

Vitamin D in Human Health

Pomen vitamina D za zdravje ljudi

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Ključne besede:

vitamin D, priporočeni dnevni vnos, prehrana, dodatki k prehrani

Key words:

vitamin D, recommended daily intake, nutrition, supplements

Članek prispel / Received

3.4.2017

Članek sprejet / Accepted

24.4.2017

Naslov za dopisovanje /

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Izvleček

Vitamin D označuje skupino kemično sorodnih spojin z antirahitičnim delovanjem. Trenutno definiranje optimalnega statusa temelji na določanju serumskih koncentracijah 25-hidroksi vitamina D [25(OH)D]. V organizem se lahko vnese s hrano (predvsem mastno ribo, mlekom, z obogatitvenimi živili ter s prehranskimi dodatki), ali pa se sintetizira v koži po izpostavitvi kože soncu. Vlogo in pomen vitamina D so podrobneje preučili pri rahitisu, ki so ga skoraj izkoreninili s dodajanjem vitamina D prehrani. V zadnjem času je prišlo do ponovnega velika zanimanja za vitamin D, ker so številne opazovalne študije dokazale pomembnost vitamina D, ne samo pri zdravi kostni gostoti, temveč tudi pri kardiovaskularnih, nalezljivih, imunskih, metaboličnih, degenerativnih boleznih in raku. Kljub temu imajo številni zdravi otroci in odrasli pomanjkanje, kar je še bolj izraženo pri posameznikih s kroničnimi boleznimi, predvsem pri boleznih gastrointestinalnega trakta. V prihodnosti bo opredelitev različnih

Abstract

The generic term vitamin D designates a group of chemically related compounds that possess antirachitic activity. Today, the definition of optimal level of vitamin D is based on serum concentrations of 25-hydroxyvitamin D [25(OH)D]. It can be introduced into the organism through ingested food (especially oily fish, milk, with enrichment food and food supplements), or can be dermally synthesized by exposure of the skin to sunlight. Vitamin D deficiency in the past was defined by the clinical recognition of nutritional rickets, a disease nearly eradicated by vitamin D fortification. In addition to its well-recognised role in musculoskeletal health, over the last decade evidence has suggested that low serum concentrations of 25-hydroxyvitamin D, 25(OH)D, are associated with a number of non-skeletal disorders including heart disease, immune and metabolic diseases as well as age-related cognitive decline and cancer. For that reason, there has been a renewed interest in the nutrient vitamin D. Despite its important role in the health,

funkcionalnih učinkov vitamina D omogočila individualiziran pristop k dodajanju vitamina D glede na zdravstveno stanje in tveganje posameznika za določene bolezni ter njegov odgovor na dodajanje vitamina D.

many healthy children and adults are deficient in this important vitamin which is even more pronounced in individuals with chronic diseases, especially of gastro-intestinal tract. The future of vitamin D will likely bring with it a more individualized approach to assessing vitamin D status and needs depending on the health status, the risk of getting particular disease and his response to the addition of vitamin D.

INTRODUCTION

The term vitamin, today a common word in everyday language, was born of a revolution in thinking about the interrelationships of diet and health that occurred at the beginning of the 20th century. It was around that time that several empirical associations had been made between diet (eg. the lack of certain nutrients) and disease. Vitamins are defined as organic compounds of low molecular weight that distinct from fats, carbohydrates, and proteins, play a key role in metabolism and cannot be synthesized by the host in amounts adequate to meet normal physiological needs. Since the body is capable of producing vitamin D₃, vitamin D does not meet the classical definition of a vitamin. A more accurate description of vitamin D is that it is a prohormone; thus, vitamin D is metabolized to a biologically active form that functions as a steroid hormone. However, since vitamin D was first recognized as an essential nutrient, it has historically been classified among the lipid-soluble vitamins. The generic term vitamin D designates a group of chemically related compounds with the structure of a secosteroid molecule that mutually differ only in the structure of the side chains (1). The two most prominent members of this group are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). The source of vitamin D₂ is plant food, while vitamin D₃ is found in foods of animal origin (eg. fish oil or egg yolk). Vitamin D₃ is the form of vitamin D obtained when radiant energy from the sun strikes the skin and converts the precursor 7-dehydrocholes-

terol. The latter is subsequently converted in the liver to 25 - hydroxy vitamin [25(OH)D], which serves as a biomarker of the concentration of the vitamin D in the body, as it represents the main inactive form, which circulates through the body. Its hydroxylation in kidneys is strictly controlled and converts it into a biologically active compound, a steroid hormone 1,25-dihydroxyvitamin D₃. Regardless of the starting compound, it is first metabolised in the liver to calcidiol and then in the kidneys to calcitriol. Calcitriol functions to maintain calcium homeostasis together with two peptide hormones, calcitonin and parathyroid hormone (PTH). In addition, calcitriol, produced in other tissues, has numerous other biological functions not related to calcium homeostasis and also affects gene expression in the target cell (1). Activation of vitamin D₂ follows the same pathway as for vitamin D₃, but has only 25-30 % of the biological activity of vitamin D₃ (1). The absorption of vitamin D takes place in the small intestine with the aid of bile salts and is transmitted via the lymphatic system with chylomicrons. As only about 50% of vitamin D is absorbed from the diet, the endogenous synthesis of this vitamin is very important. Together with calcitonin and PTH, vitamin D has an important role in the calcium and phosphorus homeostasis participating in this way in the bone mineralization. In addition, in recent years it has been shown that vitamin D is associated with a broad range of diseases and conditions, bone health representing only the tip of the iceberg.

It plays an important role in the normal functioning of the innate immune system through stimulating of epithelial cells, macrophages, monocytes and granulocytes, to synthesize antimicrobial peptides such as defensins and catelicidin. In that way, the inflammatory response (or the severity of infection) was lower in subjects with higher levels of serum vitamin D (2). Some scientists stress that sufficient concentrations of vitamin D effectively protect against flu (2). Furthermore, normal levels of vitamin D reduce the likelihood for the development of autoimmune diseases such as multiple sclerosis, diabetes type I and rheumatoid arthritis. It has been demonstrated that the occurrence of multiple sclerosis is affected by the deficiency of the vitamin D as the result of disrupted functioning of the immune system and the inflammation (3). Calcitriol, that is synthesized in a variety of tissues, prevents the division and proliferation of cells and thus has also an anticancer activity (3). Unfortunately, the negative effects of vitamin D supplementation had also been reported and were connected with the increasing incidence of atopic and allergic diseases, especially among children population (4).

The increased need for vitamin D occurs in children, nursing mothers and in the elderly. However, to determine the optimal dosage of vitamin D in pregnancy additional studies are necessary (5). Vitamin D deficiency in pregnancy is associated with various complications in pregnancy and neonatal diseases. The highest increase of bone density and the fastest growth of fetus happens during the third trimester of pregnancy, and at that time the optimal concentration of vitamin D is extremely important (5). This rapid growth continues in the period immediately after birth until the two years of age, when it temporarily slows down until puberty (6).

Given the fact that only 10 to 20% of vitamin D enters the body through diet, the lack of it, especially in children and adolescents, is largely due to the short exposure of children/adolescents to sunlight and excessive use of sunscreens because of the fear of skin cancer (1). The concentration of 25(OH)D, which is optimal for bone health, may be very different from

those required for other needs of the organism (immune, cardiovascular metabolic etc.). There are significant differences in the functional needs for vitamin D among individuals and therefore in the near future we expect an individualized approach to the assessment of the optimal vitamin D intake for the highest physiological benefit. Recently, many controversies about how, when and what substitute appeared, as well as which values indicate inadequate, insufficient, sufficient or optimal concentration of serum vitamin D. Although scientists indicate different optimal serum concentrations of 25(OH)D, they largely agree that it is between 20 to 29 ng/mL (50–72 nmol/L), and that values lower than 20 ng/ml (50 nmol/l) mean extreme deficiency (7). It has been known that prolonged deficiency of vitamin D would lead to rickets in children and osteomalacia in adults. Numerous epidemiological studies have shown that only a slight vitamin D deficiency in apparently healthy children and adolescents represents a significantly greater health problem around the world, both in developed countries and in countries in development (8–12). In addition, little is known about the consequences of such lack of vitamin D on musculoskeletal health in children and adolescents with no clinical signs of rickets (8). It is interesting that vitamin D deficiency is also present in countries of tropical longitude, where sufficient dermal synthesis of vitamin D is possible throughout the year (9, 13). Persistent vitamin D deficiency is associated with elevated levels of parathyroid hormone in the serum, which over time leads to the gradual loss of bone mass and results in low bone mineral density over time (9, 11).

Different units for vitamin D concentration are used in the literature. The most commonly used are μg , nmol and international units (IU).

Equivalents can be calculated from the following formulas (7):

$1 \mu\text{g} = 2.5 \text{ nmol}$ $1 \mu\text{g} = 40 \text{ IU}$ $1 \text{ ng/ml} = 2.5 \text{ nmol/l}$

It is also important to know the abbreviations and the various forms of vitamin D:

- 25-hydroxy vitamin D = 25(OH)D or calcidiol
- 1,25-dihydroxyvitamin D = 1,25(OH)₂D or calcitriol
- Vitamin D = calciferol
- Vitamin D₂ = ergocalciferol
- Vitamin D₃ = cholecalciferol

The purpose of this review article is to present the current knowledge on vitamin D and its impact on human health and to present recommendations on the dietary intake of vitamin D.

A Historical Overview

Vitamin D deficiency in the past was defined by the clinical recognition of nutritional rickets and osteomalacia in adults, a disease nearly eradicated by vitamin D fortification. Rickets are characterized by impaired mineralization of the growing bones with accompanying bone pain, muscular tenderness, and hypocalcemic tetany. Affected children develop deformations of their softened, weight-bearing bones, particularly those of the rib cage (lat. Pectus carinatum), legs and arms. Rickets could also be reflected in inadequate mineralization of enamel and dentin (14). The first descriptions of clinical manifestations of rickets appeared in ancient times. Second century Roman physician Soranus published a text in which he recommended swaddling to prevent deformities common in city dwellers (14, 15). Investigators began studying the potential relationships between rickets and both cod liver oil and sunlight in the early 19th century. Soon after they successfully started using the cod liver oil for preventing rickets in children (15). In 1822 Sniadecki noted a higher incidence of rickets in children living in Warsaw than children living in surrounding rural communities; he blamed inferior sunlight exposure within the city as the causative factor (16). Hugh Owen Thomas treated rachitic children with sunlight exposure on hospital balconies in Wales in 1878 (17). By the turn of the 20th century, speculations regarding the etiology of rickets varied from syphilis, scurvy, genetics, acidosis causing bony decalcification to strep infection, exercise deprivation, over-eating, or disorders of the thymus, thyroid,

adrenal or parathyroid (18). At this time rickets had become epidemic in the US and Europe: autopsy studies identified rickets in 80 – 96% childhood deaths, oral exams in London school children saw rickets in the teeth of 80%, and estimates of children living in industrialized cities exceeded 90% (16). Women with pelvises flattened by the effects of childhood rickets required Cesarean section (16). The early 1900s represented a turning point in rickets research. German pediatrician Kurt Huldchinsky treated over 100 cases of childhood rickets with quartz mercury-vapor lamp UVB irradiation and then noted that UVB exposure to a single limb produced X-ray evidence of full skeletal healing (17). Harriett Chick and her colleagues treated children with rickets at a Vienna hospital after World War I. They treated children with mercury-vapor lamp UVB exposure, sunlight, cod liver oil, or a combination of UVB and cod liver oil and compared with those who were not treated for rickets. They found several interesting results: healing rates depended on amount of UVB exposure; partial body UVB exposure produced full body healing; no new cases of rickets developed during the summer months in any group; and most rapid healing occurred in children receiving both UVB exposure and cod liver oil (18, 19). The next boom in vitamin D research started in the 1960s. Researchers at the University of Wisconsin isolated a metabolite chromatographically-distinguishable from vitamin D₃, subsequently determined its structure as 25-hydroxyvitamin D (25(OH)D) and discovered it was produced in the liver. They found a third distinct metabolite and researchers in Cambridge, after determining production occurred in the kidney, diagrammed our modern understanding of vitamin D synthesis and metabolism (19). The incidence of rickets, dramatically dropped due to vitamin D fortification and was considered as rare in the 1960s. Despite these efforts, rickets started to appear again and at the same time there is a great concern regarding the high prevalence of low concentrations of vitamin D in apparently healthy population worldwide.

Vitamin D Today

In the 19th and 20th century, the prevalence of rickets in children in Europe and the United States

reached its peak. After the discovery of the role of diet and sunlight in maintaining the adequate serum vitamin D levels, the incidence of rickets drastically declined (21). Today, the definition of vitamin D deficiency has expanded from the clinical diagnosis of rickets to a definition based on the serum concentration of 25(OH)D. Much is known about vitamin D and its importance to overall health, but there is still much uncertainty to set a clear guidelines on recommended daily intake. Many countries have their own recommendations on an adequate intake of vitamin D, which would according to their expectations maintain adequate levels of vitamin D in majority of healthy individuals. However, due to the lack of consensus and definitions between countries, a range of terminology and associated values in the literature arised to describe vitamin D status, including the terms 'deficiency', 'insufficiency', 'adequacy' and 'optimal'. There is also a lot of controversy about how, when and which form of vitamin D to recommend. In addition, the inconsistency in the cut-off levels and the interchangeable use of terminology makes accurate comparisons of reported prevalence between the countries difficult. Anyhow, the recommended daily intake of vitamin D depends on the age of the individual, his overall health and time spent outside, exposed to the sun.

A blood 25(OH)D concentration below 10 ng/ml (or 25 nmol/l) is considered the lower threshold of vitamin D status and/or an indicator of vitamin D deficiency. This cut-off value was set with regard to prevention of rickets and/or symptomatic osteomalacia (1).

The US Institute of Medicine (IOM) recommendations for vitamin D (IOM 2011), based on a review of the evidence, concluded that (21):

- 25(OH)D < 25 nmol/l severe deficiency;
- 25(OH)D med 25 in 50 nmol/l deficiency;
- 25(OH)D med 50 nmol/l in 80 nmol/l insufficient;
- 25(OH)D > 80 nmol/l sufficient for the majority of the population (97,5 %).

However, the clinical utility of the term 'insufficiency' is not at all clear. Because the functional effect of a given 25(OH)D value is widely variable, it is likely that the range defined as insufficiency represents adequate vitamin D status for some and deficiency for others. The requirement for vitamin D appears to be lower when the calcium intake is adequate. Definitions of insufficiency have been based on analysis of parathyroid suppression and/or calcium absorption (22).

Certainly, children/adolescents, pregnant and breast-feeding women as well as elderly are at high risk for vitamin D deficiency. The health implications of vitamin D status in pregnant and lactating mothers and their infants had been investigated in significant amount. In pregnant women, as in non-pregnant women, the serum concentration of vitamin D varies depending on season of the year and food intake. However, during the pregnancy (especially during the last trimester), the concentration of calcitriol is increased when compared to non-pregnant women, despite similar levels of 25(OH)D, which reflects the increased metabolism of vitamin D due to the increased needs in pregnancy (23). 25(OH)D passes through the placenta and the serum concentration of 25(OH)D is similar in the mother and the newborn. Vitamin D deficiency in pregnancy is highly widespread and if severe, it could lead to osteomalacia in pregnancy and skeletal abnormalities in childhood. Low vitamin D levels during pregnancy are associated with increased risk developing pre-eclampsia, gestational diabetes mellitus, fetal growth restriction and premature delivery (22). Although the exact mechanisms are not known yet, vitamin D has a positive effect on maturation of immune system of the fetus, it affects the cytokine production by monocytes and lymphocytes. In addition, the vitamin D deficiency in pregnancy coincides with the rise of autoimmune diseases in infants in the last decades (22). Hypovitaminosis D extends into sunny climates. Due to the low levels of vitamin D in breast milk even infants in a tropical climate suffer from rickets, if they are excessively protected from the sun. The study of Seth et al. found that 48% of mothers and 43% of newborns had a concentration of 25(OH)D lower than 10 ng/ml (23). Vitamin D

deficiency in infants and young children could lead to rickets, where deformation of the skeleton, muscle weakness and hypotonia are observed. Severely low levels of vitamin D in adults result in the breakdown of bones and contribute to osteoporosis later in life. Even though osteomalacia is considered to be a rare disease today, nonspecific pain associated with low levels of vitamin D is quite frequent (1). Older people are prone to develop low vitamin D levels. This phenomenon results from reduced capacity of the skin to produce vitamin D, low sun exposure, skin pigmentation, sunscreen use, skin covering clothes and a diet low in fish and dairy products. In the elderly the reduced dermal synthesis of vitamin D is unlikely to be compensated by dietary intake of vitamin D (7).

What is the actual situation or how frequent is the deficiency of vitamin D is very difficult to assess because of the lack of consensus between the countries and poorly defined cut-off values between optimal, satisfactory (sufficient) and unsatisfactory (unsufficient) levels of serum vitamin D, which are used in European studies (24). Another difficulty arises when comparing these studies due to often differently designed studies, different methodology of the study, the season when the study was performed, the latitude, the age of population, ethnicity and gender of individuals included in the study (24, 26). It is estimated that the worldwide vitamin D deficiency exceed 1 billion individuals (21, 26, 27). Vitamin D deficiency is not restricted to the temperate climate but also extends in the tropical zone. The study that included healthy individuals who were regularly exposed to sunlight in Hawaii found that 51% people enrolled in the study had serum concentrations of 25(OH)D less than 30 ng/ml (28). Several factors may contribute to the prevalence of hypovitaminosis D and the resurgence of rickets in the modern society such as: the geographic location, lifestyle, and various individual factors (pregnancy/lactation, pigmentation of the skin, the use of sun protection, alcoholism, etc.) (29). A variety of medical conditions interfere with vitamin D absorption (i.e. celiac disease, cystic fibrosis, Crohn's disease, or gastric bypass surgery), hepatic conversion or renal synthesis of vitamin D metabolites (30). Medications, including anticonvulsants, glucocorticoids,

antiretrovirals, and antirejection drugs can interfere with vitamin D metabolism as well (21). The prevalence of obesity has increased throughout the world and fat soluble vitamin D is sequestered in adipose tissue. Therefore, there is a consistent association between increasing BMI and lower serum 25(OH)D concentrations (31).

The status of vitamin D in Slovenia

As in other European countries, the deficiency of vitamin D presents a health problem in Slovenia. According to the recent Slovenian study on dietary habits, the healthy preschool children achieved only about 21% of their recommended daily intake, and adolescents 60%, reflecting poorly meeting the needs for vitamin D (32). The problem of insufficient vitamin D intake occurs especially in winter, because of much shorter exposure to sunlight than in summer.

In children with chronic diseases vitamin D deficiency is more frequently. Topal and colleagues in 2015 included 52 children with celiac disease in their study and determined the level of 25(OH)D, vitamin A, vitamin E, iron and zinc. They found that all children had deficient levels of vitamin D, iron and zinc in serum and therefore proposed their regular control (33).

The study of Blazina et al., which was held at the Pediatric Clinic, UKC Ljubljana included 55 children and adolescents with celiac disease. Patients were on the gluten-free diet for at least two years, but to a different extent. The study found that bone mineral density correlated strongly with the strictness of the gluten-free diet, and patients who poorly adhered to the principles of gluten-free diet had lower bone mineral density. Moreover, the results of the study showed low serum concentrations of vitamin D and inadequate intake of calcium in children and adolescents with celiac disease. The results of the latter study support the regular supplementation of calcium and vitamin D in these patients, especially during the winter and spring months (34).

The study of Ferant et al., which took place at the Pediatric Clinic, University Medical Centre Maribor, in-

cluded 114 children (age between 10 and 18 years). It was found that the serum vitamin D levels in children with newly discovered celiac disease and with active inflammatory bowel disease (IBD) were significantly lower when compared to the control group of healthy children. This could be explained with malabsorption and gastrointestinal loss (as a result of inflammatory bowel) and potentially shorter exposure to the sun. The same study found that the bone mineral density in patients with IBD, in a stable remission, was comparable with the bone density of the control group of healthy children (35). The study also determined the levels of vitamin D in the group of healthy children who were included as control group. Interestingly, when comparing the average value of vitamin D in the serum of healthy children of the control group with some other European countries, lower values were observed (49.9 nmol/L compared with 57.1 nmol/L of other European countries) (36), which can be attributed to a different diet (lower intake of foods rich in vitamin D such as oily fish), shorter exposure to sunlight and changing levels of vitamin D synthesis during the year. The effect of supplementation of vitamin D and calcium on mineral bone density in children with specific chronic diseases is confirmed, as the supplementation improves the condition while no supplementation does not (37). It is very encouraging that adolescents with IBD and celiac disease, who are treated from an early age have bone mineral density values similar to their healthy peers due to long-term supplementation of vitamin D and calcium (38).

Dovnik et al. in his prospective observational study, which was carried out in Maribor maternity hospital and represents the first such study in Maribor region, included 400 pregnant women and their newborns during all four seasons of the year 2014. The main purpose of the study was to determine the average vitamin D concentrations in pregnant women at term and in their neonates, to determine the incidence of vitamin D deficiency, the factors influencing vitamin D concentrations, and possible connection between vitamin D concentrations and pregnancy and neonatal complications. The blood sample of pregnant women was obtained in the course of hospitalisation no

later than two days after birth. The cord blood sample was obtained immediately after birth after umbilical cord clamping. The results showed that sufficient concentrations of vitamin D were present in only 7.0% of pregnant women. 23.6% of participants had severe vitamin D deficiency, 41.5% had vitamin D deficiency, and 27.9% had vitamin D insufficiency. The average neonatal vitamin D concentration was 55.2 ± 30.9 nmol/L. The study showed that the season of the year, the time spent in the sunlight especially during the last month of the pregnancy, the frequency of fish consumption and taking pregnancy supplements with vitamin D greatly influenced the level of serum vitamin D. In addition, women with preterm labor and with caesarean section had lower vitamin D concentrations compared with controls (39).

A prospective study of Jakopin et al., which included 101 hemodialysis patients (51.5% men and 48.5% women; age 63.3 ± 13.5 years), was conducted from May 2008 to May 2010 in the dialysis center at the University Medical Centre Maribor. Because studies have shown higher mortality rates in haemodialysis (HD) patients with vitamin D deficiency, the purpose of the research was to develop a protocol for replacing vitamin D in these patients. Vitamin D, intact parathormone (iPTH), calcium (Ca) and phosphorus (P) concentrations were determined in the beginning of the study and then every 4 months. Initially, only three patients had adequate levels of vitamin D. 28.7% of patients had insufficient levels of vitamin D, 51.5% were deficient in vitamin D and 16.8% had a severe deficiency. The result of this prospective study was the preparation of safe and affordable guidelines for replacing vitamin D in hemodialysis patients.⁴⁰

Recommended daily allowances

Most European countries have their own recommendations regarding the adequate intake of vitamin D, which according to their expectations would maintain adequate serum levels of vitamin D in majority of individuals. There are many dietary supplements available on the market, yet scientific recommendations are inconsistent. Significant controversy exists regarding optimal supplementation dosing, partly related to

the lack of universally accepted optimal serum values. Additionally, while D2 and D3 supplements both increase in 25(OH)D values, D3 has produced slightly superior results, suggesting a higher dose of D2 needed to achieve similar serum 25(OH)D concentrations. The general rule is supplementation when deficiency is observed but even though vitamin D deficiency is well-documented worldwide, there is a lack of supplementation policies and programs preventing and treating the health consequences due to the vitamin D insufficiency. The recommended daily intake of vitamin D depends on the age of the individual, of his health condition and exposure to the sun. In Slovenia, for infants and young children under three years of age, who are minimally exposed to the sun, the recommended daily intake of vitamin D is 10 µg/day ie. 400 IU, irrespective of sun exposure, skin pigmentation, or gender. For older children, adolescents and adults, these values increase from 10 to 25 µg/day respectively (or 400 IU to 1000 IU) compensating in this way for the lower capacity of the endogenous synthesis of vitamin D (41, 42).

Vitamin D deficiency can affect any age, gender, and ethnicity; however, certain populations are affected disproportionately. Children, elderly, and pregnant women are vulnerable subgroups for vitamin D de-

ficiency. Pregnancy is a period in which the mother's diet plays an important role in the health and development of children. Recommendations for vitamin D intake in pregnancy varies greatly between countries. Adequate intake of vitamin D during this period, which would cover the needs of pregnant women and the fetus is around 20 µg/day (41).

In Europe, the European Food Safety Authority (EFSA) adopted the upper intake values for vitamin D. According to EFSA, adults require 15 µg/day of vitamin D (Table 1) (43). This quantity can be obtained either through the diet or through the endogenous synthesis of vitamin D. This recommendation will ensure the adequate serum levels of vitamin D for skeletal health but does not take into account the fact that higher concentrations are needed to prevent the development of other health conditions such as diabetes mellitus, autoimmune and other diseases, where the function of vitamin D is not yet sufficient investigated (44).

The recommendation of a daily intake of 15 µg of vitamin D will be sufficient to maintain serum concentrations of about 50 nmol/l (20 ng/ml) in majority of healthy individuals, but it will not be enough during the winter months when exposure to the sunlight is much shorter (7,43).

Table 1. Dietary reference values for vitamin D (µg/day) in European countries, at different life stages (7)

	Infants	Toddlers	Children	Adolescents	Adults	Elderly	Pregnancy	Lactation
Country	<1 y	1–3 y	4–10 y	11–18 y				
Austria	10	20	20	20	20	20	20	20
Belgium	10	10	10	10–15	10–15	15	20	20
France	20–25	10	5	5	5	5	10	10
Germany	10	20	20	20	20	20	20	20
Ireland	7–8,5	10	0–10	0–15	0–10	10	10	10
Spain	10	15	15	15	15	20	15	15
Switzerland	10	20	20	20	20	20	20	20
Turkey	10	10	10	10	10	10	10	10
Netherlands	10	10	10	10	10	20	10	10
UK	8,5	7	–	–	10	10	10	10

Vitamin D supplementation discussions usually bring a concern for toxicity and irrespective of the beneficial properties of vitamin D. Excessive intake of vitamin D is associated with an increase in circulating 25(OH)D, which may lead to increased intestinal absorption and bone resorption of calcium, in turn leading to hypercalcaemia. Signs of vitamin D intoxication include anorexia, vomiting, headache, risk of calcification of soft tissues and presence of urinary calcium stones etc. Treatment consists of simply removing of vitamin D from the diet (18). EFSA specifies the permitted upper limit of daily intake of vitamin D for infants up to 1 year of age 25 µg (1000 IU); for children under the age of 10 years 50 µg (ie. 2000 IU) and 100 µg (ie. 4000 IU) for healthy adults (44). Studies indicate that the sensitivity to excessive intake of vitamin D varies with the age of individual. Infants certainly represent the most vulnerable group (18, 21, 22).

Sources of vitamin D

Several sources of vitamin D include sun exposure, natural diet foods, fortified foods, and supplements. Vitamin D, a fat-soluble micronutrient, is obtained from a limited number of naturally occurring foods. It is primarily found abundantly in fatty fish (ie. salmon, sardines, tuna, mackerel and cod), eggs (especially yolk), meat (especially liver) and shiitake mushrooms. Further sources of dietary vitamin D are fortified foods (most often milk and dairy products, margarine and spreads and some breakfast cereals) (21). Foods that make the highest contribution to dietary intakes of vitamin D vary from country to country according to habitual dietary patterns and fortification policies. Shiitake mushrooms may contain up to 25 µg/g of vitamin D₂ (44).

Both cholecalciferol (D₃) and ergocalciferol (D₂) are used in fortification and as dietary supplements. Vitamin D₂ is obtained from plant sources (fungi and yeast) whereas vitamin D₃ is traditionally obtained from animal sources (7).

In non-breastfed infants and very young children, the major contributor to dietary vitamin D intake is formula milk, providing an average of 85% of intake

for children aged 4–6 months, 80 and 72 % for those aged 7–9 months and 10–11 months, respectively, and 29% for children aged 12–18 months. For children aged 4–11 months, the second largest contributor were commercial infant foods, particularly cereal based foods and dishes that are often fortified. For children aged 12–18 months, the second largest contributor to vitamin D intake were milk and milk products. In older children aged 1.5–3 years and 4–10 years, foods contributing to vitamin D intake include milk and milk products, meat and meat dishes, and cereal and cereal products (7).

The best way to obtain vitamin D is sun exposure. Sun exposure enables UVB rays to reach exposed skin to produce vitamin D₃. UVB rays, which have a shorter wavelength than the UVA are more important for endogenous synthesis of vitamin D. They stimulate the synthesis of cholecalciferol (D₃) in the skin, which is then stored in the adipose tissue or is metabolised through hydroxylation in the liver to 25(OH)D and in the kidneys to the biologically active form of 1,25(OH)D. Exposure to the sunlight and dermal synthesis of vitamin D have a greater effect on the serum concentrations of vitamin D than the diet itself (45). Factors that affect synthesis include the geographic location, season of the year, time of day, duration of exposure, pollution, skin pigmentation, sunscreen use, age etc (7). However, in our temperate zone, the dermal synthesis of vitamin D is possible only from March to October. During this period it is recommended to expose hands and face to the sunlight between 10 and 16 hours for 15 minutes three times a week. At this time, the intensity of UVB rays is highest but it is precisely at this time of day that dermatologists recommend avoiding the sun and using clothing and sunscreens for skin cancer prevention. Furthermore, the pigmentation of the skin has an important role in the endogenous capacity of vitamin D synthesis. Melanin, which absorbs UVB in the range between 290 and 320 nm, acts as a filter, which determines the proportion of rays, that will penetrate through the three outer layers of the skin. For example, an adult with light complexion can in less than 30 minutes of sunbathing during the summer synthesize up to 20,000 IU (45).

Unfortunately today's lifestyle and the fact that children spend less time playing outside significantly contributed to the increasing prevalence of vitamin D deficiency in both children and adults (who spend most of the day indoors). Certainly, there is a great challenge to find the right balance between the recommendations of dermatologists, who emphasize the dangers of the sun and nutritionists that stress the importance of sun exposure because only through diet, an adult can cover only about 10 to 20% of his daily needs for vitamin D (47). Food fortification is an important way to improve vitamin D intake in the general population. The food fortification policies differ greatly between the countries but generally include similar food products (such as milk and dairy products, margarine, various spreads and breakfast cereals). EFSA approved the following health claims in the labeling of food products, that are a good source of vitamin D: "contributes to normal absorption/aquisition of calcium and phosphorus", "contributes to normal blood calcium levels," "helps to keep bones healthy" "contributes to the muscle strength," "contributes to the maintenance of healthy teeth," "contribute to the activity of the immune system" and "has a role in cell division" (48).

When dietary intake of vitamin D is restricted or otherwise unavailable, and the levels of 25(OH)D are too low, supplementation is another option to help improve vitamin D status. Supplementation for vulnerable populations as a preventative strategy is more cost effective than screening for vitamin D status among all individuals (20, 21). There are many dietary supplements available on the market, however, scientists are not entirely uniform what, when and how much to recommend. There is much debate regarding the

vitamin D supplementation as various countries have different recommendations for vitamin D supplementation and different definitions for vitamin D inadequacy. Both cholecalciferol (D3) and ergocalciferol (D2) are used as dietary supplements (49, 50). When deficiency has been detected, particularly in high-risk groups, a regular monitoring of biochemical parameters is necessary.

CONCLUSION

The vital role of vitamin D in bone health is universally accepted. However, a plethora of publications over the past several years shows that the role of vitamin D extends far beyond the skeleton. The future of vitamin D will be determined by establishing the non-skeletal benefits of vitamin D and individualizing vitamin D recommendations based on functional outcomes and disease risk. Observational data have demonstrated already the relationships between vitamin D status and infectious, immune, metabolic, degenerative, and neoplastic diseases. Although our knowledge of vitamin D has grown exponentially since ancient descriptions of rickets, many questions still remain. The future of vitamin D will likely bring with it a more individualized approach to assessing vitamin D status and needs. With more widespread use of genotypic analysis, it may be possible to personalize an individual's vitamin D requirement, particularly in view of other disease risk factors. The recommended vitamin D intake may require adjustment for calcium intake, body size, body fat, ethnicity, and usual sun exposure. As individualized medicine becomes more of a reality in all areas of medical care, the optimal role of vitamin D will certainly be better defined in near future.

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