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Vitamin D i srčanožilne bolesti
Vitamin D and cardiovascular diseases

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SAŽETAK: Vitamin D je važan hormon u regulaciji mineralnog metabolizma i u procesu mineralizacije kostiju. Kako je receptor za vitamin D prisutan u mnogobrojnim tkivima, postoji veliko zanimanje za istraživanje drugih potencijalnih uloga vitamina D, pogotovo u srčanožilnim bolestima (SŽB). Mnoge studije su pokazale da je manjak vitamina D povezan s povećanim rizikom od razvoja SŽB, uključujući arterijsku hipertenziju, zatajivanje srca i ishemijsku bolest srca. Prospektivne studije su pokazale da manjak vitamina D povećava rizik za razvoj arterijske hipertenzije i iznenadne srčane smrti u bolesnika s postojećim SŽB.

KLJUČNE RIJEČI: vitamin D, srčanožilne bolesti, kardiovaskularni rizik.

SUMMARY: Vitamin D is an important hormone in the regulation of mineral metabolism and bone mineralization process. Since the receptor for vitamin D is present in many tissues, there is a great interest in exploring other potential roles of vitamin D, particularly in cardiovascular diseases (CVDs). Many studies have shown that vitamin D deficiency is associated with an increased risk of developing CVDs, including hypertension, heart failure and ischemic heart disease. Prospective studies have shown that vitamin D deficiency increases the risk of developing hypertension and sudden cardiac death in patients with existing CVD.

KEYWORDS: Vitamin D, cardiovascular diseases, cardiovascular risk.

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Uvod

Klasična uloga vitamina D je povećanje apsorpcije kalcija u crijevima[1]. Aktivni oblik vitamina D, 1,25-dihidroksikolekalciferol (1,25(OH)$_2$D) ponaša se kao steroidni hormon vežući se na vitamin D receptor (VDR) koji je prisutan u mnogim stanicama, uključujući kardiomiocite[2], glatke mišićne stanice krvnih žila[3] i stanice endotela[4]. Istraživanja su pokazala da manjak vitamina D uzrokuje povećanje rizika od razvoja srčanožilnih bolesti (SŽB). Način na koji vitamin D štiti pojedinca od SŽB nije do kraja istražen. Postoje mnoge teorije, uključujući negativnu regulaciju renina i time snižavanje arterijskog tlaka (AT), snižavanje razine paratiroidnog hormona (PTH) i poboljšanje kontrole glikemije (**Tablica 1**).

Fiziologija vitamina D

Vitamin D se pojavljuje u dva oblika: vitamin D$_2$ (ergokalciferol) i vitamin D$_3$ (kolekalciferol). Vitamin D$_2$ koji se nalazi u biljkama i kvascu, proizvod je djelovanja ultraljubičastih zraka na ergosterol dok se vitamin D$_3$ nalazi u masnoj ribi i ulju dobivenom iz bakalarove jetre te maslacu. Vrlo su male količine u mesu, kravljem i ljudskom mlijeku. Vitamin D iz hrane apsorbira se u tankom crijevu ovisno o apsorpciji lipida i hilomikronima prelazi u limfu i u krv te u jetru. Općenito se apsorbira 50% vitamina D unešenog hranom (**Slika 1**).

Introduction

The traditional role of vitamin D is to increase the absorption of calcium in intestines[1]. The active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D) acts as a steroid hormone binding to the vitamin D receptor (VDR), which is present in many cells, including cardiomyocytes[2], smooth muscle cells of blood vessels[3] and endothelial cells[4]. The trials have shown that vitamin D deficiency causes an increase in the risk of developing cardiovascular disease (CVD). The way in which vitamin D protects an individual against CVD has not been fully explored. There are many theories, including the negative regulation of renin and thus lowering blood pressure (BP), lowering the level of parathyroid hormone (PTH) and improved glycemic control (**Table 1**).

Vitamin D physiology

Vitamin D comes in two forms: vitamin D$_2$ (ergocalciferol) and vitamin D$_3$ (cholecalciferol). Vitamin D$_2$ which is found in plants and yeast is the product of action of ultraviolet rays while the ergosterol vitamin D$_3$ is found in fatty fish and oil obtained from cod liver and butter. There are very small amounts of it in meat, cow and human milk. Vitamin D from food is absorbed in the small intestine depending on the absorption of lipids and chylomicrons and enters the lymph, blood and liver. Generally it absorbs 50% of vitamin D which is entered by food (**Figure 1**).

Table 1. *Distribution of VDR in normal tissues/cells.*

Organ/tissue	Expression level	Cell types
Digestive system		
Small intestine	++++++++++	Epithelium
Large intestine	+++++++	Epithelium
Liver	—	
Pancreas	+++	Epithelium
Kidney		
Distal tubule	++++++++	Epithelium
Proximal tubule	++	Epithelium
Glomerular podocytes	+	Podocytes
Respiratory system		
Lung alveolar cells	—	
Bronchus	+++++	Epithelium
Bone		
Osteoblasts	+++++	Osteoblasts
Chondrocytes	+	Chondrocytes
Muscle system	—	
Immune system		
Thymus	+++++	Epithelium
Spleen/lymph node	++	Monocyte/macrophage/T-cell
Endocrine system		
Thyroid	—	
Parathyroid	++++++++	Epithelium
Pituitary gland	+++	Epithelium
Adrenal gland	—	
Brain		
Cerebrum	— ?	
Cerebellum	— ?	
Spinal cord	— ?	
Reproductive system		
Testis	++	Germ cells
Prostate gland	++++	Epithelium
Mammary gland	++++	Epithelium

? — Not completely defined

Izvor: Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor?. Arch Biochem Biophys. 2012 Jul 1;523(1):123-33. doi:10.1016/j.abb.2012.04.001.

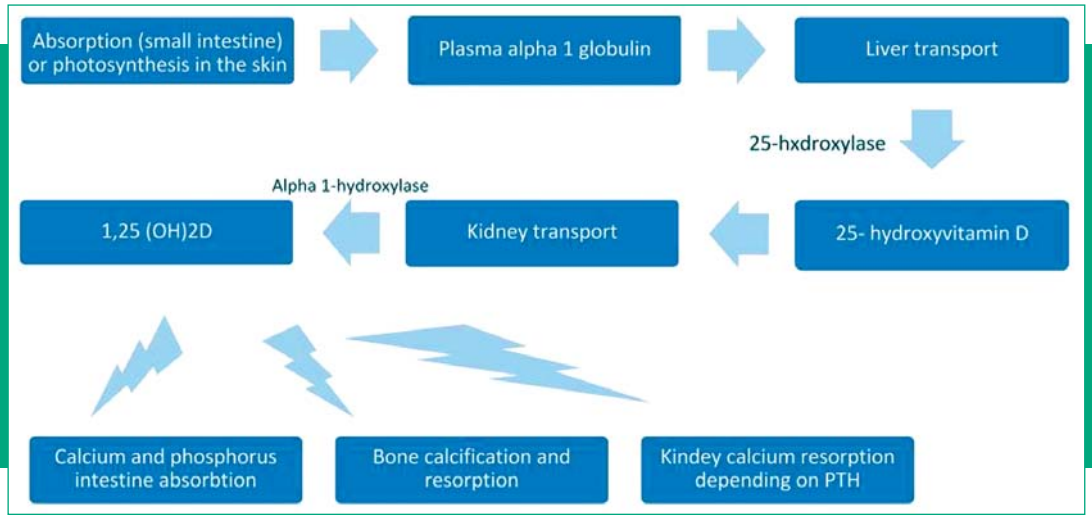

Figure 1. *Vitamin D metabolism.*

U čovjeka se u koži iz 7-dehidrokolesterola djelovanjem ultraljubičastih B zraka iz sunčeva svijetla stvara previtamin D_3, a nakon toga vitamin D_3. U tkiva dospijeva uz pomoć prijenosničke bjelančevine na koju je vezan u krvi. Pretjerano izlaganje sunčevoj svjetlosti ne može dovesti do hipervitaminoze D i toksičnosti jer ultraljubičaste zrake pretvaraju višak vitamina D_3 u biološki inertan izomer[5]. Metabolizam vitamina D_2 ili D_3 u organizmu je jednak. U jetri se D vitamin djelovanjem enzima 25-hidroksilaze citokroma P 450 pretvara u 25-hidroksivitamin D (25(OH)D, kalcidiol) koji nije biološki aktivan[6]. U bubregu se događa najvažniji korak gdje iz 25(OH)D djelovanjem PTH na 1-alfa-hidroksilazu nastaje 1,25 — dihidroksivitamin D ($1,25(OH)_2D$, kalcitriol), čiji učinak u jezgri i građa odgovaraju onima steroidnih hormona[5]. Receptor za vitamin D je prisutan u većini tkiva, uključujući stanice endotela, glatke mišićne stanice krvnih žila i stanice miokarda[7]. I glatke mišićne stanice krvnih žila i stanice endotela imaju sposobnost pretvaranja kalcidiola u kalcitriol[8]. Učinci vitamina D se postižu interakcijom kalcitriola i VDR[5,9,10]. Cirkulirajući kalcitriol prolazi kroz staničnu membranu, ulazi u citoplazmu te se u jezgri veže za VDR. Kompleks VDR-$1,25(OH)_2D$ stvara heterodimer s X-receptorom retinoične kiseline, spaja se s akceptorskim mjestom DNA te potiče transkripciju gena i sintezu nove mRNA. Direktno i indirektno kalcitriol regulira preko 200 gena, uključujući gene važne za proizvodnju renina u bubregu, proizvodnju inzulina u gušterači, oslobađanje citokina iz limfocita, rast i proliferaciju glatkih mišićnih stanica vaskulature i stanica miokarda[5]. S relativnom niskom biološkom aktivnošću, kalcidiol je oblik koji ima najveću koncenraciju u cirkulaciji i uzima ze za određivanje ukupnih zaliha vitamina D_5. Dok endokrino djelovanje aktivnog metabolita, kalcitriola, karakterizira održavanje homeostaze kalcija i fosfata[11], novija istraživanja su usmjerena na autokrine i parakrine aktivnosti vitamin D. Autokrino/parakrino djelovanje vitamina D je najbolje naznačeno u koži i imunološkom sustavu gdje regulira staničnu diferencijaciju i sazrijevanje. Nedavna istraživanja ukazuju da autokrino/parakrino djelovanje u glavnim stanicama kosti također regulira proliferaciju i diferencijaciju. Istraživanja na štakorima su pokazala da je odgovarajuća serumska koncentracija kalcidiola kritična za optimalno zdravlje kosti i za zaštitu od osteoporoze što se podudara s rezultatima kliničkih istraživanja na ljudima[12].

Definicija i prevalencija manjka vitamina D

Iako je kalcitriol aktivan oblika vitamina D, njegova serumska koncentracija ne odražava ukupni status vitamina D te klinički nije od značaja. Serumska koncentracija kalcidiola koja odražava koncentraciju vitamina D i endogenog i egzogenog podrijetla se uzima kao mjera za kliničko određivanje vitamin D statusa[5]. Nekoliko je razloga za to: **1.** vrijeme poluživota kalcidiola je duže od vremena poluživota kalcitriola (-3 tjedna u odnosu na -8 sati), **2.** koncentracija kalcidiola u cirkulaciji je 1.000x veća od koncentracije kalcitriola (ng/ml u odnosu na pg/ml), **3.** stvaranje kalcitriola je uglavnom pod utjecajem PTH koji regulira i koncentraciju kalcija. Zbog toga je moguće da koncentracija kalcitriola bude povišena u bolesnika s teškim manjkom vitamina D, kako bi se održala normalna koncentracija kalcija. Većina stručnjaka se slaže da cirkulirajuća koncentracija kalcidiola predstavlja ukupni vitamin D status pojedinca, ali koja je optimalna koncentracija vitamina D ostaje upitno. Trenutno

Previtamin D_3 is produced in the skin from 7-dihydroxycholesterol by action of ultraviolet B rays from the sunlight, which thereafter turns into vitamin D_3. It enters the tissues with a help of transmission protein to which it is bound in blood. Overexposure to sunlight cannot lead to hypervitaminosis D and toxicity, because ultraviolet rays convert excess vitamin D_3 into biologically inert isomer[5]. Metabolism of vitamins D_2 or D_3 in the organism is the same. In the liver, by activity of the enzyme 25-hydroxylase of cytochrome P 450 vitamin D converts into 25-hydroxyvitamin D (25(OH)D, calcidiol) which is biologically less active[6]. The most important step occurs in the kidney where 1.25-dihydroxyvitamin D ($1.25(OH)_2D$, calcidiol) is produced from 25(OH)D by the activity of PTH on 1-alpha-hydroxylase, the effect of which in the nucleus and composition equals those of steroid hormones[5]. Vitamin D receptor is present in most of the tissues, including endothelial cells, smooth muscle cells of blood vessels and myocardial cells[7]. Both smooth muscle cells of blood vessels and endothelial cells are capable of converting calcidiol to calcitriol[8]. The effects of vitamin D are achieved by the interaction calcitriol and VDR[5,9,10]. Circulating calcitriol passes through the cell membrane, enters the cytoplasm and binds to VDR in the nucleus. VDR complex-$1,25(OH)_2D$ forms heterodimer with X-retinoic acid receptor, binds to the DNA acceptor site and stimulates transcription of genes and the synthesis of new mRNA. Directly and indirectly, calcitriol regulates over 200 genes, including the genes important for the production of renin in the kidney, production of insulin in the pancreas, release of cytokines from lymphocytes, growth and proliferation of vascular smooth muscle cells and myocardial cells[5]. With relatively low biological activity, calcidiol is the form that has the largest concentration in the circulation and is taken for determining the total stock of vitamin D_5. While endocrine activity of the active metabolite, calcitriol, is characterized by maintaining homeostasis of calcium and phosphate[11], recent studies have focused on the autocrine and paracrine actions of vitamin D. Autocrine/paracrine action of vitamin D is best indicated in the skin and the immune system, where it regulates cellular differentiation and maturation. Recent studies indicate that the autocrine/paracrine action in the main bone cells also regulates the proliferation and differentiation. Studies in rats have shown that adequate serum concentration of calcidiol is critical for optimal bone health and for the prevention of osteoporosis which coincides with the results of clinical studies in humans[12].

Definition and prevalence of vitamin D deficiency

Although calcitriol is the active form of vitamin D, its serum concentration does not reflect the overall status of vitamin D and is of no clinical significance. Serum calcidiol concentration that reflects the concentration of vitamin D and of endogenous and exogenous origin is taken as a measure for the clinical determination of vitamin D status[5]. There are several reasons for this: **1.** half-life of calcidiol is longer than the half-life of calcitriol (-3 weeks compared to -8 hours), **2.** concentration of calcidiol in the circulation is 1,000x greater than the concentration of calcitriol (ng/ml compared to the pg/ml) **3.** formation of calcitriol is mainly influenced by regulating PTH which regulates the calcium concentration. For that reason the calcitriol concentration may be elevated in patients with severe vitamin D deficiency, in order to maintain normal calcium concentration. Most experts agree that the circulating concentration of calcidiol represents total vitamin D status of

se manjak vitamina D definira kao koncentracija kalcidiola manja od 20 ng/ml[5,13,14]. Postoji i definicija da koncentracija kalcidiola između 20 i 30 ng/ml označava relativnu insuficijenciju vitamina D, dok koncentracija iznad 30 ng/ml predstavlja zadovoljavajuću koncentraciju vitamina D[5,15,16]. Intoksikacijske koncentracije vitamina D smatraju se one iznad 150 ng/ml i uzrokuju tešku hiperkalcemiju, hiperfosfatemiju i bubrežno oštećenje (**Tablica 2**)[5,13,14]. Čimbenici rizika za manjak vitamina D su sljedeći: nedovoljno izlaganje sunčevoj svjetlosti, tamnija put, uznapredovale godine, hospitalizacija, manjak unosa vitamina D hranom, život u sjevernoj Zemljinoj polutki, sindrom malapsorpcije, lijekovi koji ubrzavaju metabolizam kalcitriola (fenitoin, fenobarbital, kortikosteroidi), kronična bubrežna bolest, disfunckija jetre, pretilost.

an individual, but what is the optimal concentration of vitamin D remains questionable. Currently, vitamin D deficiency is defined as a concentration of calcidiol less than 20 ng/ml[5,13,14]. There is a definition that calcidiol concentration between 20 and 30 ng/ml indicates the relative insufficiency of vitamin D, while the concentration above 30 ng/ml is a sufficient concentration of vitamin D[5,15,16]. Intoxication concentrations of vitamin D are considered to be those above 150 ng/ml and cause severe hypercalcemia, hyperphosphatemia and renal damage (**Table 2**)[5,13,14]. The risk factors of vitamin D insufficiency are the following: insufficient exposure to sunlight, brown tan, advanced age, hospitalization, insufficient intake of vitamin D with food, life in the northern hemisphere, malabsorption syndrome, drugs that speed up the metabolism of calcitriol (phenytoin, phenobarbital, corticosteroids), chronic kidney disease, liver dysfunction, obesity.

Table 2. *Relationship between serum 25-hydroxyvitamin — concentration and health.*

25-Hydroxyvitamin D Concentration (ng/ml)	Status	Health Consequence
< 15	Severe deficiency	Can lead to rickets and severe bone disease
< 20	Deficient	Inadequate bone health and osteoporosis
20-30	Relative insufficiency	Recently considered inadequate for optimal health status
>30	Adequate stores	Optimal health status
>150	Toxicity	Hypercalcemia, hyperphosphatemia, and renal impairment

Patofiziologija vitamina D u srčanožilnim bolestima

Dosadašnja mnogobrojna istraživanja upućuju na inverznu povezanost serumske koncentracije vitamina D i disfunkcije srčanožilnog sustava[17-19]. Prva istraživanja koja su pokušala dokazati povezanost vitamina D i SŽB su rađena na modelima štakora s manjkom vitamina D prije više od 20 godina[20-22]. Ta istraživanja na životinjama su pokazala vezu između manjka vitamina D i hipertrofije srčanih klijetki, fibroze, arterijske hipertenzije. Podupirala su ulogu vitamina D u održavanju srčanožilnog sustava putem neposrednog utjecaja kalcitriola na kardiomiocite i posredno putem djelovanja na cirkulirajuće hormone i kalcij.

Prvi klinički dokazi da bi manjak vitamina D mogao imati utjecaj na razvoj SŽB viđeni su u bolesnika s terminalnim stadijem kronične bubrežne insuficijencije (ESRD)[23]. Zbog smanjene bubrežne funkcije, pretvorba kalcidiola u kalcitriol je smanjena što dovodi do manjka aktivnog oblika vitamina D[24]. Zbog manjka kalcitriola razvija se sekundarni hiperparatireoidizam što dovodi do porasta koncentracije PTH[11,25]. Povišena koncentracija PTH se povezuje s porastom AT i povećanom kontrakcijom miokarda što dovodi do hipertrofije i fibroze miokarda te zatajivanja srca[26]. Smanjenje hiper-

Pathophysiology of vitamin D in cardiovascular diseases

Numerous studies conducted so far suggest an inverse association of serum concentrations of vitamin D and cardiovascular system dysfunction[17-19]. The first studies that were to prove the connection between vitamin D and CVDs were conducted on models of rats with vitamin D deficiency more than 20 years ago[20-22]. These trials on animals showed a link between vitamin D deficiency and cardiac ventricular hypertrophy, fibrosis and arterial hypertension. They supported the role of vitamin D in maintaining the cardiovascular system through the direct impact of calcitriol on cardiomyocytes and indirectly through the effect on circulating hormones and calcium.

The first clinical evidence that vitamin D vitamin deficiency could have an impact on the development of CVDs was seen in patients with end-stage chronic renal disease (ESRD)[23]. Because of the impaired renal function, the conversion of calcidiol to calcitriol is reduced causing thus deficiency of the active form of vitamin D[24]. Calcitriol deficiency causes a development of secondary hyperparathyroidism leading to an elevated concentration of PTH[11,25]. The high PTH concentration is associated with a BP elevation and elevated myocardial contraction which leads to myocardial hypertrophy

trofije lijeve klijetke (HLK)[27] uz smanjenje kardiovaskularne smrtnosti[28, 29] primjećeno je u bolesnika s ESRD i sekundarnim hiperparatireoidizmom koji su dobivali aktivni oblik vitamina D (kalcitriol ili analog). U toj grupi bolesnika povišena koncentracija PTH se smatra primarnim uzrokom srčane disfunkcije te je terapija usmjerena na smanjenje koncentracije PTH. Nekoliko istraživanja je pokazalo da nakon paratireoidektomije u bolesnika s ESRD dolazi do smanjenja AT i HLK, ali neka istraživanja nisu uočila takve rezultate[27,30,31]. Iz tog je proizašlo pitanje da li je povišena razina PTH jedini uzrok srčane disfunkcije u bolesnika s ESRD. Tako je nastala hipoteza o direktnom učinku vitamin D na srčanu funkciju. Receptor za vitamin D je prisutan u mnogim tkivima koja nemaju ulogu u regulaciji metabolizma kalcija kao što su limfociti, stanice kolona, hepatociti i srčani miociti[32]. Izražena ekpresija VDR na drugim tkivima jača teoriju da vitamin D ima i drugu endokrinu ulogu, a ne samo reguliranje homeostaze kalcija9. Vitamin D djelovanjem na VDR u srčanim stanica regulira ulazak kalcija u stanice, kontrolira količinu slobodnog kalcija u citosolu te time regulira kontraktilnost miokarda i kontrolira rast i proliferaciju stanica[20-22,33,34]. Izravne fiziološke posljedice nepostojanja VDR na srčanu funkciju su proučavane u nekoliko studija na životinjama[35-37]. U tim studijama, vitamin D receptor knockout miševi su uspoređeni s miševima divljeg tipa koji imaju prisutan VDR[35,36]. Histološko bojenje miokarda pokazalo je vrlo značajnu staničnu hipertrofiju u vitamin D receptor knockout miševa u usporedbi s miševima divljeg tipa. Hipertrofija miokarda i fibroza miokarda zabilježena je isključivo u vitamin D receptor knockout miševa[35,36]. Istraživanje na vitamin D receptor knockout miševima također dokazuje da vitamin D posredno utječe na rad srca zbog svoje uloge kao negativni regulator renin-angiotenzin-aldosteron sustava (RAAS)[37,38]. Ustanovilo se da je u vitamin D receptor knockout miševa bila prisutna trostruko izraženija ekspresije renin glasničke RNA (mRNA) i više od 2,5x povećanje koncentracije angiotenzin II u plazmi u usporedbi s divljim tipom miševa[38]. Kako kalcitriol regulira PTH i održava koncentraciju kalcija, sekundarni hiperparatiroidizam i hipokalcemija su se neminovno razvili u vitamin D receptor knockout miševa. Vitamin D receptor knockout miševi su prije razvoja sekundarnog hiperparatiroidizma dobivali kalcija za održavanje odgovarajuće razine u serumu. Usprkos normalnoj koncentraciji serumskog kalcija i PTH, u vitamin D receptor knockout miševa i dalje je zabilježena povišena proizvodnja renin mRNA i angiotenzina II što ukazuje da kalcitriol ima izravan utjecaj na RAAS koji je neovisan o kalciju ili PTH.

Osim RAAS aktivacije, pojačana aktivacija imunosnog sustava često se povezuje s SŽB, točnije s aterosklerozom i kalcifikacijom valvula i nestabilnim plakom i njegovim pucanjem[39]. Prekomjerno stvaranje upalnih citokina doprinosi razvoju i progresiji zatajenja srca[40]. Eksperimentalne studije su pokazale da vitamin D igra važnu ulogu u regulaciji nekoliko važnih upalnih i protuupalnih citokina[41-43]. U jednoj studiji je opažena smanjena proizvodnja upalnih citokina (interleukin [IL]-6 i čimbenika tumorske nekroze [TNF] kada su aktivirani monociti bili izloženi kalcitriolu[42]. Slično, u drugoj studiji, produkcija protuupalnog citokina IL-10 se značajno povećala kada su dendritičke stanice bile izložene kalcitriolu u usporedbi s kontrolnim stanicama koje nisu[41]. Ove studije su pokazale da hormonsko djelovanje vitamina D ima aktivnu i izravnu ulogu u regulaciji nekoliko imunomodulatorskih citokina što dovodi do smanjenja upale.

Iz rezultata eksperimentalnih laboratorijskih studija proizašla su mnoga klinička ispitivanja o poveznosti manjka vitamina D i arterijske hipertenzije, a neka od njih su dobila poz-

and fibrosis as well as the heart failure.[26] Reduction of the left ventricular hypertrophy (HLK)[27] along with a reduction of cardiovascular mortality[28, 29] was observed in patients with ESRD and secondary hyperparathyroidism who received the active form of vitamin D (calcitriol or its analog). In this group of patients, the high PTH level is considered to be the primary cause of cardiac dysfunction and the therapy is aimed at reducing the PTH levels. Several trials have shown that parathyroidectomy in patients with ESRD is followed by a decrease in BP and LVH, but some trials have not observed such results[27,30,31]. This brings up a question of whether the high PTH level is the only cause of cardiac dysfunction in patients with ESRD. This is the way how the hypothesis on a direct effect of vitamin D on cardiac function was set up. Receptor for vitamin D is present in many tissues, which do not have a role in the regulation of calcium metabolism such as lymphocytes, colon cells, hepatocytes and cardiac myocytes[32]. The pronounced expression of VDR in other tissues supports the theory that vitamin D also has another endocrine role, not only the regulation of calcium homeostasis9. By activity on VDR, vitamin D in cardiac cells regulates the flux of calcium into the cells, controls the amount of free calcium in the cytosol and thereby regulates myocardial contractility and controls the growth and proliferation of cells[20-22,33,34]. Direct physiological consequences of non-existence of VDR on the cardiac function were studied in several trials on animals[35-37]. In these studies, the vitamin D receptor knockout mice were compared to wild type mice, which have present VDR[35,36]. Histological staining showed a significant cell hypertrophy in the vitamin D receptor knockout mice compared to the wild type mice. Myocardial hypertrophy and myocardial fibrosis was observed only in the vitamin D receptor knockout mice[35,36]. The trial on vitamin D receptor knockout mice also proves that vitamin D directly affects the heart function due to its role as a negative regulator of renin — angiotensin-aldosterone system (RAAS)[37,38]. It was found that the vitamin D receptor knockout mice had three times more pronounced expression of renin messenger RNA (mRNA) and more than 2.5x increase in concentration of angiotensin II in plasma compared to the wild type mice[38]. Since calcitriol regulates PTH and maintains calcium concentration, secondary hyperparathyroidism and hypocalcemia inevitably developed in the vitamin D receptor knockout mice. Vitamin D receptor knockout mice received calcium for maintenance of appropriate serum levels before the development of secondary hyperparathyroidism. Despite normal serum calcium and PTH level, an increased production of renin mRN and angiotensin II is still recorded in vitamin D receptor knockout mice, indicating that calcitriol has a direct impact on RAAS which is independent of calcium or PTH.

In addition to RAAS activation, an increased activation of the immune system is often associated with CVDs, to be more specific, atherosclerosis and calcification of heart valves and unstable plaque and its rupture[39]. Excessive production of inflammatory cytokines contributes to the development and progression of the heart failure[40]. Experimental studies have shown that vitamin D plays an important role in the regulation of several important inflammatory and anti-inflammatory cytokines[41-43]. One trial showed a decreased production of inflammatory cytokines (interleukin [IL]-6 and tumor necrosis factors [TNF] when the activated monocytes were exposed to calcitriol[42]. Similarly, another trial showed that the production of anti-inflammatory cytokine IL-10 significantly increased when dendritic cells were exposed to calcitriol in comparison to control cells that were not exposed to it[41]. These trials showed that hormonal effect of vitamin D has a direct and active role in the regulation of several immunomodulatory cytokines leading to a reduction of inflammation.

itivnu povezanost između deficita vitamina D i arterijske hipertenzije, dok neke studije nisu uspjele dobiti takve rezultate[44].

Dong i sur. su dokazali da kalcitriol djeluje vazoprotektivno na krvne žile u bolesnika s arterijskom hipertenzijom. Djelovanjem na VDR, kalcitriol djeluje povoljno na renovaskularnu disfunkciju u hipertenziji putem učinka na ekpresiju i aktivnost pojedinih ključnih proteina koji sudjeluju u stvaranju slobodnih radikala. Kalcitriol uravnotežuje stvaranje slobodnih radikala, hiperpordukciju angiotenzin 1 receptora te podjedinica NADPH oksidaze te tako sudjeluje u očuvanju funkcije endotela u hipertenziji[45].

Bolesti kardiovaskularnog sustava i vitamin D

Budući da se aktivacija RAAS i imunološkog sustava povezuje s vaskularnim bolestima, istraživanja odnosa nedostatka vitamina D u ljudi i vaskularnih bolesti je logičan korak. Nedostatak vitamina D se povezivao s mnogim bolestima vaskularnog sustava, uključujući bolesti perifernih arterija, aterosklerozu, infarkt miokarda i ishemijski moždani udar. Pojedina istraživanja su pokazala da postoji povezanost između nižih koncentracija kalcidiola i veće učestalosti periferne arterijske bolesti sugerirajući da male razlike u koncentraciji kalcidiola u serumu mogu uvelike utjecati na rizik od razvoja bolesti perifernih arterija[46]. U istraživanju provedenom na bolesnicima sa šećernom bolešću uočeno je da je teška ateroskleroza koja je mjerena debljinom intime medije karotidnih arterija povezana s nižim koncentracijama vitamina D[47]. Bolesnici s manjkom vitamina D imali su značajno veću debljinu intime medije karotidne arterije od bolesnika sa zadovoljavajućom koncentracijom vitamina D .

Jasna povezanost između koncentracije vitamina D i pojave akutnog infarkta miokarda (AIM) nije utvrđena. Jedno istraživanje je čak pokazalo da su bolesnici koji su doživjeli AIM imali povećan unos vitamin D u usporedbi s kontrolnom skupinom, ali nedostatak tog istraživanja je bio što nije navedena serumska koncentracija kalcidiola[48]. Nakon ovog istraživanja proizašle su mnoge studije koje su proučavale koncentraciju kalcidiola bolesnika s AIM i kontrolne zdrave skupine te su došle do rezultata da se razina vitamina D nije bitno razlikovala između skupina[49-51]. Novija istraživanja su ipak uočila povezanost niže koncentracije kalcidiola i povećanog rizika za nastanak AIM, u kojima se manjak vitamina D pokazao kao nezavisni čimbenik rizika za razvoj nefatalnog AIM ili fatalne koronarne bolesti srca s tim da su ispitanici s koncentracijom vitamin D 30 ng/ml i više imali upola manji rizik[52].

Povezanost manjka vitamina D i SŽB koje su definirane kao koronarnih bolest srca, bolest perifernih arterija i cerebrovaskularna bolest također je proučavana u nekoliko studija[53,54]. U istraživanju na preko 400 bolesnika sa šećernom bolešću uočeno je da bolesnici s manjkom vitamina D (definirano kao <20 ng/ml) imaju veću prevalenciju SŽB koja je ostala statistički značajna i nakon prilagodbe za bubrežnu funkciju, lijekove, vrijednost LDL, prisutnost metaboličkog sindroma i vrijednost hemoglobina A1c .

Jedna studija je proučavala može li manjak vitamina D biti prediktor za razvoj SŽB[54]. Proučavano je 1.739 bolesnika bez poznatih SŽB ili bubrežne bolesti te su im izmjerene koncentracije kalcidiola. Bolesnici su praćeni prosječno 5,4 godine te se pratila učestalost AIM, moždanog udara, an-

The results of experimental lab trials resulted in many clinical studies on association between vitamin D deficiency and hypertension, and some of them showed a positive association between vitamin D deficiency and hypertension, while some studies failed to obtain such results[44].

Dong et al. have proved that calcitriol acts in a vasoprotecive way on the blood vessels in patients with arterial hypertension. By action of the VDR, calcitriol has a beneficial effect on renovascular hypertension through the effect on the expression and activity of specific key proteins that are involved in the creation of free radicals. Calcitriol balances the formation of free radicals, hyperproduction of angiotensin receptor 1 and subunits of NADPH oxidase and thus participates in the preservation of endothelial function in hypertension[45].

Cardiovascular diseases and vitamin D

Since the activation of RAAS and the immune system is associated with vascular diseases, the research of the relationship of vitamin D deficiency and vascular diseases is a logical step. Vitamin D deficiency was associated with many vascular diseases, including peripheral artery diseases, atherosclerosis, myocardial infarction and ischemic stroke. Some trials have shown that there is a correlation between lower calcidiol concentrations and higher incidence of peripheral arterial disease, suggesting that small differences in the concentration of calcidiol in serum can greatly affect the risk of developing peripheral artery diseases[46]. The trial conducted on patients with diabetes showed that severe atherosclerosis as measured by intima media thickness of the carotid arteries is associated with lower concentrations of vitamin D[47]. The patients with vitamin D deficiency had significantly greater intima media thickness of the carotid artery than the patients with sufficient concentration of vitamin D.

A clear correlation between the concentration of vitamin D and the occurrence of acute myocardial infarction (AMI) has not been established. One trial even showed that the patients who had a history of AMI showed an increased intake of vitamin D compared with the control group, but the disadvantage of this trial was that the serum concentration of calcidiol was not indicated[48]. This trial was followed by many studies that studied the concentration of calcidiol in patients with AMI and healthy control group and reached a conclusion that the level of vitamin D did not significantly differ among the groups[49-51]. Recent studies have, however showed the connection between a lower concentration of calcidiol and an increased risk of AMI, where vitamin D deficiency proved to be an independent risk factor for the development of non-fatal AMI or fatal coronary heart disease, provided that the subjects with vitamin D concentration of 30 ng/ml and more had twice lower risk[52].

The connection between vitamin D deficiency and CVD defined as coronary heart disease, peripheral artery disease, and cerebrovascular disease has also been studied in several trials[53,54]. The trial conducted on over 400 patients with diabetes showed that patients with vitamin D deficiency (defined as <20 ng/ml) had higher prevalence of CVD which remained statistically significant even after the adjustment for renal function, medications, LDL, presence of metabolic syndrome and value of hemoglobin A1c.

One trial studied whether vitamin D deficiency can be a predictor for the development CVD[54]. 1,739 patients without known CVD or kidney disease were studied and their concentrations of calcidiol were measured. Patients were followed up over a median period of 5.4 years and incidence of

gine pektoris, tranzitorne ishemijske atake, klaudikacija ili zatajivanja srca. Pokazalo se da je nedostatak vitamina D (<5 ng/ml) povezan s povećanim rizikom za razvoj SŽB.

Mnoga opservacijska istraživanja upućuju na povezanost manjka vitamina D i SŽB, uključujući perifernu vaskularnu bolest[46], povećano zadebljanje intime medije karotidnih arterija[47] i AIM[52]. Nadalje, nedostatak vitamina D je povezan sa smrtnošću od SŽB, ali i ukupnom smrtnosti[52,55-57]. Iako su ta istraživanja opservacijska, njihovi podaci podupiru hipotezu predloženu od strane ranih eksperimentalnih studija. Iz meta-analize Autiera i Gandinija koja je uključivala 18 randomiziranih kontroliranih studija je proizašlo da terapija vitaminom D dovodi do smanjenja ukupne smrtnosti za 7%. Bitna je činjenica da su studije koje su bile uključene u analizu koristile međusobno jako različite doze vitamina D[58,59].

Wang i sur. su proučili 8 randomiziranih kontroliranih studija i zaključili da je smanjenje rizika od oboljenja od SŽB pri korištenju srednjih do visokih doza vitamina D neznačajno[58,60].

Vitamin D i zatajivanje srca

Aktivacija RAAS i imunološkog sustava povezana s nedostatkom vitamina D ima potencijal da uzrokuje štetne učinke u bolesnika sa zatajivanjem srca. Odnos između razine vitamina D te učestalost i stupanj zatajivanja srca je istražena u nekoliko studija[60-66]. Istraživanje na Afroamerikancima koji su bili podijeljeni u tri skupine srčanog zatajivanja nije dokazalo povezanost između koncentracije kalcidiola i stupnja srčanog zatajivanja. Jedno drugo istraživanje je proučavalo bolesnike sa zatajivanjem srca koji su prolazili testiranja za listu čekanja za transplantaciju srca[64]. Bolesnici koji su imali teži stupanj zatajivanja srca imali su značajno niže koncentracije kalcidiola od onih s blažim stupnjem.

Podaci iz studije LURIC koja je proučavala povezanost koncentracije kalcidiola i renin-angiotenzin sustava u bolesnika koji su bili podvrgnuti koronarografiji[55] služili su za pročavanje odnosa između manjka vitamina D i smrtnog događaja uzrokovanog srčanim zatajivanjem ili iznenadnom srčanom smrću[67]. Pokazalo se da su bolesnici s teškim nedostatkom vitamina D (kalcidiol <10 ng/ml) imali značajno veći rizik za smrt zbog zatajivanja srca i iznenadne srčane smrti u usporedbi s bolesnicima s optimalnom koncentracijom vitamina D (kalcidiol ≥30 ng/ml). Također se pokazalo da je serumska koncentracija kalcidiola obrnuto proporcionalna koncentraciji NT-proBNP i stupnju NYHA klasifikacije.

Vitamin D i koronarna bolest srca

Koronarna bolest srca (KBS) je i dalje jedan od vodećih uzroka smrti u razvijenim zemljama unatoč napretku medicine. Stariji bolesnici koji su preboljeli akutni koronarni sindrom imaju teže kliničke posljedice što je vezano uz brojne komorbiditete, ali i uz malnutriciju, a snižene koncentracije vitamina D se također spominju kao jedan od bitnih čimbenika. Niske vrijednosti vitamina D se povezuju s pojačanim odlaganjem kacija u koronarnim arterijama, oštećenom funkcijom endotela i povećanim vaskularnim otporom[46,47,68]. *Chen i sur.* su proučavali povezanost vitamina D i težine KBS. Težina KBS je mjerena SYNTAX ljestvicom. Bolesnici koji su imali koncentraciju vitamina D <20 ng/mL, imali su veći rezultat prema ljestvici SYNTAX[69]. *Bajaj i sur.* su pratili 3.019 bolesnika od 65 godina i starije kroz šest godina. Proučavali su dvije grupe bolesnika, jedna s koncentracijom

AMI, stroke, angina pectoris, transient ischemic attack, claudication or heart failure was monitored. It has been shown that vitamin D deficiency (<5 ng/ml) was associated with an increased risk for the development of CVD.

Many observational studies suggest a connection between vitamin D deficiency and CVD, including peripheral vascular disease[46], increased thickening of intima media of the carotid arteries[47] and AMI[52]. Furthermore, vitamin D deficiency is associated with mortality from CVDs, but also with the total mortality[52,55-57] Although these studies are observational ones, their data support the hypothesis suggested by the early experimental studies. Meta-analysis of Autiero and Gandini which included 18 randomized controlled trials showed that the therapy with vitamin D leads to a reduction in total mortality by 7%. The important fact is that the studies that were included in the analysis used doses of vitamins D that differed from each other to a great extent[58,59].

Wang et al. studied eight randomized controlled trials and concluded that the reduction of the risk of CVD while using medium to high doses of vitamin D was insignificant[58,60].

Vitamin D and heart failure

Activation of RAAS and immune system associated with a vitamin D deficiency may cause adverse effects in patients with heart failure. The relation between vitamin D level and incidence and degree of heart failure has been explored in several studies[60-66]. The trial on African-Americans who were divided into three groups of heart failure has not proven the correlation between the concentration of calcidiol and a degree of heart failure. Another trial studied the patients with heart failure who were undergoing the tests for the list for the heart transplant[64]. Patients who had a more severe degree of heart failure had significantly lower concentrations of calcidiol than those with a milder degree.

Data from the LURIC trial which studied the correlation between calcidiol and the renin-angiotensin system in patients who underwent coronarography[55] were used for studying the relationship between vitamin D deficiency and fatal event caused by heart failure or sudden cardiac death[67]. It was shown that patients with severe vitamin D deficiency (calcidiol <10 ng/ml) had a significantly higher risk of death due to heart failure and sudden cardiac death compared to patients with optimal concentration of vitamin D (calcidiol ≥30 ng/ml). It was also shown that the serum concentration of calcidiol is inversely proportional to the concentration of NT-proBNP and degree of NYHA classification.

Vitamin D and coronary heart disease

Coronary artery disease (CAD) remains the leading cause of death in developed countries despite the advance in medicine. Elderly patients who have a history of acute coronary syndrome suffer from severe clinical consequences, which is related to a number of comorbidities, but also to malnutrition, whereas reduced concentrations of vitamin D are also mentioned as one of the important factors. Low levels of vitamin D are associated with an increased depositing of calcium in the coronary arteries, impaired endothelial function and increased vascular resistance[46,47,68]. *Chen and et.* studied the association of vitamin D and severity of CAD. The severity of CAD was measured by SYNTAX scale. Patients who had vitamin D concentration <20 ng/mL, had a higher score on the SYNTAX scale[69]. *Bajaj and et.* have followed up 3,019 patients aged 65 and older for six years.

vitamina D manjom od 20 ng/mL, a druga s koncentracijom ≥20 ng/mL. Konačni ishod koji su pratili je bila KBS i cerebrovaskularni događaj. Nisu uočili značajnu razliku između grupa za rizik od KBS, ali su uočili veći rizik za oboljenje od cerebrovaskularnih događaja u grupi s nižom koncentracijom vitamina D[70].

Unatoč dosadašnjim istraživanjima, samo nekoliko randomiziranih kontroliranih studija je proučavalo učinke dodatka vitamina D na prevenciju SŽB. Većina istraživanja je proučavala učinke niskih doza vitamina D na populaciji relativno niskog rizika[68]. Potrebna su daljnja istraživanja na starijoj populaciji visokog rizika s akutnim koronarnim sindromom kako bi se potvrdila učinkovitost vitamina D u prevenciji.

Nedostatak vitamina D i životna dob

U dječjoj dobi nedostatak vitamina D uzrokuje rahitične promjene na kostima. U odrasloj dobi nedostatka vitamina D se manifestira osteomalacijom (bolovi u kostima, deformacija skeleta) i najčešće se javlja u starijoj dobi. Kod takvih osoba serumska koncentracija kalcidiola je ispod 20 nmol/L, uz povišenu vrijednost PTH.

U zadnjih nekoliko godina postalo je očito da nedostatak vitamina D manjeg stupnja može dovesti do sekundarnog hiperparatireoidizma koji dovodi do razvoja osteoporoze s mogućim teškim komplikacijama i javnozdravstvenim posljedicama[71-73]. Pokazalo se da bolesnici koji su imali spontani prijelom kostiju imaju niže koncentracije vitamina D nego kontrolna skupina.

Dodatak vitamina D i kalcija se pokazao učinkovit u liječenju insuficijencije vitamina D, sekundarnog hiperparatireoidizma i smanjenja rizika od prijeloma kuka i drugih nevertebralnih fraktura u pojedinaca smještenih u domovima za starije osobe[74]. Novija istraživanja nisu uspjela dokazati taj povoljni učinak u osoba koje su smještene u vlastitim domovima[75,76]. Prije mnogo godina manjak vitamina D je bio problem dijagnosticiranja i liječenja dječije dobi pretežno u velikim gradovima. Danas je manjak vitamina D veliki javnozdravstveni problem koji zahvaća populaciju starije dobi koja boravi u domovima za starije osobe. Unatoč brojnim istraživanjima, terapija preparatima kalcija i vitaminom D ne dovodi uvijek do željenog učinka.

Zaključak

Eksperimentalna istraživanja na životinjama pokazala su da nedostatak vitamina D dovodi do povećanog izlučivanja paratiroidnog hormona i aktivacije RAAS i imunološkog sustava. Brojne opservacijske studije na ljudima su također povezala manjak vitamina D i SŽB. Unatoč velikom broju istraživanja, mali broj randomiziranih, kontroliranih studija je proučavao korist dodatka vitamina D za snižavanje kardiovaskularnog rizika. Manji broj istraživanja sugerira da povećanje koncentracije kalcidiola može biti od koristi u bolesnika sa zatajivanjem srca ili povišenim AT.

Iako procjena vitamin D statusa i liječenje dodatkom vitamina D nije rutinski dio liječenja, možda bi se trebao uzeti u obzir u bolesnika kod kojih se ne postižu optimalni rezultati liječenja unatoč provedenoj zadovoljavajućoj terapiji. Potrebna su velika randomizirana kontrolirana istraživanja kako bi se ispitalo ima li liječenje vitaminom D učinka na prevenciju ili liječenje SŽB.

They studied two groups of patients, one with a concentration of vitamin D less than 20 ng/mL, and the other with a concentration ≥20 ng/mL. The final outcome they obtained was CAD and cerebrovascular event. They did not notice a significant difference between the groups regarding the risk of CAD, but noticed a greater risk of cerebrovascular events in the group with a lower concentration of vitamin D[70].

Despite previous trials, only a few randomized controlled trials studied the effects of the addition of vitamin D to prevent CVDs. Most trials studied the effects of low doses of vitamin D on the population of a relatively low risk[68].Further trials are needed on elderly populations with a high risk of acute coronary syndrome in order to verify the effectiveness of vitamin D in prevention.

Vitamin D deficiency and age

In childhood, vitamin D deficiency causes rachitic changes in the bones. In adulthood, vitamin D deficiency was reflected in osteomalacia (bone pain, skeletal deformities) and most often it occurs in older age. In such persons, serum concentration of calcidiol is below 20 nmol/L , with elevated PTH level.

In the last few years it has become apparent that the lack of vitamin D of a minor degree can cause secondary hyperparathyroidism, which leads to the development of osteoporosis with possible severe complications and public health consequences[71-73]. It was shown that the patients who had spontaneous bone fracture have lower concentration of vitamin D than the control group.

The addition of vitamin D and calcium proved to be effective in the treatment of vitamin D insufficiency, secondary hyperparathyroidism and reduction of the risk of hip fracture and other non-vertebral fractures in individuals accommodated in the nursing homes for the elderly[74]. Recent studies failed to demonstrate the beneficial effect in persons who are accommodated in their own homes[75,76]. Many years ago, vitamin D deficiency was the problem regarding diagnosis and treatment at children age mainly in large cities. Today, vitamin D deficiency is a public health problem that affects the elderly population residing in the nursing homes for the elderly. Despite numerous trials, the therapy by using preparations of calcium and vitamin D do not always lead to the desired effect.

Conclusion

Experimental trials on animals have shown that vitamin D deficiency leads to increased secretion of parathyroid hormone and activation of the RAAS and the immune system. Numerous observational studies on humans were also associated with vitamin D deficiency and CVDs. Despite a great number of trials, a small number of randomized, controlled trials have studied the benefit of addition of vitamin D for lowering cardiovascular risk. A small number of trials suggest that increasing concentrations of calcidiol may be beneficial in patients with heart failure or elevated BP.

Although the evaluation of vitamin D status and the treatment by adding vitamin D is not a routine part of the treatment, maybe it should be considered in patients in whom optimal treatment results are not achieved in spite of a satisfactory therapy conducted. Large randomized controlled trials are required to examine whether the treatment with

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vitamin D has an effect on the prevention or treatment of CVD.

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