Rocz Panstw Zakl Hig 2014;65(3):179-184

HEALTH OUTCOMES OF VITAMIN D. PART I. CHARACTERISTICS AND CLASSIC ROLE

Julia Wranicz[1], Dorota Szostak-Węgierek[2]*

[1] Chair of Dietetics, Department of Nutritional Physiology, Faculty of Human Nutrition and Consumer Sciences, Warsaw University of Life Sciences, Warsaw, Poland
[2] Department of Human Nutrition, Faculty of Health Sciences, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Vitamin D is a compound responsible for maintaining mineral homeostasis. It protects against calcium and phosphate deficiency through the effects on the intestine, kidney, parathyroid gland and bone. All mechanisms that help maintain mineral homeostasis of the body are regulated by the vitamin D hormonal form - calcitriol. Synthesis of vitamin D starts in the skin as a non-enzymatic process, which begins during exposure to sunlight, when the absorption of ultraviolet B (UVB) radiation results in convertion of 7-dehydrocholesterol, a metabolite of cholesterol that is stored in the skin, to precholecalciferol (previtamin-D_3) that is immediately converted into cholecalciferol (vitamin D_3). After the skin synthesis cholecalciferol is transported to the liver where it undergoes hydroxylation, what results in formation of calcidiol (25(OH) D_3). The second metabolic process takes place in the kidney, where calcidiol undergoes hydroxylation at the C-1 position to the hormonal, the most active metabolite - 1,25-dihydroxyvitamin D (calcitriol). Vitamin D deficiency may result in bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults. Symptoms of osteomalacia affect mainly the skeletal system and are similar to that observed in rickets. It concerns thoracic kyphosis, pelvis deformities and also the varus knee. Osteoporosis is another condition that is related to abnormalities of mineral homeostasis. It is characterized by the progressive loss of bone mass, impaired bone microarchitecture, and consequently increased fragility and susceptibility to fracture. For the last several years other, non-classic actions of vitamin D_3 have been discussed. It was engendered by the discovery of vitamin D_3 receptor (VDR) in the most of body tissues and cells. Hence, there are many hypotheses which suggest the inverse relationship between vitamin D status and various diseases, such as cancer, autoimmune diseases, diabetes mellitus and others.

Key words: *vitamin D, vitamin D_3, cholecalciferol, mineral homeostasis, vitamin D deficiency, vitamin D_3 receptor, VDR, pleiotropic actions*

STRESZCZENIE

Witamina D jest związkiem chemicznym odpowiedzialnym za utrzymanie homeostazy mineralnej organizmu. Poprzez wpływ na jelita, nerki, przytarczyce i kości zapobiega niedoborowi wapnia i fosforanów. Aktywną formą witaminy D_3 o właściwościach hormonalnych jest kalcytriol, który odpowiada za utrzymanie homeostazy mineralnej organizmu. Pierwszy etap syntezy witaminy D zachodzi w skórze, pod wpływem ekspozycji na światło słoneczne (UVB). Polega on na nieenzymatycznej przemianie 7-dehydrocholesterolu do prowitaminy D (pre-D_3), która natychmiast ulega przekształceniu do cholekalcyferolu (witaminy D_3). Wyprodukowana w skórze witamina D_3 jest następnie transportowana do wątroby, gdzie ulega hydroksylacji, w wyniku której powstaje kalcydiol (25(OH)D_3). Drugi proces metaboliczny zachodzi w nerkach, gdzie kalcydiol ulega hydroksylacji w pozycji C-1 do hormonalnie najbardziej aktywnego metabolitu witaminy D - 1,25-dihydroksywitaminy D (kalcytriol). Niedobór witaminy D może prowadzić do chorób kości, takich jak krzywica u dzieci oraz osteomalacja i osteoporoza u osób dorosłych. Objawy osteomalacji dotyczą głównie układu kostnego i są zbliżone do tych obserwowanych w krzywicy. Są to m.in.: kifoza piersiowa, deformacje miednicy i szpotawość kolan. Osteoporoza to choroba, która także związane jest z zaburzeniem homeostazy mineralnej. Charakteryzuje się postępującą utratą masy kostnej, uszkodzeniami mikroarchitektury kości, i w konsekwencji zwiększoną ich kruchością i podatnością na złamania. Na przestrzeni ostatnich lat pojawiły się doniesienia dotyczące innych, nieklasycznych działań witaminy D_3. Stwierdzono obecność receptora witaminy D (VDR) w wielu tkankach organizmu, które nie biorą udziału w utrzymaniu homeostazy wapniowo-fosforanowej. Świadczy to o wielokierunkowym działaniu tego związku. Pojawiło się wiele hipotez sugerujących związek między niedoborem witaminy D a występowaniem wielu różnych chorób, takich jak: nowotwory, choroby autoimmunologiczne, cukrzyca i inne.

*** Corresponding author:** Julia Wranicz, Chair of Dietetics, Department of Nutritional Physiology, Faculty of Human Nutrition and Consumer Sciences, Warsaw University of Life Sciences – SGGW, Nowoursynowska street 159c, 02-776 Warsaw, Poland, phone +48 22 59 37 030, fax +48 22 59 37 031, e-mail: julia_wranicz@sggw.pl

Słowa kluczowe: *witamina D, gospodarka mineralna, niedobór witaminy D, witamina D_3, cholekalcyferol, receptor witaminy D_3, działanie plejotropowe*

INTRODUCTION

Vitamin D is a compound responsible for maintaining mineral homeostasis. It regulates serum calcium and phosphorus concentrations by affecting their metabolism and absorption. Vitamin D acts mainly in the kidneys, the intestine and the bone by its hormonal form calcitriol ($1,25(OH)_2D_3$). Vitamin D deficiency may result in bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults [10, 21].

However, for the last several years other, non-classic actions of vitamin D_3 have been discussed. It was engendered by the discovery of vitamin D_3 receptor in the most of body tissues and cells. Hence, there are many hypotheses which suggest the inverse relationship between vitamin D status and various diseases, such as cancer, autoimmune diseases, diabetes mellitus and others [1, 5]. Researchers point out that calcitriol, an active metabolite of vitamin D, affects gene activity. It binds to the nuclear VDR receptor what results in its activation and regulation of 5% of human genome activity. It indicates effectiveness and pleiotropic actions of vitamin D_3 [16].

Vitamin D_3 (cholecalciferol) is formed in the skin from 7-dehydrocholesterol that is present in plasma membranes of the epidermis and dermis, under the influence of UVB rays [11]. The effectiveness of skin synthesis depends on insolation and varies by region and season. In Poland efficient irradiation occurs from April to September, between 10 am and 3 pm. It is recommended to expose 18% of the skin surface of the body for at least 15 minutes daily, without the use of protective UV filters. Skin synthesis is the major vitamin D source. Other sources are food products, such as oily fish and cod liver oil [3]. Vitamin D can be ingested also through supplements and fortified foods.

CHARACTERISTICS OF VITAMIN D

Vitamin D is a generic term for the group of chemical compounds of molecular steroid structure. The most valuable are ergocalciferol-vitamin D_2, found in plants and fungi, and cholecalciferol-vitamin D_3, present in animal products [20]. Vitamins D_2 and D_3 do not reveal biological activity. In humans ergocalciferol and cholecalciferol are transformed to 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$,) - calcitriol, recognized as the most active form of vitamin D [11, 21].

Vitamin D, discovered by *Mc Collum* et al. in 1918, differs from other vitamins. The human body can produce it in sufficient amount from its provitamin that is present in the skin. In addition, vitamin D is characterized by hormonal activity, what means that its active metabolites are synthesized in the kidney and in the liver and transported by the blood to various target tissues and organs, such as intestinal epithelium and bones [17].

Skin synthesis of vitamin D is a non-enzymatic process, which begins during exposure to sunlight, when the absorption of ultraviolet B (UVB) radiation results in conversion of 7-dehydrocholesterol, a metabolite of cholesterol that is stored in the skin, to precholecalciferol (previtamin-D_3). Precholecalciferol is inherently unstable and is immediately converted into cholecalciferol - vitamin D_3, under the influence of body temperature, and then is absorbed into the blood stream [15]. Apart from skin synthesis, cholecalciferol can be supplied by the diet.

After the skin synthesis of vitamin D_3, its metabolic processes are continued in the internal organs. Cholecalciferol is transported from the skin to the liver by the blood. In hepatic cells it undergoes hydroxylation, what results in formation of 25-hydroxyvitamin D, that is called calcidiol ($25(OH)D_3$). After getting into the blood, calcidiol binds to the specific transport protein - gc-globulin (DBP). The $25(OH)D_3$-DBP complex is the transport form of vitamin D [22]. The second metabolic process takes place in the kidney, where calcidiol undergoes hydroxylation at the C-1 position to the hormonal, the most active metabolite - 1,25-dihydroxyvitamin D (calcitriol), and also hydroxylation at C-24 position to the probably inactive metabolite 24,25-dihydroxyvitamin D (24 -hydroxycalcidiol) [4, 15].

On the contrary to the non-enzymatic synthesis of vitamin D in the skin, its metabolism in the liver and kidney requires enzymes – hydroxylases. Their activity depends on many factors. It was found that the liver 25-hydroxylase activity increases with the amount of substrate, concentration of vitamin D-binding protein and certain drugs (e.g. antiepileptic). Its activity is decreased by the final vitamin D metabolites. Activities of the enzymes that catalyze 1-α and 24-hydroxylation of calcidiol depend on the serum concentrations of calcium and phosphate, and also some hormones and prostaglandins [17, 21].

The strongest stimulators of calcitriol synthesis are: parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), hypocalcemia and hypophosphatemia. Because of the feedback system, increased calcitriol level exerts the inhibitory effect on its own formation. Other factors that inhibit the synthesis of calcitriol are: deficiency of parathyroid hormone and

PTHrP, hypercalcemia, hyperphosphatemia and calcitonin [17, 21].

Concentration of vitamin D metabolites in the blood is determined not only by their synthesis, but also by the process of catabolism and excretion. There are three major metabolites of vitamin D present in the serum: $25(OH)D_3$, $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$, which are regularly eliminated from the body by conversion to more polar compounds in the target tissues and their excretion in bile, faeces and urine. Calcidiol, the hepatic metabolite, is eliminated by the 1- and 24-hydroxylation and excreted in bile, after its combination with glucuronic or sulfuric acid [17]. Other metabolites of vitamin D are also combined with glucuronic or sulfuric acid in the liver, excreted in bile into the intestine, and pass into the enterohepatic recirculation. It was found that physiologically only 3% of vitamin D metabolites circulating in the blood are excreted in urine and faeces. The daily excretion of vitamin D in humans is 1-7μg, mainly in the faeces, with the aid of bile salts. Small amounts appear also in urine. Human resources of vitamin D are stored mainly in the liver and adipose tissue [4, 17].

ROLE IN MINERAL HOMEOSTASIS – CLASSIC FUNCTION OF VITAMIN D

Vitamin D is the major regulator of calcium and phosphate homeostasis. It protects against calcium and phosphate deficiency through the effects on the intestine, kidney, parathyroid gland and bone. All mechanisms that help maintain mineral homeostasis of the body are regulated by vitamin D hormonal form - calcitriol [21]. Calcitriol acts in the gut affecting the intestinal absorption of calcium and phosphate. It increases calcium entry into enterocytes and accelerates calcium flux through the cell cytosol. Calcitriol enhances calcium transfer through the basement membrane of the intestinal epithelium into the circulatory system. In the phosphate transport through the intestinal mucous vitamin D-dependent sodium-phosphate co-transporter is involved.

Vitamin D is essential for proper bone mineralization. This is carried out by maintaining appropriate level of calcium and phosphate in the blood. Besides, calcitriol can stimulate production of collagen by osteoblasts [15].

In the mineral homeostasis $1,25(OH)_2D_3$ works in concert with parathyroid hormone to exert its beneficial effects on the plasma levels of ionised calcium and phosphate. The physiologic cycle starts in parathyroid gland where calcium is sensed by the calcium receptor. When the level of calcium in plasma decreases, parathyroid hormone is secreted and stimulates the renal enzyme 25(OH)D-1-aa-hydroxylase to produce more $1,25(OH)_2D$ from 25(OH)D. Parathyroid hormone, which stimulates the production of calcitriol in the kidney, also increases renal and intestinal reabsorption of calcium, whereas the phosphate transport is inhibited [6]. The resulting rise in $1,25(OH)_2D$ causes a boost in calcium transport within the intestine, bone, and kidney.

Calcitriol, $1,25(OH)_2D$, acts together with parathyroid hormone to mobilize calcium from bone tissue by osteoclastic stimulation. In the case of deficiency of the active form of vitamin D, resistance to the action of parathyroid hormone on the bone occurs [19]. Additionally, calcitriol works like a hormone in the intestinal tract where its activity is related to the interaction with VDR. Inactive calcitriol receptor in intestinal epithelial cells is located in the cytoplasm. After binding $1,25(OH)_2D$, the calcitriol-receptor complex translocates to the nucleus. The ligand-receptor complex acts like a transcription factor by promoting the expression of the gene encoding calcium binding protein. As a result, levels of calcium binding protein increase what enables the cells to transport more calcium (Ca^{2+}) from the intestine [20].

As a result of the feedback system high calcium plasma level achieved by the action of parathyroid hormone and calcitriol returns to normal. It is sensed by calcium receptors of the parathyroid gland, which regulate PTH secretion. Inhibition of PTH secretion depends not only on the feedback action of calcium, but also on the feedback loop involving $1,25(OH)_2D$ that directly suppresses PTH synthesis in the parathyroid gland [7].

CLASSIC DISORDERS RELATED TO VITAMIN D DEFICIENCY AND OVERDOSE

The most common diseases resulting from vitamin D deficiency, are: rickets that occurs in children and osteomalacia and osteoporosis that affect adult population [12, 22, 23]. In rickets severe lack of vitamin D_3 is followed by inhibition of calcium absorption in the intestine, excessive phosphate and calcium excretion in the kidney, and consequently decrease in the serum calcium concentration. In the aim to maintain proper calcium level parathyroid hormone is secreted. It stimulates release of calcium from the bones. This process results in the bone decalcification and subsequently symptoms of active rickets [22].

Rickets occurs in young children, and its first characteristic symptom is occipital malacia. Softening of the skull bones is usually recognized during palpation. In consequence of malacia, the occiput becomes flattened and the skull bones form a square shape with enlarged circumference [14, 22]. In children who start to walk varus or valgus deformities of the knees and also pelvis defects may occur. They may be accompanied by skeletal muscle flaccidity, which results in a delay in motor development, increase in abdominal circumference,

abdominal distension and constipation. The described above early symptoms usually disappear in the later life. Late symptoms which remain in adulthood are: the flat feet, defects of the spine and chest construction [22]. Tetany is another rickets symptom. It results from hypocalcaemia and is characterized by excessive electrical and mechanical excitability of the neuromuscular system and is followed by tonic cramps [14].

The initial phase of rickets is characterized by the decreased serum concentration of the vitamin D_3 metabolite ($25(OH)D_3$), increased alkaline phosphatase activity, followed by the increased excretion of phosphate in urine. Additionally, in the advanced rickets a decreased level of serum phosphorus is observed. Calcium concentration is usually in the lower normal range. Prevention of rickets is based on the exposition to ultraviolet rays, and application of vitamin D_3 preparations [14].

Osteomalacia is a disease similar to rickets, but affects the adult population. It is caused by the deficiency or absence of vitamin D_3 in the body, what results in impaired absorption of calcium and phosphate ions in the intestine, and subsequently in their reduced resources in the body. It is followed by reduction of the bone mineral density, which makes them less resistant to mechanical damage and fracture. Apart from the vitamin D deficiency, also other factors, such as use of antiepileptic drugs, consumption of large amounts of alcohol and hepatic cirrhosis, may contribute to osteomalacia [12, 18, 23].

Symptoms of osteomalacia affect mainly the skeletal system and are similar to that observed in rickets. It concerns thoracic kyphosis, pelvis deformities and also the varus knee. Other characteristic symptoms are: the disturbance of gait called "the duck walk", and muscle weakness, which results in the rapid fatigue [18, 23]. Osteomalacia therapy is based on the oral supplementation of vitamin D_3 and calcium, as well as administration of phosphates. Exposure to UV radiation, which stimulates the cutaneous synthesis of vitamin D_3 is also recommended [23].

Osteoporosis is another condition that is related to abnormalities of mineral homeostasis. It is characterized by the progressive loss of bone mass, impaired bone microarchitecture, and consequently increased fragility and susceptibility to fracture [12, 13]. Among factors that contribute to this disease there is the deficiency of vitamin D in the body. The beginning of the disease is usually asymptomatic. The most common clinical signs, that develop in advanced cases of osteoporosis, include loss of height due to vertebral compression fractures, back pain and the formation of senile i.e. excessive thoracic kyphosis. The disease is often complicated by bone fractures, that occur even at minor injuries, such as the so-called falls from "the own height" [13].

The increased risk of fractures in osteoporosis due to deficiency of vitamin D is also related to its effect on the function of skeletal muscles. The vitamin D active metabolite - $1,25(OH)_2D_3$ binds to the VDR nuclear receptor in muscle cells and thus stimulates biosynthesis of proteins that are responsible for the growth of these cells, what results in the increase in muscle strength. Therefore, it is postulated that vitamin D deficiency leads to weakening of the antigravity muscles, grip strength and also impairment of physical endurance of patients. Apart from pharmacological treatment of osteoporosis, it is important to comply with a well-balanced diet, rich in calcium, vitamin D and protein [13].

Another problem is the vitamin D hypervitaminosis. It is unlikely to be caused by the diet or intense exposure to ultraviolet radiation. However, during the treatment of certain diseases, such as sarcoidosis, tuberculosis, or idiopathic hypercalcemia, therapeutic doses of vitamin D may cause symptoms of poisoning. The 25-hydroxyvitamin concetrations in the blood of more than 200 ng/mL (500 nmol/L) are considered to be potentially toxic and may lead to hypercalcemia and hyperphosphatemia. Among symptoms of hypercalcemia there are: nausea and vomiting, loss of appetite, constipation, weakness, fatigue, excessive thirst, increased urination, itching and headaches. Besides, hypercalciuria may result in formation of calcium deposits in tissues and organs, and also calcification in the kidneys and hence the failure of this organ [8, 9].

PLEIOTROPIC ACTION OF VITAMIN D

Development of molecular biology and diagnostic methods enabled the more detailed research of functions of vitamin D in the human body. A number of new types of its activities were identified. It was even proposed that proper vitamin D supplementation is rather an endocrinologic than nutritional issue. Calcitriol binds to the nuclear VDR receptor, what results in control of 500 gens. This indicates pleiotropic actions of vitamin D_3. Apart from the tissues and organs responsible for maintaining calcium and phosphate homeostasis, the

Table 1. Cells, tissues and organs with the vitamin D_3 receptor (VDR) [16]

Cells, tissues and organs with the VDR		
Adipose tissue	Skin tissue	Placenta
Osseous tissue	Hair follicle	Uterus
Cartilaginous tissue	Kidney	Ovary
Smooth muscles	Fetal liver	Testicle
Cardiac muscle	Lungs	Epididymis
Fetal muscle tissue	Brain	Parotid gland
Adrenal gland	Parathyroid gland	Retina
Cancer cells	Pituitary gland	Bone marrow
Stomach	Thymus gland	Pancreatic β-cells
Small intestine	Thyroid gland	Osteoblasts
Large intestine	Mammary gland	Lymphocytes B and T

vitamin D receptor was identified in 36 other sorts of tissues and cells in the human organism (Table 1.), e.g. in the cardiac muscle, smooth muscles, brain, endocrine glands and lymphocytes B and T.

In addition, 1-α-hydroxylase, the enzyme that converts non-active $25(OH)D_3$ to the active form $1,25(OH)_2D_3$, was found in many various localizations, apart from the kidney (Table 2). For example, 1α-hydroxylase activity was observed in endothelial cells, smooth muscle cells of the blood vessels, and also activated macrophages. This type of the enzyme is called a peripheral hydroxylase. Its importance for the vitamin D effect in the human body is increasingly distinguished.

Table 2. Presence and activity of the peripheral 1α-hydroxylase of 25-hydroxyvitamin D [16]

Site	mRNA	Protein	1-α-hydroxylase activity
Large intestine	+	+	+
Dendritic cells	+	-	-
Endothelial cells	+	+	+
Brain	-	+	-
Mammary gland	+	+	+
Pancreatic islands	+	+	+
Parathyroid gland	+	+	+
Placenta	+	+	+
Prostate gland	+	+	+
Skin (keratinocytes)	+	+	+
Macrophages (activated)	+		+

Discovery of the vitamin D pleiotropic activity in the majority of body cells and tissues stemmed from numerous epidemiological surveys that revealed correlation between low vitamin D status and increased risk of diseases of various etiologies, including autoimmune and cardiovascular diseases, cancers, diabetes and also infectious diseases [2].

The role of vitamin D in the pathogenesis of these diseases will be described in the second part of this paper.

SUMMARY

The classic role of vitamin D is maintaining mineral homeostasis. Its deficiency may result in rickets, osteomalacia and osteoporosis. Except of the bone, intestine and kidney, vitamin D also acts in other tissues and organs. Further studies addressing the mechanisms by which vitamin D affects and the proper supplementation required are needed.

REFERENCES

1. *Agmon-Levin N., Shoenfeld Y.*: From a vitamin to hormone and eventually to immunomodulator. Booklet Vitamin D, 2012: 1-2.
2. *Agmon-Levin N., Theodor E., Segal R.M., Shoenfeld Y.*: Vitamin D in systemic and organ-specific autoimmune diseases. Clin. Rev. Allergy Immunol. 2013 Oct.;45(2):256:66, doi:10.1007/s12016-012-8342-y.
3. *Charzewska J., Chlebna-Sokół D., Chybicka A., Czech-Kowalska J., Dobrzańska A., Helwich E., Imiela J.R., Karczmarewicz E., Książyk J.B., Lewiński A., Lorenc R.S., Lukas W., Łukaszkiewicz J., Marcinowska-Suchowierska E., Milanowski A., Milewicz A., Płudowski P., Pronicka E., Radowicki S., Ryżko J., Socha J., Szczapa J., Weker H.*: Position of the Panel of Experts. Polish recommendations for the prevention of vitamin D deficiency - 2009. Ginekol Pol 2010; 81: 149-153 (in Polish).
4. *Christakos S., Ajibade D., Dhawan P., Fechner A.J., Mady L.J.*: Vitamin D: Metabolism. Endocrinol Metab Clin North Am 2010; 39(2): 243–253. doi: 10.1016/j.rdc.2012.03.003.
5. *Christakos S., DeLuca H.*: Minireview: vitamin D: is there a role in extraskeletal health? Endocrinology 2011; 152: 2930-2936. doi: 10.1210/en.2011-0243.
6. *Coetzee M., Kruger MC.*: Osteoprotegerin-receptor activator of nuclear factor-kappaB ligand ratio: a new approach to osteoporosis treatment? South Med J 2004; 97(5): 506-11.
7. *FAO/WHO* expert consultation on human vitamin and mineral requirements, 2001: 109-120.
8. *Granado-Lorencio F., Blanco-Navarro I., Pérez-Sacristán B., Donoso-Navarro E., Silvestre-Mardomingo R.*: Serum levels of 3-epi-25-OH-D3 during hypervitaminosis D in clinical practice. J Clin Endocrin Metab 2012; 97(12): 2266-2270. doi: 10.1210/jc.2012-2627.
9. *Gronowska-Senger A.*: Fat-soluble vitamins. In: *Gawęcki J., Hryniewiecki L.* eds. Human Nutrition. Fundamentals of food science. Warsaw, Wydawnictwo Naukowe PWN, 2007 (in Polish).
10. *Holick M.*: Vitamin D: Sources and health benefits. Standardy Medyczne. Pediatria 2012; 9: 705-715.
11. *Holick M.*: The Vitamin D epidemic and its health consequences. American Society for Nutrition 2005; 2739-2748.
12. *Holick M.*: High Prevalence of Vitamin D Inadequacy and implications for health. Mayo Clin Proc. 2006; 81(3): 353-373.
13. *Jasik A., Tałałaj M., Paczyńska M., Walicka M., Wąsowski M., Marcinkowska-Suchowierska E.*: Vitamin D and osteoporosis. Postępy Nauk Medycznych 2008; 1: 8-13 (in Polish).
14. *Kaludjerovic J., Vieth R.*: Relationship between Vitamin D during perinatal development and health. J Midwifery Womens Health 2010; 55(6): 550-560. doi: 10.1016/j.jmwh.2010.02.016.
15. *Karczmarewicz E., Łukaszkiewicz J., Lorenc R.*: Vitamin D - the mechanism of action, epidemiological studies, the standard of supplementation. Standardy Medyczne 2007; 4: 169-174 (in Polish).
16. *Lorenc R., Kaczmarewicz E., Kryśkiewicz E., Płudowski P.*: Vitamin D provision and suplementation standards. Standardy Medyczne. Pediatria 2012; 9: 595-604 (in Polish).

17. *Marcinowska-Suchowierska E., Walicka M., Tałałaj M., Horst-Sikorska W., Ignaszak-Szczepaniak M., Sewerynek E.*.: Vitamin D supplementation in adults – guidelines. Postępy Nauk Medycznych 2010; 2: 160-166 (in Polish).
18. *Pack A.*: Bone health in people with epilepsy: Is it impaired and what are the risk factors? Seizure 2008; 17(2): 181-186. doi: 10.1016/j.seizure.2007.11.020.
19. *Rodriguez M., Muñoz-Castañeda J.R., Almaden Y.*: Therapeutic use of calcitriol. Curr Vasc Pharmacol 2013; 5.
20. *Voet D., Voet J.G.*: Biochemistry. Volume one. Biomolecules, mechanisms of enzyme action, and metabolism. New York, John Wiley&Sons, 2004: 663-664.
21. *Walicka M., Jasik A., Paczyńska M., Wąsowski., Tałałaj M., Marcinowska-Suchowierska E.*: Deficiencies of vitamin D - social problem. Post Nauk Med 2008; 1: 14-22 (in Polish).
22. *Wagner C., Greer F. and the Section on Breastfeeding and Committee on Nutrition:* Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122: 1142-1152.
23. *Zagaria M.*: Osteomalacia: Vitamin D deficiency and bone pain. U.S. Pharmacist 2009; 34(3): 22-24.

Received: 20.12.2013
Accepted: 18.04.2014