VITAMIN D ACROSS THE LIFE SPAN

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Vitamin D is a secosteroid hormon with pleiotrophic functions and essential for normal development and health throughout the entire life span. Vitamin D deficiency has epidemic proportions worldwide and interferes with important metabolic processes. Its prevalence is estimated in various populations of different ethnicity and age from 50% up to 100% in certain groups. The main source of vitamin D for men is skin production by ultraviolet B radiation acting on 7-dehydrocholesterol. This is cholecalciferol or vitamin D3. Less than 20% is obtained from food. The active form, 1,25-dihydroxy-vitamin D (calcitriol) is synthesized in the kidney. Synthetic capacity declines with ageing. The main function of vitamin D is calcium homeostasis important for musculoskeletal health, innate immunity, arterial integrity, endocrine function, antiinflammation, and various local processes (autocrine and epicrine functions) in more than 30 tissues where receptors exist. Vitamin D is also important for cognitive function, mainly executive in the frontal lobe. Normal vitamin D levels are above 75 nmol/L. Vitamin D deficiency is mostly due to the lack of sun exposure but can also be secondary to some individual characteristics. Deficiency during intrauterine development can lead to early and late negative consequences in bone growth, immune system, and cognition. The extreme deficiency causes rickets. In adults vitamin D deficiency has been suggested as a risk factor for infectious and autoimmune diseases, carcinomas (especially of the breast and colon), multiple sclerosis, falls, osteoporosis, bone fractures,
cardiovascular and cerebrovascular diseases, diabetes mellitus type I and II, infertility, cognitive decline and dementia. Oral supplementation with serum level normalization can lead to reduction of these risks but even amelioration of some pathological states. Recommendation ranges from 400 IU of vitamin D in infants to 2000 IU in older population, but it should be guided by individual clinical circumstances.

**Key words:** Vitamin D, cognition, immunity, ultraviolet B radiation

**INTRODUCTION**

Vitamin D is a vitamin acting as secosteroid hormone, involved in a broad range of metabolical processes, and is crucial for the development and maintaining the wellbeing of human organism in all ages (Pavlović, 2012; Pludowski et al., 2013). Vitamin D deficiency is broadly present in population and causes serious health hazard if it remains untreated, mostly with long term consequences. Low vitamin D levels increase the risk of infectious and autoimmune diseases, carcinomas (especially of the breast and colon), multiple sclerosis, falls, osteoporosis, bone fractures, cardiovascular diseases, diabetes mellitus type I and II, cognitive decline and dementia.

Estimates are that at least 50% of global population suffer from vitamin D deficiency (Mithal et al., 2009). The prevalence increases with age, up to nearly 100% in some populations with the cut off of 75 nmol/L (30 ng/mL) in the population over 65 years (Gouveri et al., 2012). Epidemiological data show that the world is facing vitamin D deficiency pandemic in all age groups (Rathi & Rathi, 2011). Even the young and healthy are not spared. The main source of vitamin D is synthesis in the skin with sun exposure, fluctuating according to the length of exposure (lifestyle, latitude, climate etc.), and less from ingested food.

**Sources of vitamin D**

All foods are poor sources of vitamin D, so humans depend on sunlight driven processes in the skin. Some amounts of this vitamin are found in certain fish. Food and supplements usually contain cholecalciferol or ergocalciferol. More than 80% of vitamin D is produced in the skin. The substrate is 7-dehydrocholesterol (7-DHC) which under insolation
containing ultraviolet B spectrum radiation (UVB; 290–315 nm) converts to provitamin D3 that is further converted to vitamin D3 called cholecalciferol by local heath (Gouveri et al., 2012; Rathi & Rathi, 2011). Vitamin D3 is synthesized by all mammals. Skin production can be limited or influenced by the amount of sunlight exposure, latitude, clothing, mobility, occupation and personal behavior. Dark skin colour reduces the amount of vitamin D production due to UVB absorption by melanocytes (Clemens et al., 1972). Concentration of 7-dehydrocholesterol, the precursor of vitamin D3 in the skin, declines with age, so the capacity of vitamin D synthesis is substantially reduced in old people (Holick & Chen, 2008).

Vitamin D3 is then transported in the circulation by the vitamin D-binding protein to the liver and kidney. Liver contains enzyme vitamin D 25-hydroxylase that converts vitamin D3 to 25(OH)D$_3$ (calcidiol) (Barnard & Colón-Emeric, 2010). Ergocalciferol (vitamin D2 – synthesized by plants) is converted to 25(OH)D$_2$ also in liver. These are the two metabolites that are measured in serum to show vitamin D status. The active form, 1,25-dihydroxy-vitamin D (calcitriol) is synthesized in the kidney by 1-alpha-hydroxylase and is unstable. Calcitriol acts as a hormone, regulating the concentration of calcium and phosphate in the blood, supporting the bone and also influencing neuromuscular and immune function. The main targets of active vitamin D are bones and intestine where it mobilizes osteoclastic activity and enhances intestinal calcium absorption via VDR (Holick & Chen, 2008). With aging, especially after the age of 70, the skin becomes thinner and the ability to synthesize vitamin D reduces (Need et al., 1993).

Risks of too much insolation increase the probability of skin cancers, eye diseases and viral infections, as UV light induces immunosuppression (Lucas et al., 2006). It has been shown that due to the strength of UV-B radiation cutaneous vitamin D synthesis is maximum between 10 AM to 3 PM when the majority of population is indoors (workin hours, school hours) making it less available. Insolation is decreased by air pollution, cloud cover, increased water vapour and sunscreen used as well as cloths cover. Epidermal melanin pigment, increased in dark skins protects from skin cancer but reduces vitamin D levels absorbing UVR. Vitamin D is delivered to foetus from mother via placenta and is essential for intrauterine development.

Local vitamin D synthesis is found in many non-skeletal tissues where it acts locally in autocrine and epicrine manner regulating up to 200 genes
(Holick & Chen, 2008). There is some extrarenal production in prostate, breast, colon, lung, pancreatic beta cells, monocytes, parathyroid cells, endothelial cells and some other tissues (Gouveri et al., 2012).

**Mechanisms of action**

Vitamin D regulates calcium balance through calcium absorption, bone mineralisation and general muscle and bone health but has also extraskeletal or so-called pleiotropic functions. The approximate measure of vitamin D storage is serum 25(OH)D level (Rosen, 2011). Vitamin D3 has also autocrine (acts on the same cell autoreceptors) and paracrine (acts on nearby cells) properties and mediates inhibition of cell proliferation, promoting of cell differentiation and immune regulation. Vitamin D receptors (VDR) are found in the heart, skin, brain, pancreas, prostate, breast, immune cells and other tissues, altogether more than 30 (Rathi & Rathi, 2011). Autocrine function of vitamin D is nonskeletal and occurs in various tissues where it is synthesized. Local calcitriol concentrations are higher than serum concentrations. No calcitriol produced locally enters the systemic circulation as it is degraded by 24-hydroxylase. Calcitriol acting on VDR induces DNA activation resulting in protein production.

Other vitamin D actions are mediated by its effects on endocrine, immune and cardiovascular systems, neuropsychological performance and neuromuscular functions (Rathi & Rathi, 2011). Vitamin D also possesses important antioxidant properties and induces cellular differentiation. Hypovitaminosis D undermines the abilities of various tissues to deal with stimuli. There are some data on potential role of vitamin D deficiency in immunological diseases like multiple sclerosis, diabetes mellitus type I, asthma, rheumatoid arthritis and others and infectious diseases also. Vitamin D is important in activations of innate immune system which explains the importance in aforementioned diseases. Vitamin D protects to certain extent against cancers via its prodifferentiation (cell maturation) and antiproliferative actions, induction of apoptosis and decreasing angiogenesis (Holick & Chen, 2008). Also it has immunomodulatory activity on monocytes and activated T and B lymphocytes.

There are also connections with low vitamin D and children’s health, diabetes mellitus type II, arterial hypertension, obesity and vascular
diseases. It is still premature to draw definite conclusions about all these functions and more randomized controlled studies are needed.

**Vitamin D and the brain**

Human brain has the ability to synthesize 1,25-dihydroxyvitamin D which is the active form of this vitamin, mostly in the hypothalamus and substantia nigra (Eyles et al., 2005). Vitamin D regulates many genes important for various functions including neuroprotection modulating nerve growth factor, neurotrophin 3, nitric oxide synthase and choline acetyl transferase (Balion et al., 2012). It also protects cerebral blood vessels.

Vitamin D receptors (VDR) can be found in neuronal and glial cells in the hippocampus, cortex and subcortex (Annweiler et al., 2010). Vitamin D has antiinflammatory capacities and reduces amyloid beta accumulation in the brain, reduces toxic oxygen species, stimulates dendritic growth and regulates neuronal excitability in the hippocampus (Tuohimaa et al., 2009).

Vitamin D is crucial for the neurodevelopment with signaling role in neuronal differentiation, regulation of neurotrophic factors and neurotoxins and protection from inflammation as well as through its endocrine functions (Whitehouse et al., 2012). Vitamin D influences also the development of perisylvian language area and consequently the development of speech.

Many neuropsychological studies demonstrated impairments in executive functions, particularly in mental shifting and information updating in adults with lower vitamin D levels, implying dorsolateral frontal lobe as the brain area of importance (Annweiler et al., 2012).

**Vitamin D deficiency**

Low serum vitamin D level is associated with all-cause mortality (Pludowski et al, 2013). Vitamin D deficiency is defined by most studies as the blood level of less than 50 nmol/L and insufficiency as the level between 50 and 75 nmol/L (Gouveri et al., 2012). Calcium intestine absorption is in vitamin D sufficient states between 30-80% and reduces to 10-15% in vitamin deficiency that leads to hypocalcaemia and increased parathormone (PTH) secretion (Rathi & Rathi, 2011). Consequent processes lead to bone
demineralization with rickets in children and osteomalacia in adults. But there is also growing body of information on importance of subclinical vitamin D deficiency, especially in non-skeletal functions.

The main reason for vitamin D deficiency is insufficient sun exposure, but on the other hand excessive insolation introduces various health hazards making it challenging to determine safe practices. Foods are generally poor sources of vitamin D. Also, diet rich in fibres and low calcium level depletes vitamin D storage in the organism. There are also some genetic factors, mostly in South Asians and African Americans (Rathi & Rathi, 2011).

It has been shown that certain drugs such as antiepileptics and glucocorticoids can cause vitamin D deficiency (Holick & Chen, 2008). Malabsorption leads to vitamin D hypovitaminosis as well. Hypovitaminosis D can lead to secondary hyperparathyroidism as the parathyroid glands tend to compensate for low calcium. This can be the cause of high calcium so one should always be alert and not wrongly diagnose primary hyperthyroidism before vitamin D level has been normalized. In secondary hyperparathyroidism, parathormone levels will drop to normal. Obese people tend to have lower vitamin D serum levels as most of the vitamin is sequestred in fat cells (liposoluble vitamin!) and also because of the reduced mobility, exercising and sun exposure.

Vitamin D deficiency should be considered if a patient is presented with risk factors and appropriate signs and symptoms. Known risk factors are shown in Table 1. Laboratory findings of low calcium, low phosphate or raised alkaline phosphatase should prompt vitamin D serum determination.

### Table 1 – Common risk factors for vitamin D deficiency

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Contributing Factors</th>
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<tr>
<td>Older age (&gt;65 years)</td>
<td>Vegan/vegetarian diet, intestinal malabsorption (coeliac disease, Crohn’s disease, gastrectomy, cholestatic liver)</td>
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<tr>
<td>Children under 5 years of age</td>
<td>Liver or renal disease, medications: anticonvulsants, cholestyramine, colestipol, rifampicin, glucocorticoids, highly active antiretrovirals</td>
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<tr>
<td>Darker skin coloration</td>
<td>Pregnancy, short interval pregnancies, breastfeeding</td>
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<tr>
<td>Predominantly indoor activities</td>
<td>Medications: anticonvulsants, cholestyramine, colestipol, rifampicin, glucocorticoids, highly active antiretrovirals</td>
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<tr>
<td>Regular use of high factor sunscreen (15 or above)</td>
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<tr>
<td>Covering whole body in clothes</td>
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<tr>
<td>Obesity (BMI &gt;30)</td>
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Important influence of vitamin D on human development begins during intrauterine period when fetus is completely dependent on vitamin from maternal circulation. This means that maternal serum vitamin D is a good measure for vitamin availability for the fetus. Low maternal vitamin D serum levels do not correlate with offspring behavioral and emotional problems but are associated with language impairment at 5 and 10 years of age, growth-restriction, reduced bone accrual and wheeze (Whitehouse et al., 2012). There is also an increased risk for multiple sclerosis in children whose mothers were in the first and second trimesters of pregnancy during winter and spring months (Staples et al., 2010). Low serum vitamin D levels in women are associated with infertility and preeclampsia (Rathi & Rathi, 2011; Holick & Chen, 2008). Physiological states as pregnancy and lactation increase the needs for vitamin D and makes deficiency more likely. Vitamin D deficiency in infants is frequent and can hardly be counteracted by mother milk alone without supplements and sun exposure of the child (Rathi & Rathi, 2011).

Rickets is associated with an elevated serum alkaline phosphatase, elevated serum parathyroid hormone, low 25(OH)D, low or low normal serum phosphorus and either a normal or low serum level of calcium (Pludowski et al., 2013). Severe vitamin D deficiency results in hypocalcaemia with seizures and weak bones prone to fractures. Rickets is seen from infant period up to adolescence with peak incidence between 3 and 18 months of age (Wagner et al., 2008). Children manifest letargy, irritability, growth failure and are prone to respiratory infections. There are three stages of vitamin D deficiency. In the first stage 25-OH-D level decreases, with consequent hypocalcemia and euphosphatemia while 1,25-OH2-D may increase or remain unchanged. In the second stage, 25-OH-D level are even lower but there is compensation as PTH increases calcium mobilizing from bones, as a result of which there is euchalcemia and hypophosphatemia. In stage three, there is severe 25-OH-D deficiency with hypocalcemia and hypophosphatemia. There is skull enlargement, legs skeletal malformations of varus and valgus type and other deformities.

There is another, less known consequence of vitamin D deficiency in young people with diabetes mellitus type I (Kaur et al., 2011). It has been found that hypovitaminosis D is associated with an increased prevalence
of retinopathy due to inflammatory and angiogenic effects. Low levels of vitamin D have been associated with asthma (Bose et al., 2013).

Low vitamin D can trigger certain autoimmune disorders as it might play a role in the regulation of auto-antibodies production via T-helper cell modulation and induction of CD4+CD25high regulatory T-cells. Interestingly, it has been shown that autistic children have significantly lower serum levels of 25-hydroxy vitamin D than healthy children and anti-MAG auto-antibodies are found in 70% of autistic patients (Mostafa & Al-Ayadhi, 2012).

Epidemiological studies from the United States before World War II showed positive correlation between higher latitudes and occurrence of common malignancies (Apperly, 1941). Subsequent papers reported similar results with increased risk of breast, colon, prostate, pancreatic, oesophageal, non-Hodgkin lymphoma and other cancers connected with low serum vitamin D (Holick & Chen, 2008). It can be suggested that lower levels of vitamin D3 production because of progressively less sunlight in higher latitudes are the reason for these findings. The risk is present both in men and women. With daily supplementation of 400 IU to 1000 IU there was a substantial risk reduction of cancer (Holick & Chen, 2008).

Higher latitudes and low vitamin D status have also been connected with the increased risk of autoimmune diseases such as multiple sclerosis, diabetes mellitus type I, rheumatoid arthritis, systemic lupus erythematosus and psoriasis (Holick & Chen, 2008; Wagner et al., 2008). Deficiency has been also linked to arterial hypertension (Holick, 2006). Increased intake of vitamin D preparations was followed by reduction of aforementioned conditions (Holick, 2006). Innate immune system enhancing and antiinflammatory properties are the probable explanation. This is also true for infectious diseases such as tuberculosis. The predominance of environmental factors over genetic factors is supported by studies in identical twins (Islam et al., 2007). The current hypothesis is that certain genetic factors can be influenced by vitamin D levels during childhood leading to activation of immune system, production of autoantibodies and nerve tissue lesions. Several studies showed that vitamin D supplementation reduces risk of relapses.

Vitamin D deficiency is an independent risk factor for lower bone density, falls and fractures. It has been found that vitamin D supplementation
greater than 700 IU a day appears to decrease falls by approximately 20% (Bischoff-Ferrari et al., 2009). Falls seem to be more due to cognitive changes than to gait contribution to instability, but vitamin D deficiency also leads to proximal muscle weakness. Patients with osteomalacia complain of bone discomfort and pains in joints and muscles due to mineralization defect (Holick & Chen, 2008). Moreover, people with non-specific musculoskeletal pain, chronic low back pain or fibromyalgia have lower vitamin D levels and might improve with supplementation.

Recent studies showed interaction of vitamin D and cognitive functions. Lower vitamin D concentrations correlate with the decline of cognitive function both in nondemented and demented subjects (Balion et al., 2012; Pavlović, 2013). This can be the result of increase of inflammatory processes, hyperoxidation and disregulation of hippocampal excitability among other possible mechanisms (Tuohimaa et al., 2009). Positive correlations that have been found between vitamin D serum levels and cognitive status warrants therapeutic trials (Briones & Darwish, 2012). There is ongoing unicentre, double-blind, randomized, placebo-controlled, intent-to-treat, superiority trial of treating demented patients with combination of memantine, an antidementia drug, and vitamin D supplementation as a new multi-target therapeutic class for the treatment of Alzheimer’s disease (Annweiler et al., 2011). The rationale for such treatment are multitarget actions of vitamin D on causes of neurodegeneration as it has immunoregulatory, antioxidant and anti-ischemic actions. It also regulates neurotrophic factors, acetylcholine neurotransmitter, clearance of amyloid beta peptide and other functions (Annweiler & Beauchet, 2011). VDR polymorphisms are associated with late onset Alzheimer’s disease (Gezen-Ak et al., 2012).

Another neurodegenerative disease, Parkinson’s disease is influenced by vitamin D (Butler et al., 2011). VDR gene is the most probable susceptibility gene playing an importante role in Parkinson’s disease with varous polymorphisms (Gezen-Ak et al., 2012).

Vitamin D serum levels are inversely correlated with depression according to several studies (Barnard & Colón-Emeric, 2010). Vitamin D supplementation for a year did not have adverse effects and showed improvement in measures of depression in one study but there were still some methodological issues so these results warrant confirmation studies. Besides, some studies found correlation between poor vitamin D status
and schizophrenia (Holick & Chen, 2008). The recent trial in patients with schizophrenia showed significantly lower vitamin D serum concentrations than in depressed and psychiatrically healthy controls (Itzhaky et al., 2012). This might be the manifestation of autoimmune mechanisms. VDR polymorphisms can also be important as they have been implicated in behavioral control and regulation. Vitamin D supplementation during pregnancy and during infancy and early childhood have positive effects on mental functioning.

Vitamin D influences arteries both directly and via metabolic factors (Gouveri et al., 2012). Low levels of vitamin D are associated with risk for diabetes mellitus, arterial hypertension, hyperlipidemia, metabolic syndrome and central and peripheral arterial disease. Therefore, the deficiency can lead to myocardial infarction and stroke, peripheral arterial disease and possibly increase overall mortality. Vitamin D down-regulates pro-inflammatory cytokines, and up-regulates anti-inflammatory cytokines, it regulates the production of multiple proteins in the vascular wall and also inhibits cholesterol uptake by macrophages, preventing foam cell formation and the process of atherosclerosis (Gouveri et al., 2012). Potential therapeutical effects of vitamin D supplementation are still controversial.

**Supplementation and therapeutical doses**

Supplementation with vitamin D preparations has protective and possibly therapeutic properties in a range of diseases. It has a potential role in prevention of musculoskeletal disorders, infectious diseases, autoimmune diseases, cardiovascular disease, type I and type II diabetes mellitus, different cancers, cognition and mental illness, infertility and complications of pregnancy (Pludowski et al., 2013).

Diagnosis of vitamin D deficiency relies on serum 25(OH)D level as it is the storage form of vitamin D and has much longer half life (Rathi & Rathi, 2011). One should not rely on 1,25(OH)_{2}D levels because hypocalcemia induces parathormone (PTH) production and pseudonormal serum levels of vitamin D. The golden standard for laboratory diagnostics is liquid chromatography–tandem mass spectroscopy.
Recomended daily intake doses vary but according to recent US Endocrine Society’s Clinical Practice Guideline for children under a year it is 400–1000 IU daily, for children over one year 600–1000 IU daily and for adults over 19 years 1500–2000 IU for keeping the vitamin D level above the optimal cut-off of 75 nmol/L (Pramyothin & Holick, 2012). There are various units of measure: 400 international units (IU) equals 10 mcg or 26 nmol (Rathi & Rathi, 2011). Some other recommendations are more conservative, suggesting 400 IU daily of vitamin D3 for infants, children and adolescents with progressively higher tolerable upper level with maturation (Wagner et al., 2008). Vitamin D2 is also effective in treating vitamin D deficiency but may need somewhat higher doses than D3 supplementation. In plants and yeast, vitamin D2 is obtained from UVB influence and is used for supplementation production (Rathi & Rathi, 2011).

In some Western industrialized countries fortification of milk and other foods with vitamin D has become a routine practice unlike other countries leading to less hypovitaminosis and its consequences (Marwaha & Sripathy, 2008). Unanswered questions are weather such supplementation can also correct subclinical deficiencies and if there are any unwanted effects. Populations with higher frequency of hypovitaminosis D tend to suffer more from osteoporosis ant osteoporotic bone fractures. Vitamin D and calcium supplementation reduces the risk of falls and fractures.

For therapeutical purposes both D2 and D3 are used, while 1-alphacalcidol is not appropriate for treating vitamin D deficiency. Daily doses are between 1000 IU and 10,000 IU. There are also different protocols with once a week high doses for several months. Vitamin D supplies are usually restored in about three months and then the maintenance doses can be introduced, usually 800-1000 IU daily (D2 or D3) (Rathi & Rathi, 2011; Holick & Chen, 2008).

Sun exposure can not lead to hypervitaminosis D so moderate outdoors activites are of favourable effect for all ages. (Wagner et al., 2008). Individuals with darker pigmentation require 5 to 10 times more sunlight exposure than adults with lighter pigmentation. It is hard to determine the right amount of insolation for any particular individual but outdoor activities are favourable. Another possibility is artificial UVB radiation. Oral supplementation is better option and intoxication is very rare.
Vitamin D toxicity occurs after excessive supplementation for several months and not due to excessive sun exposure (Ross et al., 2011). According to currently available evidence, adverse affects can be encountered in serum vitamin D levels of >150 nmol/L (>60 ng/mL). Toxic daily doses are above 10,000 IU. High level of vitamin D (especially over 250 nmol/L i.e. 100 ng/mL) are followed by hypercalcaemia with possible changes in heart rate, headaches and gastrointestinal disturbances, kidney stones and kidney failure and growth restriction in children. In bone complications due to vitamin D depletion, calcium should be co-supplemented with vitamin D (Rathi & Rathi, 2011).

CONCLUSION

Epidemic proportions of vitamin D deficiency have been recognized worldwide. Vitamin D interferes with important metabolic processes, influencing calcium homeostasis and affecting musculoskeletal health, innate immunity, arterial integrity, endocrine function and antiinflamatatory mechanisms in more than 30 tissues where its receptors exist, including the brain. Deficiency during intrauterine development can lead to serious sequelae in bone growth, immune system and cognition, while extreme deficiency leads to rickets. In adults, vitamin D deficiency has been identified as a risk factor for infectious and autoimmune diseases, carcinomas, multiple sclerosis, falls, osteoporosis, bone fractures, cardiovascular and cerebrovascular diseases, diabetes mellitus type I and II, infertility, cognitive decline and dementia. Oral supplementation with serum level normalization can be beneficial in reducting these risks and even lead to amelioration of certain pathological conditions.

REFERENCES


VITAMIN D U SVIM DOBIMA ŽIVOTA

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Sažetak

Vitamin D je sekosteroidni hormon sa pleotropnim funkcijama i presudan za pravilan razvoj i zdravlje kroz ceo životni vek. Nedostatak vitamina D ima razmere epidemije širom sveta i ometa važne metaboličke procese. Procene u različitim populacijama različitog etničkog porekla i starosti su od 50% do 100% u pojedinim grupama. Glavni izvor vitamina D kod ljudi je sinteza u koži pod dejstvom ultraljubičastog B zračenja na 7-dehidrocholesterol. To je vitamin D3 ili holekalciferol. Manje od 20% se dobija iz hrane. Aktivni oblik, 1,25-dihidroksi-vitamin D (kalcitriol) se sintetiše u bubrezima. Sintetički kapaciteta opada sa starenjem. Glavna funkcija vitamina D je homeostaza kalcijuma, zdravlje muskuloskeletnog sistema, urođeni imunitet, integritet arterija, endokrine funkcije, antiinflammatorno dejstvo i različiti lokalni procesi (autokrine i epikrine funkcije) u više od 30 tkiva gde postoje receptori.


Ključne reči: vitamin D, kognicija, imunitet, ultravioletna B radijacija