and a higher risk of bone fractures.³⁸

A prolonged vitamin D deficiency can lead to reduced bone mineral density (BMD) and predispose older individuals, particularly postmenopausal women, to osteoporosis.^{39,40}

Central to vitamin D supply is the body's endogenous production in the skin, which contributes 80–90% to vitamin D levels, while dietary intake provides only a minor contribution unless supplementation is used.⁴¹

Vitamin D deficiency or inadequate calcium intake can lead to secondary hyperparathyroidism, a condition characterized by elevated parathyroid hormone (PTH) and low calcium levels, emphasizing the importance of maintaining sufficient vitamin D and calcium intake.⁴²

Risk factors for vitamin D deficiency

UVB exposure and skin factors

UVB light is necessary for vitamin D synthesis.⁴³ Vitamin D production in the skin can only occur with UVB wavelengths between 295 nm and 300 nm, ideally at 297 nm.⁴⁴ At too low angles of incidence, vitamin D can no longer be synthesized in the skin.⁴⁵ During the day, the most vitamin D can be synthesized around midday.¹⁵

Depending on the angle of incidence, vitamin D cannot be synthesized in many regions during certain seasons. This phenomenon is also known as the “vitamin D winter”.⁴⁶ Vitamin D synthesis in Germany is significantly affected by geographical latitude and seasonal variations. For example, in Berlin (Germany, 52.2 degrees North), vitamin D synthesis is limited between October and April due to insufficient UVB radiation during these months.⁴⁷ Ozone absorbs UVB, so in regions with higher ozone concentrations, less vitamin D is synthesized. Additionally, UVB can be absorbed, scattered or reflected by various substances during its journey through the Earth's atmosphere, including oxygen and nitrogen, aerosols, water vapor and various pollutants.⁴⁸

A simple yet often overlooked reason for vitamin D deficiency is body coverage by clothing.^{48,49} Light, non-synthetic fibers like cotton and linen are less effective at blocking UV radiation compared to wool, silk, nylon and polyester.⁴⁹

When using sunscreen, vitamin D synthesis is either significantly reduced or does not occur at all.⁵⁰

Melanin absorbs electromagnetic radiation efficiently across the entire UV and visible light spectrum.⁵⁰ Compared to individuals with lighter skin pigmentation, people with higher melanin concentrations (darker skin) require longer UV exposure to produce an equivalent amount of vitamin D.⁵¹

The levels of 7-dehydrocholesterol significantly impact cutaneous vitamin D₃ synthesis, which can be diminished in scar tissue, for instance.⁵²

Age

The capacity of the skin to synthesize vitamin D diminishes with advancing age, which is likely attributable to a decline in the concentration of 7-dehydrocholesterol.⁵³

Malabsorption

Malabsorption, which can occur following bariatric surgery or in gastrointestinal disorders such as celiac disease or chronic pancreatitis, is a potential cause of vitamin D deficiency.^{54,55}

Obesity

In our population, obesity is an increasing medical issue that can lead to vitamin D deficiency through several factors.⁵⁶

Due to social stigma and physical inactivity, obese individuals often spend less time outdoors, and when they do, they frequently cover their bodies with clothing.⁵⁷ Vitamin D is fat-soluble and thus gets bound in excess body fat, leading to reduced availability in the body; another theory suggests that the prevalent inflammation in fat cells may hinder the metabolism, particularly the conversion to its active form.⁵⁸

Medications

Certain medications, such as phenobarbital, phenytoin, carbamazepine, rifampicin, as well as corticosteroids and antiretroviral drugs, upregulate the enzyme CYP3A4, which leads to decreased levels of calcidiol and calcitriol, thereby impairing vitamin D metabolism and potentially contributing to vitamin D deficiency.⁵⁹

Kidney disease

Changes in vitamin D metabolism in chronic kidney disease are multifactorial and complex.⁶⁰ Two key changes are as follows. Firstly, a reduction in 25-hydroxyvitamin D-1 α -hydroxylase activity leads to decreased conversion of vitamin D into its active form, calcitriol.⁶¹ On the other hand, there is increased phosphate retention, which is a strong inhibitor of 25-hydroxyvitamin D-1 α -hydroxylase.⁶² The resulting hypocalcemia, due to reduced intestinal absorption, leads to an elevation in PTH levels, which in turn inhibits the activity of 25-hydroxyvitamin D-1 α -hydroxylase.⁶³

Table 1. Recommendations for vitamin D supplementation from various organizations.

Regulatory authorities	Vitamin D target level	Daily vitamin D intake in IU for younger individuals	Daily vitamin D intake in IU for older individuals
BAG 2012 ⁵	50 nmol/l	600 IU (18–65 years old)	800 IU (over 65 years old)
U.S. Endocrine Society 2011 ⁷¹	70 nmol/l	600 IU (19–50 years old)	600–800 IU (over 50 years old)
EFSA 2016 ⁸	50 nmol/l	600 IU	600 IU
WHO-FAO 2004 ⁷²		200 IU	200 IU

BAG, Swiss Federal Office for Public Health; EFSA, European Food Safety Authority; FAO, Food and Agriculture Organization; IU, International Units; WHO, World Health Organization.^{5,8,71,72}

Liver disease

In cholestatic liver diseases, there is a reduction in the intestinal availability of bile acids, which consequently leads to impaired absorption of fat-soluble vitamins such as vitamin D.⁶⁴

In severe parenchymal liver diseases, there is both malabsorption of vitamin D and reduced capacity for its 25-hydroxylation, leading to a deficiency of 25-hydroxyvitamin D.⁶⁵ In the liver, the synthesis of vitamin D-binding protein (DBP), which serves as the primary transport protein for vitamin D, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the bloodstream, plays a crucial role in extending the half-life of these compounds and facilitating their uptake into target tissues, and in severe liver diseases, a deficiency of DBP may occur.⁶⁶

Additional risk factors

Vitamin D deficiency results from insufficient intake of vitamin D (such as in anorexia or malnutrition) or increased demand (such as in conditions like bone fractures, primary hyperparathyroidism, thyroid disorders, pregnancy/lactation, chronic inflammation or tumors).⁶⁷ There are also conditions that can accumulate multiple risk factors for vitamin D deficiency, such as poorly managed diabetes (which may involve limited sun exposure, impaired kidney function, inflammatory states and obesity) or smokers (who experience reduced endogenous production in the skin and absorption in the gut), and chronic inflammatory states can impair the activity of enzymes responsible for converting vitamin D into its active form.⁶⁸

Current guidelines for vitamin D supplementation

Measurement of 25-hydroxyvitamin D (25-OH-D) is recommended for screening because, unlike 1,25-dihydroxyvitamin D, it has a longer half-life of 2-3 weeks and a higher concentration in the blood.⁶⁹ Various institutions and professional societies have issued guidelines for maintenance doses of vitamin D ([Table 1](#)). However, specific recommendations for maintenance doses are often lacking for particular at-risk groups, and recommendations for deficiency situations tend to be generally formulated.⁷⁰

BAG guidelines

According to the most recent guidelines from the BAG in 2012, a serum vitamin D3 level below 10 ng/mL is classified as a severe deficiency. Levels below 20 ng/mL are considered deficient, and a level of 30 ng/mL is identified as the threshold for preventing fractures and falls in patients with osteoporosis, indicating vitamin D insufficiency.⁵

Vitamin D3 levels should be measured in at-risk patients. Therefore, the BAG issued the following recommendations in 2021: individuals aged 3–60 years should have a daily intake of 600 International Units (IU) (15 µg), while those over 60 years should have a daily intake of 800 IU (20 µg). During the summer months (June to September), light-skinned individuals should be exposed to the sun for 10 min per day, while those with darker skin should aim for 20–60 minutes to achieve adequate vitamin D synthesis. It is preferable to sunbathe in the morning or afternoon and to avoid midday sun exposure.⁷³ In winter, natural vitamin D synthesis is insufficient to meet needs, so it is recommended to consume vitamin D-rich foods or fortified products or to take vitamin D3 supplements. For individuals over 60 years of age, it is generally advised to use vitamin D3 supplements. Special risk groups, such as those with obesity, have an increased need for vitamin D.⁷³

In patients with malabsorption issues or after gastrectomy, the oral dosage and duration of therapy depend on the individual's absorption capacity. High doses of vitamin D, ranging from 10,000 to 50,000 IU per day, may be necessary in certain cases.⁷⁴

Monitoring of vitamin D levels in the context of the above cases can only be billed a maximum of every 3 months.⁷⁵ A reimbursement of 25-hydroxyvitamin D testing is only possible with limitations for selected groups of patients ([Table 2](#)).⁷⁶⁻⁷⁸

Guidelines of the US Endocrine Society

In 2011, the US Endocrine Society issued the latest guidelines regarding the measurement, threshold values and potential need for supplementation of vitamin D.⁷¹ It is recommended that patients with risk factors for vitamin D deficiency be screened, while routine measurement of vitamin D levels is not advised for all others. The recommended screening parameter is 25-hydroxyvitamin D.⁷⁹ A deficiency is defined as levels below 20 ng/mL, and insufficiency is defined as levels between 20–30 ng/mL. Adults aged 19–50 require at least 600 IU/day of vitamin D as a maintenance dose. For those over 50 years of age, a dosage of 600–800 IU/day is recommended. To raise vitamin D levels, supplementation of 1500–2000 IU/day is advised. The daily supplementation should not exceed 4000 IU/day.⁴⁴

Table 2. Selected groups of patients for whom reimbursement of 25-hydroxyvitamin D testing is possible through the basic health insurance in Switzerland.⁷⁸

Osteomalacia, rickets, osteopenia and osteoporosis
Non-traumatic fracture
After an unclear fall event in patients aged ≥ 65 years
In patients aged ≥ 65 years with a history of increased fracture risk
Kidney diseases, including urolithiasis
Disorders of parathyroid hormone, calcium levels and/or phosphate levels
Gastrointestinal diseases
Malabsorption syndrome
Liver diseases
Medication use that affects vitamin D metabolism or its absorption

European Food Safety Authority (EFSA) recommendation issued in 2016

The EFSA panel recommends aiming for a target serum concentration of 50 nmol/l of vitamin D.⁸ For adults, this corresponds to an intake of 15 µg/day or 600 IU per day. The same thresholds and supplementation recommendations apply to pregnant and lactating women.^{80,81}

Recommendations of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO)

The joint FAO/WHO expert consultation on human vitamin and mineral requirements recommends an intake of only 200 IU per day (equivalent to 5 µg) for all age groups, excluding children.⁷³

Recommendations for the Treatment of Special Constellations

Management of Significant Deficiency (<20 ng/ml)

In Switzerland, where specific formulations of vitamin D are widely accessible, managing significant vitamin D deficiency (<20 ng/ml) requires targeted strategies to rapidly normalize serum levels:

- **High-loading regimens:** Administer a bolus dose of **100,000–300,000 IU intramuscularly (i.m.)** at monthly or biannual intervals, depending on the severity of deficiency and patient-specific factors.⁷⁶
- **Maintenance dosing:** Transition to a personalized regimen of **800–1600 IU/day** or an equivalent weekly dose (e.g., **10,000–14,000 IU**) to sustain adequate levels.⁷¹

- **Monitoring:** Conduct follow-up assessments every three months to evaluate response and adjust the maintenance dose as necessary.

Management of Secondary Hyperparathyroidism

Secondary hyperparathyroidism, a laboratory constellation characterized by elevated parathyroid hormone (PTH) and low calcium levels due to vitamin D deficiency or inadequate calcium intake, requires an integrative approach:

- **Correction of deficiency:** Employ high-dose vitamin D therapy with bolus dosing, followed by maintenance regimens that address both calcium and vitamin D needs.
- **Monitoring and prevention:** Regularly monitor serum calcium, PTH, and phosphate levels to prevent complications such as hypercalcemia. Tailor dosing based on renal function, calcium-phosphate homeostasis, and individual therapeutic response.^{71,82}

Mild Insufficiency (20–30 ng/ml)

For patients with mild insufficiency, regular, lower-dose regimens may suffice:

- **Dosing strategy:** Daily supplementation of **600–800 IU/day** or a comparable weekly dose, coupled with dietary modifications and sun exposure recommendations.⁸³
- **Periodic evaluation:** Annual monitoring may be adequate for patients without additional risk factors.⁸⁴

By recognizing and managing these distinct constellations, clinicians can align therapy with patient-specific needs, improving adherence and outcomes. These recommendations underscore the importance of an individualized, evidence-based approach that incorporates both high-dose substitution for severe deficiency and regular dosing for milder insufficiency.

Conclusions

Optimizing vitamin D levels presents a complex and evolving challenge in healthcare, including in Switzerland, where a significant proportion of the population suffers from insufficiency or deficiency. This issue is further complicated by recent policy changes that limit routine vitamin D testing, creating barriers for early detection and intervention. The disconnect between existing guidelines, the diverse needs of patients, and clinical practice highlights the need for a nuanced approach that considers individual risk factors, lifestyle, and local healthcare policies.

To overcome these challenges, it is essential to translate theoretical insights into actionable clinical practices. Personalized approaches to vitamin D testing, supplementation, and monitoring must account for demographic, environmental, and medical factors unique to each patient. In Switzerland, where specific formulations of vitamin D and calcium products are widely available, clinicians should tailor recommendations based on the actual vitamin D status of each patient. For individuals with significant deficiency (<20 ng/mL), high-dose substitution regimens, such as monthly or even biannual high-loading doses, may be appropriate to rapidly normalize levels. For those with mild insufficiency (20–30 ng/mL), lower, more regular dosing strategies may suffice. Furthermore, secondary hyperparathyroidism, a laboratory constellation characterized by elevated parathyroid hormone (PTH) and low calcium levels due to vitamin D deficiency or inadequate calcium intake, should be recognized and managed appropriately in clinical practice.

Equipping clinicians with a comprehensive understanding of vitamin D physiology, current guidelines, and the implications of deficiency will foster informed decision-making and improve patient outcomes. Addressing these gaps in practice through clear, Switzerland-specific recommendations for testing and dosing regimens would not only enhance individual patient care but also contribute to broader public health goals. Ensuring that optimal vitamin D levels are achievable for diverse patient populations remains a critical priority.

.....

Conflict of interest

The authors have declared that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

All authors have declared that no financial support was received from any organization for the submitted work.

Author contributions

All authors contributed to and approved the final manuscript.

Submitted: November 19, 2024 CEST. Accepted: December 20, 2024 CEST. Published: December 23, 2024 CEST.



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-SA-4.0). View this license's legal deed at <https://creativecommons.org/licenses/by-nc-sa/4.0> and legal code at <https://creativecommons.org/licenses/by-nc-sa/4.0/legalcode> for more information.

REFERENCES

1. Máčová L, Bičková M. Vitamin D: Current Challenges between the Laboratory and Clinical Practice. *Nutrients*. 2021;13(6):1758. doi:[10.3390/nu13061758](https://doi.org/10.3390/nu13061758)
2. Pilz S, Zittermann A, Trummer C, et al. Vitamin D testing and treatment: a narrative review of current evidence. *Endocr Connect*. 2019;8(2):R27-R43. doi:[10.1530/ec-18-0432](https://doi.org/10.1530/ec-18-0432)
3. Calcaterra V, Cena H, De Giuseppe R, et al. An Adapted Questionnaire Tailored for Assessing the Risk of Vitamin D Deficiency in Children That Is Proving Useful in Guiding Clinical Interventions. *Nutrients*. 2024;16(7):971. doi:[10.3390/nu16070971](https://doi.org/10.3390/nu16070971)
4. Guessous I, Dudler V, Glatz N, et al. Vitamin D levels and associated factors: a population-based study in Switzerland. *Swiss Med Wkly*. 2012;142:0. doi:[10.4414/smw.2012.13719](https://doi.org/10.4414/smw.2012.13719)
5. Federal Commission for Nutrition. Vitamin D deficiency: Evidence, safety, and recommendations for the Swiss population. BLV. http://www.blv.admin.ch/dam/blv/en/dokumente/das-blv/organisation/kommissionen/eck/vitamin-d-mangel/ausfuhrlicher-expertenbericht-vitamin-d-mangel.pdf.download.pdf/Vitamin_D_Bericht.pdf
6. Essig S, Merlo C, Reich O, Trottmann M. Potentially inappropriate testing for vitamin D deficiency: a cross-sectional study in Switzerland. *BMC Health Serv Res*. 2020;20(1):1097. doi:[10.1186/s12913-020-05956-2](https://doi.org/10.1186/s12913-020-05956-2)
7. Christoph P, Challande P, Raio L, Surbek D. High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. *Swiss Med Wkly*. 2020;150:w20238. doi:[10.4414/smw.2020.20238](https://doi.org/10.4414/smw.2020.20238)
8. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Dietary reference values for vitamin D. *EFSA*. 2016;14(10):e04547. doi:[10.2903/j.efsa.2016.4547](https://doi.org/10.2903/j.efsa.2016.4547)
9. Slominski A, Kim TK, Zmijewski MA, et al. Novel vitamin D photoproducts and their precursors in the skin. *Dermatoendocrinol*. 2013;5(1):7-19. doi:[10.4161/derm.23938](https://doi.org/10.4161/derm.23938)
10. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. *Dermatoendocrinol*. 2013;5(1):51-108. doi:[10.4161/derm.24494](https://doi.org/10.4161/derm.24494)
11. Phogat S, Dahiya T, Jangra M, Kumari A, Kumar A. Nutritional Benefits of Fish Consumption for Humans: A Review. *Int J Environ*. 2022;12(12):1443-1457. doi:[10.9734/ijec/2022/v12i121585](https://doi.org/10.9734/ijec/2022/v12i121585)
12. Kučan R, Soltirovska Šalamon A, Andronikov D, et al. Dietary Sources of Vitamin D, Vitamin D Supplementation, and Its Bio-Viability. 2018;14(2):115-122. doi:[10.5457/p2005-114.209](https://doi.org/10.5457/p2005-114.209)
13. Alcorta A, Porta A, Tárrega A, Alvarez MD, Vaquero MP. Foods for Plant-Based Diets: Challenges and Innovations. *Foods*. 2021;10(2):293. doi:[10.3390/foods10020293](https://doi.org/10.3390/foods10020293)
14. Mavar M, Sorić T, Bagarić E, Sarić A, Matek Sarić M. The Power of Vitamin D: Is the Future in Precision Nutrition through Personalized Supplementation Plans? *Nutrients*. 2024;16(8):1176. doi:[10.3390/nu16081176](https://doi.org/10.3390/nu16081176)
15. Bikle DD. Vitamin D: Production, Metabolism and Mechanisms of Action. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext [Internet]*. MDText.com, Inc.; 2021.
16. Pop TL, Sîrbe C, Bența G, Mititelu A, Grama A. The Role of Vitamin D and Vitamin D Binding Protein in Chronic Liver Diseases. *Int J Mol Sci*. 2022;23(18):10705. doi:[10.3390/ijms231810705](https://doi.org/10.3390/ijms231810705)
17. Pazirandeh S, Burns D. Overview of vitamin D. UptoDate. Accessed October 2020. <https://www.uptodate.com>

18. Lung BE, Mowery ML, Komatsu DEE. *Calcitriol*. StatPearls Publishing; 2023.
19. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. *Endocrinol Metab Clin North Am*. 2010;39(2):243-253. doi:[10.1016/j.ecl.2010.02.002](https://doi.org/10.1016/j.ecl.2010.02.002)
20. de Brito Galvao JF, Nagode LA, Schenck PA, Chew DJ. Calcitriol, calcidiol, parathyroid hormone, and fibroblast growth factor-23 interactions in chronic kidney disease. *J Vet Emerg Crit Care (San Antonio)*. 2013;23(2):134-162. doi:[10.1111/vec.12036](https://doi.org/10.1111/vec.12036)
21. Antwis RE, Browne RK. Ultraviolet radiation and Vitamin D3 in amphibian health, behaviour, diet and conservation. *Comp Biochem Physiol A Mol Integr Physiol*. 2009;154(2):184-190. doi:[10.1016/j.cbpa.2009.06.008](https://doi.org/10.1016/j.cbpa.2009.06.008)
22. Bouillon R, Schuit F, Antonio L, Rastinejad F. Vitamin D Binding Protein: A Historic Overview. *Front Endocrinol (Lausanne)*. 2020;10:910. doi:[10.3389/fendo.2019.00910](https://doi.org/10.3389/fendo.2019.00910)
23. Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and Novel Actions. *Ann Nutr Metab*. 2018;72(2):87-95. doi:[10.1159/000486536](https://doi.org/10.1159/000486536)
24. Haussler MR, Whitfield GK, Kaneko I, et al. Molecular mechanisms of vitamin D action. *Calcif Tissue Int*. 2013;92(2):77-98. doi:[10.1007/s00223-012-9619-0](https://doi.org/10.1007/s00223-012-9619-0)
25. Fleet JC. Vitamin D-Mediated Regulation of Intestinal Calcium Absorption. *Nutrients*. 2022;14(16):3351. doi:[10.3390/nu14163351](https://doi.org/10.3390/nu14163351)
26. Schreier K. Hormonal regulation of calcium metabolism and regulation of hormone secretion by Ca²⁺. *Monatsschr Kinderheilkd*. 1983;131(5):244-250.
27. Donati S, Palmini G, Aurilia C, et al. Calcifediol: Mechanisms of Action. *Nutrients*. 2023;15(20):4409. doi:[10.3390/nu15204409](https://doi.org/10.3390/nu15204409)
28. Conrard L, Tyteca D. Regulation of Membrane Calcium Transport Proteins by the Surrounding Lipid Environment. *Biomolecules*. 2019;9(10):513. doi:[10.3390/biom9100513](https://doi.org/10.3390/biom9100513)
29. Jeon US. Kidney and calcium homeostasis. *Electrolyte Blood Press*. 2008;6(2):68-76. doi:[10.5049/ebp.2008.6.2.68](https://doi.org/10.5049/ebp.2008.6.2.68)
30. Li Y, Zhao P, Jiang B, et al. Modulation of the vitamin D/vitamin D receptor system in osteoporosis pathogenesis: insights and therapeutic approaches. *J Orthop Surg Res*. 2023;18(1):860. doi:[10.1186/s13018-023-04320-4](https://doi.org/10.1186/s13018-023-04320-4)
31. Danik JS, Manson JE. Vitamin D and cardiovascular disease. *Curr Treat Options Cardiovasc Med*. 2012;14(4):414-424. doi:[10.1007/s11936-012-0183-8](https://doi.org/10.1007/s11936-012-0183-8)
32. Sizar O, Khare S, Goyal A, Givler A. Vitamin D Deficiency. In: *StatPearls [Internet]*. StatPearls Publishing; 2023.
33. Dahash BA, Sankararaman S. Rickets. In: *StatPearls [Internet]*. StatPearls Publishing; 2023.
34. Schafer AL, Shoback DM. Hypocalcemia: Diagnosis and Treatment. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext [Internet]*. MDText.com, Inc.; 2016.
35. Zimmerman L, Anastasopoulou C, McKeon B. Osteomalacia. In: *StatPearls [Internet]*. StatPearls Publishing; 2024.
36. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. (Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds.). National Academies Press (US); 2011.
37. Maier GS, Weissenberger M, Rudert M, Roth KE, Horas K. The role of vitamin D and vitamin D deficiency in orthopaedics and traumatology-a narrative overview of the literature. *Ann Transl Med*. 2021;9(11):942. doi:[10.21037/atm-21-779](https://doi.org/10.21037/atm-21-779)
38. Scott D, Sanders KM, Ebeling PR. Vitamin D, Muscle Function, and Falls in Older Adults: Does Reduced Deposition of Intramuscular Adipose Tissue Influence the Relationship? *J Clin Endocrinol & Metab*. 2013;98(10):3968-3970. doi:[10.1210/jc.2013-2560](https://doi.org/10.1210/jc.2013-2560)

39. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet*. 2019;393(10169):364-376. doi:[10.1016/s0140-6736\(18\)32112-3](https://doi.org/10.1016/s0140-6736(18)32112-3)
40. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. *Best Pract Res Clin Endocrinol Metab*. 2011;25(4):585-591. doi:[10.1016/j.beem.2011.05.002](https://doi.org/10.1016/j.beem.2011.05.002)
41. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79(3):362-371. doi:[10.1093/ajcn/79.3.362](https://doi.org/10.1093/ajcn/79.3.362)
42. Malik MZ, Latiwesh OB, Nouh F, Hussain A, Kumar S, Kaler J. Response of Parathyroid Hormone to Vitamin D Deficiency in Otherwise Healthy Individuals. *Cureus*. 2020;12(8):e9764. doi:[10.7759/cureus.9764](https://doi.org/10.7759/cureus.9764)
43. Holick MF. Vitamin D and sunlight: strategies for cancer prevention and other health benefits. *Clin J Am Soc Nephrol*. 2008;3(5):1548-1554. doi:[10.2215/cjn.01350308](https://doi.org/10.2215/cjn.01350308)
44. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004;80(suppl_6):1678S-88S. doi:[10.1093/ajcn/80.6.1678S](https://doi.org/10.1093/ajcn/80.6.1678S)
45. Webb AR, Engelsen O. Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochem Photobiol*. 2008;82(6):1697-1703. doi:[10.1111/j.1751-1097.2006.tb09833.x](https://doi.org/10.1111/j.1751-1097.2006.tb09833.x)
46. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Altern Med Rev*. 2008;13(1):6-20.
47. Rabenberg M, Scheidt-Nave C, Busch MA, Rieckmann N, Hintzpeter B, Mensink GB. Vitamin D status among adults in Germany-results from the German Health Interview and Examination Survey for Adults (DEGS1). *BMC Public Health*. 2015;15:641. doi:[10.1186/s12889-015-2016-7](https://doi.org/10.1186/s12889-015-2016-7)
48. Madronich S. The Atmosphere and UV-B Radiation at Ground Level. *Environmental UV Photobiology*. 1993;1-39. doi:[10.1007/978-1-4899-2406-3_1](https://doi.org/10.1007/978-1-4899-2406-3_1)
49. Davis S, Capjack L, Kerr N, Fedosejevs R. Clothing as protection from ultraviolet radiation: which fabric is most effective? *Int J Dermatol*. 1997;36(5):374-379. doi:[10.1046/j.1365-4362.1997.00046.x](https://doi.org/10.1046/j.1365-4362.1997.00046.x)
50. Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab*. 1987;64(6):1165-1168. doi:[10.1210/jcem-64-6-1165](https://doi.org/10.1210/jcem-64-6-1165)
51. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. *Photochem Photobiol*. 2008;84(3):539-549. doi:[10.1111/j.1751-1097.2007.00226.x](https://doi.org/10.1111/j.1751-1097.2007.00226.x)
52. Webb AR, Decosta BR, Holick MF. Sunlight Regulates the Cutaneous Production of Vitamin D3 by Causing Its Photodegradation. *J Clin Endocrinol & Metab*. 1989;68(5):882-887. doi:[10.1210/jcem-68-5-882](https://doi.org/10.1210/jcem-68-5-882)
53. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest*. 1985;76(4):1536-1538. doi:[10.1172/jci112134](https://doi.org/10.1172/jci112134)
54. Thompson GR, Lewis B, Booth CC. Absorption of vitamin D3-3H in control subjects and patients with intestinal malabsorption. *J Clin Invest*. 1966;45(1):94-102. doi:[10.1172/jci105327](https://doi.org/10.1172/jci105327)
55. Zuvarox T, Belletieri C. Malabsorption Syndromes. In: *StatPearls [Internet]*. StatPearls Publishing; 2023.
56. Alzohily B, AlMenhali A, Gariballa S, et al. Unraveling the complex interplay between obesity and vitamin D metabolism. *Sci Rep*. 2024;14(1):7583. doi:[10.1038/s41598-024-58154-z](https://doi.org/10.1038/s41598-024-58154-z)
57. Puhl RM, Heuer CA. Obesity Stigma: Important Considerations for Public Health. *Am J Public Health*. 2010;100(6):1019-1028. doi:[10.2105/ajph.2009.159491](https://doi.org/10.2105/ajph.2009.159491)

58. Lu S, Cao ZB. Interplay between Vitamin D and Adipose Tissue: Implications for Adipogenesis and Adipose Tissue Function. *Nutrients*. 2023;15(22):4832. doi:[10.3390/nu15224832](https://doi.org/10.3390/nu15224832)
59. Gröber U, Kisters K. Influence of drugs on vitamin D and calcium metabolism. *Dermatoendocrinol*. 2012;4(2):158-166. doi:[10.4161/derm.20731](https://doi.org/10.4161/derm.20731)
60. Kim CS, Kim SW. Vitamin D and chronic kidney disease. *Korean J Intern Med*. 2014;29(4):416-427. doi:[10.3904/kjim.2014.29.4.416](https://doi.org/10.3904/kjim.2014.29.4.416)
61. Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int*. 2006;69(1):33-43. doi:[10.1038/sj.ki.5000045](https://doi.org/10.1038/sj.ki.5000045)
62. Williams S, Malatesta K, Norris K. Vitamin D and chronic kidney disease. *Ethn Dis*. 2009;19(4 suppl_5):S5-8-11.
63. Veldurthy V, Wei R, Campbell M, Lupicki K, Dhawan P, Christakos S. 25-Hydroxyvitamin D₃ 24-Hydroxylase: A Key Regulator of 1,25(OH)₂D₃ Catabolism and Calcium Homeostasis. *Vitam Horm*. 2016;100:137-150. doi:[10.1016/bs.vh.2015.10.005](https://doi.org/10.1016/bs.vh.2015.10.005)
64. Werner A, Kuipers F, Verkade HJ. Fat Absorption and Lipid Metabolism in Cholestasis. In: *Madame Curie Bioscience Database [Internet]*. Landes Bioscience; 2000–2013.
65. Nair S. Vitamin d deficiency and liver disease. *Gastroenterol Hepatol (N Y)*. 2010;6(8):491-493.
66. Yousefzadeh P, Shapses SA, Wang X. Vitamin D Binding Protein Impact on 25-Hydroxyvitamin D Levels under Different Physiologic and Pathologic Conditions. *Int J Endocrinol*. 2014;2014:981581. doi:[10.1155/2014/981581](https://doi.org/10.1155/2014/981581)
67. Thacher TD, Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc*. 2011;86(1):50-60. doi:[10.4065/mcp.2010.0567](https://doi.org/10.4065/mcp.2010.0567)
68. Mousavi SE, Amini H, Heydarpour P, Amini Chermahini F, Godderis L. Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: Evidence and potential mechanisms. *Environ Int*. 2019;122:67-90. doi:[10.1016/j.envint.2018.11.052](https://doi.org/10.1016/j.envint.2018.11.052)
69. Wootton AM. Improving the measurement of 25-hydroxyvitamin D. *Clin Biochem Rev*. 2005;26(1):33-36.
70. Vitamin D. Fact Sheet for Health Professionals. National Institutes of Health. <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>
71. Ross AC, Manson JE, Abrams SA, 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(1):53-58. doi:[10.1210/jc.2010-2704](https://doi.org/10.1210/jc.2010-2704)
72. Vitamin and mineral requirements in human nutrition. IRIS. <https://iris.who.int/handle/10665/42716>
73. Religi A, Backes C, Chatelan A, et al. Estimation of exposure durations for vitamin D production and sunburn risk in Switzerland. *J Expo Sci Environ Epidemiol*. 2019;29(6):742-752. doi:[10.1038/s41370-019-0137-2](https://doi.org/10.1038/s41370-019-0137-2)
74. Teixeira Farinha H, Bouriez D, Grimaud T, et al. Gastro-Intestinal Disorders and Micronutrient Deficiencies following Oncologic Esophagectomy and Gastrectomy. *Cancers (Basel)*. 2023;15(14):3554. doi:[10.3390/cancers15143554](https://doi.org/10.3390/cancers15143554)
75. Bischoff-Ferrari HA, Keller UO, Burckhardt P, et al. Empfehlungen der Eidgenössischen Ernährungskommission zur Vitamin-D-Zufuhr für die Schweizer Bevölkerung. *Swiss Med Forum*. 2012;12(40):775-778. doi:[10.5167/uzh-73000](https://doi.org/10.5167/uzh-73000)

76. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911-1930. doi:[10.1210/jc.2011-0385](https://doi.org/10.1210/jc.2011-0385)
77. Gowda U, Ruwanpathirana T, Fong DP, Kaur A, Renzaho AM. Efficacy of high dose vitamin D supplementation in improving serum 25(OH) D among migrant and non migrant population: a retrospective study. *BMC Health Serv Res.* 2016;16(1):579. doi:[10.1186/s12913-016-1798-3](https://doi.org/10.1186/s12913-016-1798-3)
78. Annex 3 of the Health Care Services Ordinance (KLV): List of analyses. https://www.bag.admin.ch/dam/bag/de/dokumente/kuv-leistungen/leistungen-und-tarife/Analysenliste/al_aenderungen_020622_pdf.PDF.download.PDF/Analysenliste,%20%C3%84nderungen%20vom%202.%20Juni%202022%20per%201.%20Juli%202022.PDF
79. LeFevre ML, U.S. Preventive Services Task Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2015;162(2):133-140. doi:[10.7326/M14-2450](https://doi.org/10.7326/M14-2450)
80. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999;69(5):842-856. doi:[10.1093/ajcn/69.5.842](https://doi.org/10.1093/ajcn/69.5.842)
81. Harvey NC, Holroyd C, Ntani G, et al. Vitamin D supplementation in pregnancy: a systematic review. *Health Technol Assess.* 2014;18(45):1-190. doi:[10.3310/hta18450](https://doi.org/10.3310/hta18450)
82. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266-281. doi:[10.1056/NEJMr070553](https://doi.org/10.1056/NEJMr070553)
83. Wheeler DC, Winkelmayer WC. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl (2011).* 2017;7(1):1-59. doi:[10.1016/j.kisu.2017.04.001](https://doi.org/10.1016/j.kisu.2017.04.001)
84. O'Sullivan ED, Hughes J, Ferenbach DA. Renal aging: causes and consequences. *J Am Soc Nephrol.* 2017;28(2):407-420. doi:[10.1681/ASN.2015121308](https://doi.org/10.1681/ASN.2015121308)