



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

Wytyczne suplementacji witaminą D dla Europy Środkowej — rekomendowane dawki witaminy D dla populacji zdrowej oraz dla grup ryzyka deficytu witaminy D

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Abstract

Introduction: Adequate Vitamin D intake and its concentration in serum are important for bone health and calcium–phosphate metabolism as well as for optimal function of many organs and tissues. Documented trends in lifestyle, nutritional habits and physical activity appear to be associated with moderate or severe Vitamin D deficits resulting in health problems. Most epidemiological studies suggest that Vitamin D deficiency is prevalent among Central European populations. Concern about this problem led to the organising of a conference focused on overcoming Vitamin D deficiency.

Methods: After reviewing the epidemiological evidence and relevant literature, a Polish multidisciplinary group formulated theses on recommendations for Vitamin D screening and supplementation in the general population. These theses were subsequently sent to Scientific Committee members of the 'Vitamin D — minimum, maximum, optimum' conference for evaluation based on a ten-point scale. With 550 international attendees, the meeting 'Vitamin D — minimum, maximum, optimum' was held on October 19–20, 2012 in Warsaw (Poland). Most recent scientific evidence of both skeletal and non-skeletal effects of Vitamin D as well as the results of panellists' voting were reviewed and discussed during eight plenary sessions and two workshops.

Results: Based on many polemical discussions, including post-conference networking, the key opinion leaders established ranges of serum 25-hydroxyvitamin D concentration indicating Vitamin D deficiency [< 20 ng/mL (< 50 nmol/L)], suboptimal status [20–30 ng/mL (50–75 nmol/L)], and target concentration for optimal Vitamin D effects [30–50 ng/mL (75–125 nmol/L)]. General practical guidelines regarding supplementation and updated recommendations for prophylactic Vitamin D intakes in Central European neonates, infants, children and adolescents as well as in adults (including recommendations for pregnant and breastfeeding women and the elderly) were developed.

Conclusions: Improving the Vitamin D status of children, adolescents, adults and the elderly must be included in the priorities of physicians, healthcare professionals and healthcare regulating bodies. The present paper offers elaborated consensus on supplementation guidance and population strategies for Vitamin D in Central Europe. (*Endokrynol Pol* 2013; 64 (4): 319–327)

Key words: vitamin D deficiency, 25-hydroxyvitamin-D, general population guidelines, risk groups, Central Europe, supplementation

Streszczenie

Wstęp: Wyniki badań z ostatnich lat dokumentują wiele korzyści wynikających z działania witaminy D na organizm człowieka na wszystkich etapach jego życia. Większość badań epidemiologicznych sugeruje, że niedobór witaminy D jest powszechny wśród mieszkańców Europy Środkowej. Naturalną konsekwencją tej sytuacji jest konieczność ciągłego uświadamiania społeczeństwu oraz środowisku medycznemu, jaką rolę odgrywa witamina D w rozwoju i funkcjonowaniu organizmu ludzkiego.

Metody: Na podstawie przeglądu danych literaturowych Polski Zespół Wielodyscyplinarny opracował tezy dotyczące zasad suplementacji witaminą D, które przesłano do członków Komitetu Naukowego konferencji „Witamina D — minimum, maksimum, optimum”, 19–20 Październik, 2012, Warszawa. W trakcie powyższej konferencji z udziałem 550 delegatów oraz Ekspertów różnych dziedzin medycyny omówiono i przedyskutowano propozycje wytycznych suplementacji witaminą D populacji Europy Środkowej.

Wyniki. W efekcie przeprowadzonych dyskusji Zespół Ekspertów opracował wytyczne suplementacji witaminą D dla wszystkich grup wiekowych populacji Europy Środkowej. Określono również kryteria diagnostyczne charakteryzujące stan zaopatrzenia organizmu w witaminę D: deficyt witaminy D ustalono jako stężenie 25(OH)D < 20 ng/mL (< 50 nmol/L)], suboptymalne zaopatrzenie jako stężenie 25(OH)D wynoszące 20–30 ng/mL (50–75 nmol/L), a stężenie 30–50 ng/mL (75–125 nmol/L) uznano za docelowe dla zapewnienia efektu plejotropowego witaminy D.

Wnioski. Poprawa obecnego stanu zaopatrzenia witaminy D w grupach dzieci, młodzieży, osób aktywnych zawodowo i seniorów powinna zostać włączona do priorytetów polityki zdrowotnej społeczeństw Europy Środkowej. (*Endokrynol Pol* 2013; 64 (4): 319–327)

Słowa kluczowe: niedobór witaminy D, 25-hydroksywitamina D, wytyczne populacyjne, grupy ryzyka, suplementacja

Introduction

Recent reports have found several positive effects of Vitamin D for humans of all ages. Until recently, deficits of Vitamin D were associated mostly with the risk of developing rickets [1]. Current research, however, considers reduced Vitamin D concentration as a potential significant risk factor for diseases such as cancer [2–4], cardiovascular disease [5–7], diabetes [8–10], hypertension [11–13], autoimmune diseases [14–16], metabolic disorders [17, 18], infectious diseases caused by decreased immunity [19], and some neuropsychiatric conditions [20]. An increasing body of evidence of Vitamin D's beneficial effects prompted the development of nationwide recommendations to prevent

Vitamin D deficiency in Poland (2009), Hungary (2012) and Germany–Austria–Switzerland (2012) [21–23]. Furthermore, the Institute of Medicine of the U.S. National Academies published 'Dietary Reference Intakes for Calcium and Vitamin D' (2010) which were extensively discussed by the Endocrine Society which issued its own guidelines (2011) [24, 25]. In 2010, the International Osteoporosis Foundation released a position paper on recommendations for Vitamin D nutrition in elderly men and women [26]. In 2012, the European Food Safety Authority released the revised Tolerable Upper Intake Levels (upper limits [ULs]) of Vitamin D for all relevant population groups [27].

Unfortunately, despite available recommendations on Vitamin D supplementation and its ULs, daily Vita-

min D intake is rigorously preserved only during the first months of life; later in life, Vitamin D is given only occasionally, if at all. The evident consequence is low average Vitamin D concentration among populations of Central Europe, indicating a need for continuous awareness by the public and the medical community. Adequate Vitamin D status is associated with the overall health of infants, children, adolescents, professionally active people and the elderly. By contrast, inadequate Vitamin D concentration (even if considered an epiphenomenon) is frequently noted in patients suffering from a wide spectrum of diseases [1–20].

The Vitamin D doses recommended here are based on both well-documented skeletal effects and an increasing number of well-designed studies suggesting extra-skeletal effects. These recommendations apply not only in the context of preventing rickets or osteoporosis, but also in a broader context of preventive action against many disorders and morbidities that affect people of all ages. The main goal of proper Vitamin D supplementation is to ensure an adequate serum 25-hydroxyVitamin D [25(OH)D] concentration and, thereby, to guarantee short- and long-term effects, with appropriate safety considerations.

Sources of Vitamin D

Adequate Vitamin D intake, positive calcium balance and outdoor physical activity i.e. weight-bearing exercise are essential for appropriate skeletal growth and bone mineralisation. These environmental factors also show a liability to reduce risk of several diseases. A diverse diet rich in food containing large amounts of Vitamin D, including oily fish, is important (Table I). If the additive effect of dietary Vitamin D consumption and sunlight-induced Vitamin D synthesis in the skin is insufficient, taking supplements becomes essential to achieve optimal Vitamin D status. Because the circulating metabolite of Vitamin D has a long serum half-life (4–6 weeks) and is stored in tissues, Vitamin D can be administered other than once per day — for example, every other day, twice per week, or once weekly. This flexibility answers the technical problems of dividing drops and the higher-than-required dose of available commercial preparations.

Most Vitamin D in the human body is produced in the skin after exposure to sunlight, specifically solar ultraviolet-B irradiance. Sunscreens, which are widely used in Europe during the summer, may reduce skin synthesis by 90–95% [28]. In Central Europe, solar angle and weather conditions suitable for Vitamin D synthesis occur between late April and early September; whereas skin synthesis does not occur from

Table I. Sources of vitamin D

Tabela I. Źródła witaminy D

Source	Vitamin d content
Cod liver oil	~400–1,000 IU/tsp
Eel, fresh	~1,200 IU/100 g
Salmon, fresh wild caught	~600–1,000 IU/100 g
Herring in oil	~800 IU/100 g
Pickled herring	~480 IU/100 g
Salmon, fresh farmed	~100–250 IU/100 g
Salmon, tinned	~300–600 IU/100 g
Sardines, tinned	~300 IU/100 g
Mackerel, tinned	~250 IU/100 g
Tuna, tinned	~230 IU/100 g
Shiitake mushrooms, fresh	~100 IU/100 g
Egg yolk	~20–50 IU/yolk
Cheese	~7–28 IU/ 100 g
Breast milk	~1.5–8 IU/100 mL
Cow's milk	~0.4–1.2 IU/100 mL
Milk-corny gruels	~60–80 IU/100 mL
Infant formula (beginning formula)	~40–50 IU/100 mL
Infant formula (follow-up formula)	~40–80 IU/100 mL
Formula for children aged 12 months or older	~70–80 IU/100 mL
Skin synthesis/UVB radiation	Exposure of arms and legs to 0.25–0.50 minimal erythral dose (MED) is estimated equivalent of ~2,000–4,000 IU Vitamin D3.

October to March [29]. The efficacy of skin synthesis basically depends on two factors: the degree of skin pigmentation and age. For optimal effect, Central Europeans should expose, without sunscreen, 18% of the body surface (i.e. uncovered forearms and partially exposed legs) to a half of one minimal erythral dose (MED, defined as slight reddening of skin 24 h post exposure) two or three times per week. In practical terms, exposing 18% of the body to the sun without sunscreen for approximately 15 minutes a day between 10 a.m. and 3 p.m. is likely to be adequate for fair-skinned Central Europeans. The advantages and disadvantages of sun exposure must be balanced, at least during summer, because excessive sun exposure is a potential risk factor for skin cancer [30]. Direct exposure to the sun is not recommended for infants younger than six months. Experiencing many severe sunburns up to young adulthood is considered a serious risk factor for skin cancer. Sun exposure is not recommended for people with skin type 1 (pale white

skin, blue eyes, red hair) or with a history of sunburns or a history of skin cancer in the family.

Recommended Vitamin D intakes in the general population

1. Neonates and infants (0–12 months):

- vitamin D supplementation should be introduced from the first days of life, irrespective of nutritional option (breastfeeding or/and formula-based nutrition);
- supplementation of 400 IU/day (10.0 µg/day) up to age 6 months;
- supplementation of 400–600 IU/day (10.0–15.0 µg/day) between 6 and 12 months of age depending on daily Vitamin D intake from diet.

2. Children and adolescents (1–18 years):

- supplementation of 600–1,000 IU/day (15.0–25.0 µg/day), depending on body weight, is recommended between September and April;
- supplementation of 600–1,000 IU/day (15.0–25.0 µg/day), depending on body weight, is recommended throughout the whole year, if sufficient skin synthesis of Vitamin D is not ensured in the summer.

3. Adults (> 18 years) and the elderly:

- supplementation of 800–2,000 IU/day (20.0–50.0 µg/day), depending on body weight, is recommended between September and April;
- supplementation of 800–2,000 IU/day (20.0–50.0 µg/day), depending on body weight, is recommended throughout the whole year, if sufficient skin synthesis of Vitamin D is not ensured in the summer;
- the elderly (65 years and above) should be supplemented with 800–2,000 IU/day (20.0–50.0 µg/day) throughout the whole year, because of the reduced efficacy of Vitamin D skin synthesis.

4. Pregnant and breastfeeding women:

- women who plan pregnancy should start/maintain Vitamin D supplementation as recommended for adults. Adequate Vitamin D intake before pregnancy should be ensured;
- vitamin D supplementation of 1,500–2,000 IU/day (37.5–50.0 µg/day) should begin at least from the second trimester of pregnancy. Gynaecologists/obstetricians should consider starting Vitamin D supplementation for pregnant women soon after pregnancy is confirmed;
- if feasible, periodical monitoring of serum 25(OH)D concentration should be done to define optimum dosage and to verify efficacy of supplementation. The goal of supplementation is to achieve and maintain 25(OH)D concentration of 30–50 ng/mL (75–125 nmol/L).

Recommended Vitamin D intakes in groups at risk of Vitamin D deficiency

1. Premature infants:

- vitamin D supplementation should be introduced from the first days of life (as soon as enteral feeding is possible);
- supplementation of 400–800 IU/day (10–20 µg/day) until accomplishing the corrected gestational age of 40 weeks should be warranted; thereafter, the recommendations as for normal-term infants are adequate.

2. Obese children and adolescents (BMI > 90th percentile for age and gender using local reference in a given country):

- Supplementation of 1,200–2,000 IU/day (30–50 µg/day), depending on severity of obesity, is recommended between September and April.
- Supplementation of 1,200–2,000 IU/day (30–50 µg/day), depending on severity of obesity, is recommended throughout the whole year, if sufficient skin synthesis of Vitamin D is not ensured in the summer.

3. Obese adults and the elderly (BMI 30+ kg/m²):

- supplementation of 1,600–4,000 IU/day (40–100 µg/day), depending on severity of obesity, is recommended throughout the whole year;
- sensible exposure to sunlight in the context of additional oral Vitamin D intake is safe.

4. Night workers and dark-skinned adults:

- supplementation of 1,000–2,000 IU/day (25–50 µg/day), depending on body weight, is recommended throughout the whole year for dark-skinned persons;
- supplementation of 1,000–2,000 IU/day (25–50 µg/day), depending on body weight, is recommended for night workers throughout the whole year.

Recommended tolerable UL values for Vitamin D intake in the general population

The tolerable UL value is the highest average daily Vitamin D oral intake likely to pose no risk of adverse effects for Central European populations during growth and maturation, adulthood and ageing. The UL for Vitamin D does matter in healthy individuals, whereas at least two diseases should be considered as exceptions from the general rule, i.e.:

- Granulomatous conditions (e.g. sarcoidosis), with excessive extrarenal 1- α -hydroxylase (CYP27B1) expression, excessive uncontrolled 1,25-dihydroxyvitamin D (calcitriol) production causing hypercalcemia at relatively low serum 25(OH)D concentration [33]; in granulomatous conditions, the

recommended target for serum 25(OH)D concentration is approximately 25 ng/mL (62.5 nmol/L) [31].

- Genetic absence of, or defective, 24-hydroxylase (CYP24A1) activity (as in idiopathic infantile hypercalcemia, which can remain unnoticed until adulthood and cause nephrolithiasis in later life), a situation that compromises the ability of the kidneys or target cells to destroy 25-hydroxy-Vitamin D or calcitriol, leading to hypercalciuria and/or hypercalcemia at relatively 'normal' 25(OH)D concentrations [32]

The Panel of Experts adopted the European Food Safety Authority scientific opinion on the Tolerable Upper Intake Levels of Vitamin D for all relevant population groups, except obese adults and the elderly [27]. The highest average daily Vitamin D intakes likely to pose no risk of adverse effects are as follows:

- For neonates and infants, 1,000 IU/day (25 µg/day);
- For children aged 1–10 years, 2,000 IU/day (50 µg/day);
- For children and adolescents aged 11–18 years, 4,000 IU/day (100 µg/day);
- For adults and the elderly with normal body weight, 4,000 IU/day (100 µg/day);
- For obese adults and obese elderly people, 10,000 IU/day (250 µg/day);
- For both pregnant and breastfeeding women, 4,000 IU/day (100 µg/day).

Recommended therapeutic doses for patients with verified Vitamin D deficiency

Assessment of Vitamin D status and diagnostic criteria

The serum concentration of 25(OH)D — the main measurable circulating Vitamin D metabolite — indicates Vitamin D status. Total 25(OH)D concentration reflects delivery of Vitamin D from both cutaneous and oral sources. The 25(OH)D serum concentration is expressed in nanograms per millilitre or nanomoles per litre (1 ng/mL = 2.5 nmol/L). Recent analytical methods are, in general, applied by fully automated platforms used in routine clinical chemistry laboratories. For routine/clinical 25(OH)D testing, we recommend methods that measure both 25(OH)D₂ and 25(OH)D₃, giving a total 25(OH)D serum concentration value, with an intra-assay coefficient of variation of less than 5% and an interassay coefficient of variation of less than 10%. The best assays provide total 25(OH)D concentration, excluding a recently discovered metabolite, 3-epi-25(OH)D₃ [33, 34].

The diagnostics thresholds defining concentrations of serum 25(OH)D approved in Central Europe are as follows:

- concentrations below 20 ng/mL (50 nmol/L) indicate Vitamin D deficiency, which should be treated medically;
- concentrations of 20 ng/mL (50 nmol/L) up to 30 ng/mL (75 nmol/L) reflect a suboptimal Vitamin D status that calls for a moderate increase of Vitamin D daily dose;
- concentrations higher than 30 ng/mL (75 nmol/L) up to 50 ng/mL (125 nmol/L) reflect adequate Vitamin D status; the supplementation scheme and dose should be maintained;
- concentrations higher than 50 ng/mL (125 nmol/L) up to 100 ng/mL (250 nmol/L) indicate a high Vitamin D supply; the supplementation dose can be maintained for lower concentrations of this range or moderately decreased for higher concentrations;
- concentrations higher than 100 ng/mL (250 nmol/L) are risky for overall health outcomes and need reduction/cessation of Vitamin D supplementation until obtaining target 25(OH)D concentration;
- concentrations higher than 200 ng/mL (500 nmol/L) are considered toxic and require cessation of Vitamin D supplementation until obtaining target 25(OH)D concentration; such people may need specific medical intervention to correct toxic effects.

Indications for 25(OH)D testing

There are various clinical circumstances and conditions, involving all age groups, in which serum 25(OH)D measurements are justified. Vitamin D deficiency accompanies e.g. renal or liver malfunctions, malabsorption, maldigestion syndromes and obesity, and it can coexist with various treatments (e.g. with anticonvulsants, glucocorticoids, ketoconazole). Untreated Vitamin D deficiency can significantly reduce the effectiveness of such underlying therapy or modify the course of a disease.

We recommend 25(OH)D testing in:

- patients with rickets, osteomalacia, musculoskeletal pain, propensity to falls, idiopathic and secondary osteoporosis including patients with osteoporotic fractures, and history of low-energy fractures of different origin;
- patients with calcium/phosphate metabolism abnormalities;
- patients with hyperparathyroidism;
- patients with prolonged glucocorticoid therapy at the dose of 7 mg of prednisone per day or higher;
- patients taking anticonvulsant medications;
- patients taking ketoconazole;
- patients taking anti-AIDS medications (antiretroviral therapy);

- patients with malabsorption syndromes (coeliac disease, Crohn's disease, past gastrointestinal bypass surgery, cystic fibrosis, inflammatory bowel disease);
- patients treated with long-lasting elimination diets implemented for the management of cow's milk allergy, lactose intolerance/hypolactasia; total parenteral nutrition; eating disorders;
- patients with chronic kidney disease stage 3–5 and kidney transplant recipients
- patients with hepatic failure and/or cholestasis;
- patients with granulomatous disorders (tuberculosis, sarcoidosis);
- patients with different types of cancer;
- patients with cardiovascular diseases, especially hypertension;
- patients with some chronic autoimmune diseases (multiple sclerosis, psoriasis, rheumatoid arthritis, dermatomyositis, lupus/SLE);
- patients admitted to hospital because of some infections (hepatitis C, recurrent acute lower respiratory tract infection) and chronic allergic diseases such as atopic dermatitis or atopic asthma.

Treatment

Individuals with diagnosed Vitamin D deficiency require higher doses of Vitamin D than those recommended for the general population. The therapeutic dose in severe depletion should be 1,000–10,000 IU/day (~50,000 IU/week), depending on the patient's age and body weight. Loading doses of 300,000 IU and higher are not recommended, even for the treatment of severe deficiency [35]. The duration of supplementation usually varies from 1–3 months, depending on the severity of Vitamin D deficiency. After a patient achieves the 25(OH)D concentration of 30–50 ng/mL (75–125 nmol/L), a maintenance dose may be instituted. It is reasonable to reevaluate 25(OH)D concentration after 3–4 months and then to monitor semi-annually, especially with the coincidence of exacerbating factors such as obesity that need therapeutic doses covering the upper range of standard dosage. In cases with severe deficits, monitoring of serum calcium and phosphate concentrations, total alkaline phosphatase (ALP) activity and calciuria rate in spot urine (Ca/CR ratio) may be desirable.

Analogues such as 1α -(OH) D_3 , $1\alpha,25$ (OH) $_2D_3$, 19-nor- $1\alpha,25$ (OH) $_2D_3$, 1α -(OH) D_2 , 22-oxa- $1\alpha,25$ (OH) $_2D_3$, 22-oxa- $1\alpha,25$ (OH) $_2D_3$, and others should not be used to manage Vitamin D deficiency. Analogues may be applied in disorders of Vitamin D hydroxylation associated with chronic renal disease.

Recommended therapeutic doses of Vitamin D (treatment duration lasting 1–3 months):

- for neonates (i.e. younger than one month) with 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), 1,000 IU/day (25 μ g/day)
- for infants aged 1–12 months with 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), 1,000–3,000 IU/day (25–75 μ g/day), depending on body weight
- for children and adolescents aged 1–18 years with 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), 3,000–5,000 IU/day (75–125 μ g/day), depending on body weight
- for adults and the elderly with 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), 7,000–10,000 IU/day (175–250 μ g/day), depending on body weight, or 50,000 IU/week (1250 μ g/week)

The algorithm summarises current recommendations.

Discussion

Recommendations for serum 25(OH)D concentrations and Vitamin D supplementation are based on studies of health outcomes with respect to either serum 25(OH)D concentrations or Vitamin D intakes. Three types of observational studies deal with the analysis of health outcomes with respect to serum 25(OH)D concentrations:

- case-control studies that use serum 25(OH)D concentrations measured at the time of health outcome diagnosis;
- cohort studies that use serum 25(OH)D concentrations measured at the time of enrollment, with health outcome determined after several years of follow-up;
- cross-sectional studies that sample the population and examine correlations between serum 25(OH)D concentrations and health conditions

All three types of study are useful, but each has inconsistencies and different levels of evidence. The health condition in question may influence serum 25(OH)D concentration at the time of diagnosis. However, this possibility seems unlikely for health outcomes that are not known until diagnosed, such as cancer incidence, since there is a smooth, continuous change in cancer incidence rates with respect to follow-up time [36]. Serum 25(OH)D concentration at the time of enrollment in cohort studies may not be the concentration relevant to reducing risk of the health outcome. In addition, as serum 25(OH)D concentrations change over time, the longer the follow-up period, the lower the beneficial effect that is found [36, 37]. In cross-sectional studies, a health condition may considerably influence serum 25(OH)D concentration, for example for those

Table II. Evidence of associations between serum 25(OH)D concentrations above 30 ng/mL and optimal health**Tabela II. Przykłady badań dokumentujących związek między stężeniem 25(OH)D powyżej 30 ng/ml a optymalizacją stanu zdrowia**

Health outcome	Study type/design	25(OH)D concentrations studied	Finding	Reference
Breast cancer incidence	Meta-analysis of five case-control studies of breast cancer incidence	30 ng/mL vs. 10 ng/mL	OR = 0.44	Grant [46]
Colorectal cancer incidence	Meta-analysis of ten case-control and cohort studies of colorectal cancer incidence	30 ng/mL vs. 5 ng/mL	OR = 0.40	Grant [4]
CVD	Prospective study with mean follow-up time of 1.3 years	30 ng/mL vs. < 15 ng/mL	Adjusted HR = 1.62 (95% CI, 1.38–1.89)	Anderson et al. [5]
CVD	Random-effects meta-analysis of nine prospective studies with < 10 years of follow-up	Lowest vs. highest	Pooled relative risk = 1.86 (95% CI, 1.47–2.34) for incident CVD	Wang et al. [6]
Type 2 diabetes mellitus	Meta-analysis of seven prospective studies	> 25 ng/mL vs. <14 ng/mL	RR = 0.57 (95% CI, 0.43–0.76)	Mitri et al. [8]
Type 2 diabetes mellitus,	Prospective observational study with a mean follow-up of 2.7 years in patients with prediabetes	30.1 ng/mL vs. 12.8 ng/mL	HR = 0.72 (95% CI, 0.56–0.90)	Pittas et al. [10]
Cognitive impairment	Elderly women older than 70 years	< 10 ng/mL vs. >30 ng/mL	OR = 1.60 (95% CI, 1.05–2.42)	Slinin et al. [47]
Cognitive decline	Elderly women older than 70 years; cognitive decline 2–4 years after baseline	< 10 ng/mL vs. >30 ng/mL	OR = 1.58 (95% CI, 1.12–2.22) for > 1- σ cognitive decline from mean	Slinin et al. [47]
Hip fracture	Pooled analysis of RCTs	Highest Vitamin D intake (median, 800 IU daily; range, 792–2,000) vs. lowest	HR = 0.70 (95% CI, 0.58–0.86)	Bischoff-Ferrari et al. [43]
Mortality, all-cause	Meta-analysis of 11 prospective studies	Minimum RR near 30–35 ng/mL 25(OH)D vs. lowest 25(OH)D	Relative risk = 0.71 (95% CI, 0.50–0.91)	Zittermann et al. [48]
Respiratory infections, acute viral	Infections in autumn/winter	> 38 ng/mL vs. <38 ng/mL	RR = 0.51 (95% CI, 0.25–0.84)	Sabetta et al. [49]

CI — confidence interval; CVD — cardiovascular disease; HR — hazard ratio; OR — odds ratio; RR — risk ratio

staying indoors due to an illness. Despite several limitations of these studies, they form the primary basis of our understanding of the benefits of Vitamin D for many health outcomes. The results of such studies become more reliable in the context of meta-analyses, which combine all similar using a weighting scheme based on the number of cases in each study.

In addition, ecological studies based on geographic or seasonal variations are meaningful, especially in generating hypotheses, because solar ultraviolet-B is the primary source of Vitamin D for 90% of the population. Examples include geographical variation for many types of cancer [38, 39] and seasonal variation in cancer incidence [40]. A study on cancer incidence with respect to occupation in Nordic countries provides well-balanced evidence that solar UVB reduces risk of many types of cancer [41]. No mechanism other than Vitamin D production has been proposed to explain the findings from ecological studies of cancer incidence

and/or mortality rates with respect to solar UVB doses across countries. Furthermore, there is much additional support elsewhere for the role of Vitamin D in reducing the risk of cancer [3, 4].

Researchers conduct randomised controlled trials (RCTs) to overcome the problems of observational studies. RCTs, however, also demonstrate several methodological issues.

According to Lappe and Heaney [42], a well-conducted RCT should:

- start with a general idea of the relation between serum 25(OH)D concentration and health outcome;
- enroll people near the low end of 25(OH)D concentration;
- give those in the treatment arm enough Vitamin D to increase serum 25(OH)D concentration to the point that little additional benefit is expected;
- measure serum 25(OH)D concentration both at time of enrollment and after supplementation.

Furthermore, as many other sources of Vitamin D exist, studies have to control them all. Unfortunately, most RCTs conducted to date have not followed these guidelines. Several investigations have considered a daily Vitamin D dose of only 400 IU, which confers little health benefit. Nonetheless, a few studies have confirmed some of the findings from observational studies, such as for fractures [43], all-cancer incidence [44], and type A influenza [45], however, this was not consistently shown in all RCTs either.

While RCTs would provide an extra level of confidence to the Vitamin D recommendations, it seems that there is sufficient evidence of the beneficial effects of Vitamin D intake and/or production with very limited adverse effects that the general health of the population would be significantly improved by adopting the recommendations proposed in this paper.

Table II presents an overview of findings from the journal literature regarding health outcomes as a function of serum 25(OH)D concentration or oral Vitamin D intake. The examples chosen were generally derived from recently published papers, with an emphasis on meta-analyses.

Conclusions

There is an urgent need to improve the Vitamin D status of children, adolescents, adults and the elderly. The present paper offers elaborated consensus on supplementation guidance and population strategies for Vitamin D in Central Europe. Prophylaxis of Vitamin D deficiency should be included in the priorities of physicians, medical professionals and healthcare policy-makers.

It is postulated to adopt our practical guidelines on vitamin D supplementation to population of Central Europeans

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