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UTICAJ KO/POLIMORBIDITETA NA TERAPIJSKI ODGOVOR VITAMINOM D KOD PACIJENATA SA OSTEOPOROZOM I HIPOVITAMINOZOM D VITAMINA U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

Sažetak

Uvod: Vitamin D, njegovi aktivni metaboliti i analozi, predstavljaju grupu jedinjenja sa brojnim funkcijama u organizmu. Aktivirani receptor za vitamin D u crevima stimuliše sintezu vezujućeg proteina za kalcijum, u kostima stimuliše produkciju osteokalcina, osteoponina, alkalne fosfataze, povećava transport kalcijuma iz vanćelijskog u unutarćelijske prostore, može da mobiliše kalcijum iz unutarćelijskog kalcijumskog rezervoara i da pojača metabolizam fosfatidilinozitola.

Cilj rada: Cilj ovog rada je da se obradom prikupljenih podataka ispita moguća uzročno-posledična veza između terapijskog odgovora na primenu vitamina D i dodatnih oboljenja i terapije kod pacijenata u primarnoj zdravstvenoj zaštiti sa deficitom vitamina D i osteoporozom.

Materijal i metod: Epidemiološki monitoring osteoporoze i hipovitaminoze D vitamina, sproveden je kao retrospektivna studija kod pacijenata u primarnoj zdravstvenoj zaštiti Doma zdravlja Kragujevac, po dobijanju odluke Etičkog komiteta Doma zdravlja Kragujevac. U periodu od 01. 02. 2018. do 22. 10. 2019. u sprovedenoj studiji je na uzorku od 250 pacijenata sa različitim oboljenjima, starosti 30 do 65 godina, primenjen vitamin D u oralnoj dozi od 100 IJ dnevno, a nivoi serumskog D vitamina mereni su pre i nakon terapije.

Rezultati: Statistički značajne razilke u odgovoru na primenu vitamina D uočene su kada su u pitanju pacijenti sa hipertenzijom, dijabetesom i

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oboljenjima štitaste žlezde ($p < 0,05$). Dobijeni rezultati, takođe, ukazuju da postoje statistički značajne razlike kod pacijenata sa hipertenzijom lečenih kombinovanom terapijom ACE-inhibitora i diuretika ($p < 0,05$). T-testom uparenih uzoraka utvrđeno je statistički značajno povećanje nivoa vitamina D kod ispitanika nakon terapije vitaminom D ($p < 0,0001$).

Zaključak: Rezultatima ove studije pokazano je da je obezbeđivanje adekvatnog unosa vitamina D ključna komponenta u terapiji osteoporoze. Osobe sa visokim rizikom za nastanak fraktura imaju korist od uzimanja nadoknade vitamina D, od najmanje 800 IJ dnevno. Unosom jedne tablete dnevno postiže se bolja neuromišićna funkcija.

Ključne reči: vitamin D, osteoporoza, ko/polimorbiditeti

Summary

Introduction: Vitamin D, its active metabolites and analogs, represent a group of compounds with numerous functions in the body. The activated receptor for vitamin D in the intestines stimulates the synthesis of the binding protein for calcium, bone stimulates the production of osteocalcin, osteoponin, alkaline phosphatase, increases the transport of calcium from vancellular to intracellular cells, can mobilize calcium from the intracellular calcium reservoir and enhance the metabolism of phosphatidylinositol.

Objective: The aim of this paper is to examine the possible cause-and-effect linkages between the therapeutic response and the use of navitamin D and additional diseases and therapies in primary health care patients with vitamin D deficiency and osteoporosis.

Material and method: Epidemiological survey of osteoporosis and hypovitaminosis D vitamins, was conducted as a retrospective study in patients in primary health care of the Health Center Kragujevac, after receiving the decision of the Ethics Committee of the Health Center Kragujevac. In the period from 01. 02. 2018. to 22. 10. 2019. an study was conducted, in which patients with various diseases, ages 30 to 65, were administered vitamin D, and levels of serum D vitamins were measured before and after therapy.

Results: Statistically significant differences in the response to vitamin D were observed in patients with hypertension, diabetes and thyroid disorders ($p < 0.05$). The results obtained also indicate, that there are statistically significant differences in patients with hypertension treated with combination therapy with ACE inhibitor and diuretic ($p < 0.05$). T-assay of samples showed a statistically significant increase in the level of vitamin D in the subjects after treatment with vitamin D. ($p < 0.0001$).

Conclusion: Results of this study, ensuring adequate vitamin D intake is a key ingredient in the treatment of osteoporosis. People at high risk of developing fractures benefit from taking vitamin D supplementation, at least 800 IJ per day. By entering one tablet daily, a better neuromuscular function is achieved.

Key words: vitamin D, osteoporosis, co / polymorbidities.

Uvod:

Vitamin D, njegovi aktivni metaboliti i analozi, predstavljaju grupu jedinjenja sa brojnim funkcijama u organizmu. Primarna uloga vitamina D je u metabolizmu kalcijuma i fosfora. Danas se zna da vitamin D smanjuje fiziološku aktivnost parahormona na dva načina: direktno, delovanjem na ćelije paratiroidnih žlezdi, i indirektno, preko hiperkalcemije. Poznato je da vitamin D učestvuje u razgradnji i formiranju kostiju. Delujući na osteoblaste, preko vitamin D receptora, povećava sintezu osteokalcina, alkalne fosfataze i kolagena tip 1. Dejstvo vitamina D na osteoklaste je dvojako: indirektno – preko osteoblasta i direktno – supresijom diferencijacije promijelocita u monocite, koji su prekursori osteoklasta.[1] Alarmirajući podatak je da iz dana u dan raste broj svetske populacije kod koje je utvrđeno postojanje hipovitaminoze D i da ova pojava trenutno ima pandemijske razmere.[2]

Incidenca osteoporoze raste sa starošću i najčešće se javlja kod žena u postmenopauzi. Zbog smanjenja nivoa ovarijalnog estrogena, udruženog sa menopauzom, ubrzava se gubitak koštane mase i opada mogućnost remodeliranja kosti.[3] U Sjedinjenim Američkim Državama svaka treća žena bele rase starosti 60–70 godina ima osteoporozu, dok posle 80. godine života incidenca obolevanja osoba ženskog pola raste na 70%. Procenjeno je da očekivani rizik od frakture kod žena u postmenopauzi do kraja života iznosi 30−40% u zemljama Zapadne Evrope.[4] Farmakoterapijski protokoli za najčešće bolesti i stanja u primarnoj zdravstvenoj zaštiti ukazuju na esencijalnu ulogu lekara opšte prakse u proceni rizika za osteoporozu, koji obuhvata: ženski pol, rana menopauza pre 45. godine ili višegodišnja menopauza, starosna dob, nizak indeks telesne mase, prisustvo prethodnih preloma pri maloj traumi, pozitivna porodična anamneza za osteoporozu, prisustvo endokrinih bolesti.[6]

U Srbiji postoji tiha epidemija deficijencije vitaminom D, kao i prisustvo sve većeg broja bolesti koje su time uzrokovane, zbog čega stoji preporuka dodatnog unosa vitamina D u koncentracijama koje preveniraju stanja i bolesti uzrokovane njegovim nedostatkom.[7,8] Upoznavanjem opšte javnosti sa korisnim efektima vitamina D i njegovim izvorima, a stručne javnosti sa adekvatnim suplementacionim dozama, može se uticati na smanjenje broja deficijentnih osoba kako u našoj zemlji tako i svetu.[9]

Cilj ovog rada je da se retrospektivnom analizom prikupljenih podataka ispita moguća uzročno-posledična veza između terapijskog odgovora na vitamin D i dodat-

nih oboljenja i terapije kod pacijenata u primarnoj zdravstvenoj zaštiti sa deficitom vitamina D i osteoporozom.

Materijal i metod:

Dizajn studije

Epidemiološki monitoring osteoporoze i hipovitaminoze D vitamina sproveden je kao retrospektivna studija kod pacijenata u primarnoj zdravstvenoj zaštiti Doma zdravlja Kragujevac, po dobijanju odluke Etičkog komiteta Doma zdravlja Kragujevac (01-1546/2). Analizom medicinske dokumentacije pacijenata lečenih u Domu zdravlja Kragujevac, ogranak Aerodrom, sprovedena je studija u vremenskom periodu od 01. 02. 2018. do 22. 10. 2019. godine.

Studijska populacija

Studija je obuhvatila ukupno 250 bolesnika oba pola starosti od 30 do 65 godina odabranih na osnovu uvida u medicinsku dokumentaciju pacijenata (elektronski karton na odeljenju izabranog lekara). Ispitanici su uzimali 1000 IJ vitamina D (Detrical®) u vidu tablete, u jednoj jutarnjoj dozi. Pacijentima je pre uvođenja vitamina D utvrđen serumski nivo vitamina D, a ispitivanje je ponovljeno nakon tri meseca primene leka. Na uzorku od 250 pacijenata sa utvrđenom dijagnozom osteoporoze i hipovitaminoze D vitamina praćeni su demografski pokazatelji (starost bolesnika, pol obolelih), prisustvo komorbiditeta i najčešće upotrebljene terapijske procedure. Iz studije su isključeni ispitanici sa čestim promenama u farmakoterapiji i pacijenti koji su upotrebljavali druge preparate i lekove D vitamina u prevenciji i terapiji osteoporoze.

Statistička obrada podataka

Za uticaj pola, starosti, dodatnih oboljenja i terapije na nivoe vitamina D pre i nakon primene vitamina D 1000 IJ korišćena je metoda višestruke regresije, dok je T-uporednim testom ispitan uticaj terapije vitamina D na serumske nivoe D vitamina pre i nakon terapije.

Rezultati:

U studiju je uključeno 250 ispitanika, od čega je 115 (46%) bilo ženskog i 135 (54%) muškaraca, statističkom analizom utvrđeno je da između polova ne postoji statistički značajna razlika u nivoima vitamina D pre i posle terapije ($p > 0,005$). Prosečna starost ispitanika bila je $49,34 \pm 7,34$ godina, najmlađi ispitanik imao je 30 godina dok je najstariji imao 68 godina.

112 (40,9%) ispitanika imalo je dijagnozu deficita vitamina D, a 138 (59,1%) ispitanika imalo je dijagnozu deficita vitamina D udruženu sa osteopenijom. Utvrđena je statistički značajna razlika u nivoima vitamina D pre i posle terapije između grupe ispitanika koji su imali samo deficit vitamina D i grupe ispitanika koja je uz deficit vitamina D imala i prisutnu osteopeniju ($p < 0,005$). Niže nivoe serumskog vitamina D imala je grupa ispitanika koja je pored deficita vitamina D imala i osteopeniju. Najčešći komorbiditet među ispitanicima bio je arterijska hipertenzija – 132 (62,9%) ispitanika, takođe su bili prisutni dijabetes kod 65 (24,6%) ispitanika i oboljenja štitaste žlezde kod 53 (12,5%) ispitanika. Višestrukom regresionom analizom ispitan je uticaj pola, starosti, komorbiditeta i dodatne terapije na nivoe vitamina D u krvi ispitanika pre i nakon terapije preparatom vitamina D.

Preliminarnim analizama je dokazano da pretpostavke normalnosti, linearnosti, multikolinearnosti i homogenosti varijanse nisu bile narušene. Komorbiditeti su predstavljali 34,1% ukupne varijanse, dok su dodatna terapija pol i starost predstavljali 45,7% ukupne varijanse.

Tabela 1. *Prikaz rezultata višestruke regresije o uticaju pola, starosti, komorbiditeta i dodatne terapije na nivoe vitamina D pre uzimanja vitamina D*

Varijabla	B	SE B	β	t	p
Pol	-0,59	0,110	-0,035	-0,908	0,6
Starost	-0,042	0,008	-0,456	-5,029	>0,000001*
Hipertenzija	-0,663	0,130	-0,367	-5,081	>0,00001*
Dijabetes	-0,459	0,116	-0,316	-3,948	>0,00001*
Bolesti štitaste žlezde	-0,359	0,104	-0,243	-3,436	>0,00001*
Bubrežna insuficijencija	-0,253	0,189	-0,099	-1,341	0.182
Antihipertenzivi	0,160	0,172	0,100	0,930	0,354
Antihipertenzivi u kombinaciji sa diureticima	0,659	0,240	0,248	2,750	0,007*
Lekovi za normalizaciju hormona štitaste žlezde	0,291	0,192	0,168	1,513	0,133

*statistički značajno

Tabela 2. *Prikaz rezultata višestruke regresije o uticaju pola, starosti, komorbiditeta i dodatne terapije na nivoe vitamina D nakon uzimanja preparata Detrical® 1000.*

Varijabla	B	SE B	β	t	p
Pol	-0,55	0,122	-0,32	-0,449	0,6
Starost	-0,042	0,009	-0,444	-4,828	>0,000001*
Hipertenzija	-0,515	0,138	-0,277	-3,725	>0,00001*
Dijabetes	-0520	0,123	-0,348	-4,220	>0,00001*
Bolesti štitaste žlezde	-0,316	0,111	-0,209	-2,857	>0,000001*
Bubrežna insuficijencija	-0,322	0,200	-0,123	-1,512	0.109
Antihipertenzivi	0,109	0,233	0,066	0,466	0,682
Antihipertenzivi u kombinaciji sa diureticima	0,051	0,361	0,030	0,141	0,888
Lekovi za normalizaciju hormona štitaste žlezde	-0,104	0,402	-0,33	-0,258	0,796

*statistički značajno

Tabela 3. *Vrednosti serumskog nivoa vitamina D pre i posle terapije, rezultati T-testa uparenih uzoraka*

Vrednosti nivoa D vitamina u serumu [ng/ml]	Pre terapije	Posle terapije	P
0–9,4	106(31,2%)	90(38,6%)	<0,0001
9,5–15,9	84(50,7%)	85(43,6%)	<0,0001
16–20	57(18,1%)	75(17,8%)	<0,0001

T-testom uparenih uzoraka ispitan je uticaj terapije vitaminom D na serumske nivoe vitamina D pre i posle terapije. Utvrđeno je statistički značajno povećanje nivoa vitamina D kod ispitanika nakon terapije vitaminom D ($p < 0,0001$). Prikazanim tabelama pokazana je statistički značajna razlika u odgovoru na vitamin D, preko serumskih nivoa vitamina D, pre i posle primene vitamina D u dozi od 1000 IJ. Ta-

kođe je tabelama prikazan i uticaj pridruženih bolesti i dodatne terapije na terapijski odgovor vitaminom D.

Diskusija:

Evropsko udruženje za kliničke i ekonomske aspekte osteoporoze i osteoartritisa (*European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis – ESCEO*) od 2013. godine savetuje da minimalna koncentracija vitamina D u serumu treba da iznosi 50 nmol/l (20 ng/ml), kako bi se osigurao optimalni koštani metabolizam kod osoba mlađih od 50 godina, dok kod starijih osoba, zbog optimalnog uticaja na koštano-mišićni sistem, te vrednosti treba da budu preko 75 nmol/l. Procena optimalnog unosa vitamina D sa ciljem postizanja željene koncentracije može se odrediti na osnovu nivoa vitamina D u serumu. Svakih 2,5 μg (1000 IU) dodatih vitamina D povećaće nivo serumskog vitamina D za oko 2,5 nmol/l.[10]

Rezultati studija su pokazali da je učestalost ko/polimorbiditeta u korelaciji sa starenjem i smanjenjem adaptivnih sposobnosti organizma, stoga je neophodno koristiti terapijske smernice za svakog pacijenta, a ne za svaku bolest posebno.[11] Adekvatnim terapijskim protokolima, kod pacijenata sa ko/polimorbiditetima, koji u obzir uzimaju sve lekove i dodatke ishrani koje pacijent koristi, može se vršiti racionalna suplementacija, sve u svrhu što boljeg kvaliteta života pacijenata. Rezultati ove studije ukazuju da su arterijska hipertenzija, dijabetes i oboljenja štitaste žlezde među tri najčešća polimorbiditeta koja su imali ispitanici sa osteoporozom i hipovitaminozom, lečeni vitaminom D 1000 IJ. U terapiji ovih oboljenja, lekovi za normalizaciju hormona štitaste žlezde, oralni antidijabetici i samostalno primenjeni antihipertenzivi nisu pokazali statistički značajan uticaj na nivo D vitamina u krvi pre i nakon primene vitamina D 1000 IJ ($p > 0,05$). Statistički značajan uticaj na nivo D vitamina u krvi imaju ACE-inhibitori primenjeni u fiksnim kombinacijama sa diureticima ($r = 0,007$). Epidemiološke studije koje su se bavile ovom problematikom pokazuju da suplementacija vitaminom D, može poboljšati kontrolu krvog pritiska, što je ovom studijom potvrđeno. Mehanizam kojim D vitamin dovodi do regulacije krvnog pritiska kod pacijenata na terapiji ACE-inhibitorima i diureticima je inhibicija sinteze renina, koja rezultira padom krvnog pritiska.[12]

Poslednjih godina istraživači veliku pažnju poklanjaju studijama koje se bave terapijskim monitoringom lekova, jer je odnos serumske koncentracije i terapijskog odgovora na lek od ključnog značaja za terapiju. Studija autora *Luca Dalle Carbonare*[13] iz 2018. godine ukazuje na važnost praćenja nivoa vitamina D u krvi, nakon oralne suplementacije D vitaminom. Interesantno je da je ovom studijom objašnjen uticaj veličina obima struka, nosioca rizika na metabolička i kardiovaskularna neželjena dejstva vitamina D, što može biti jedna od budućih hipoteza za istraživanja ovog tipa.

Kod ispitanika sa bolestima štitaste žlezde pokazano je da oboljenja štitaste žlezde daju slab odgovor na terapiju vitaminom D, sa statističkom značajnošću od $p < 0,000001$, što je zabeleženo niskim nivoima vitamina D u serumu. Oboljenja štitaste žlezde javila su se kod 30% ispitanika obuhvaćenih ovom studijom.

Višestrukom regresijom pokazana je statistički značajna razlika u odgovoru na terapiju vitaminom D, kada su u pitanju pacijenti oboleli od dijabetesa. U studiji, sprovedenoj u 2018. godini, oralna suplementacija D vitaminom u dozi od 500 mg pokazala se kao korisna kod pacijenata sa dijabetesom tip 2, upravo zbog sprečavanja gubitka kostiju. Terapijski slabiji odgovor na primenjeni vitamin D može se objasniti time što su osobe sa DMT2 u višem riziku od preloma kostiju usled izmenjene koštane funkcije i ponovnog modelovanja kostiju.[14] Suplementacija vitaminom D kod ove grupe pacijenata, treba biti u pojačanom doznom intervalu, usled promenjene farmakokinetike vitamina D u organizmu, koja je uslovljena ovim oboljenjem.[15]

Iako je studija sprovedena na velikom broju ispitivane populacije, da bi se relevantno sagledao uticaj dodatih oboljenja i terapije na suplementaciju vitaminom D, neophodno je, pored praćenja serumskih nivoa vitamina D, utvrditi i uticaj primenjenog suplementa na gustinu kostiju, što je od velike važnosti za pacijente sa hipovitaminozom vitamina D i osteoporozom.

Zaključak:

Unosom jedne tablete dnevno vitamina D postiže se bolja neuromišićna funkcija, kod pacijenata sa osteoporozom i hipovitaminozom D vitamina. Arterijska hipertenzija, dijabetes i oboljenja štitaste žlezde su tri najčešća polimorbiditeta koja su imali ispitanici sa osteoporozom i hipovitaminozom, lečeni vitaminom D 1000 IJ, pri čemu tretman tih oboljenja nije pokazao statistički značajan uticaj na nivo D vitamina u krvi pre i nakon primene vitamina D.

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THE IMPACT OF CO/POLYMORBIDITY ON THE THERAPEUTIC RESPONSE TO VITAMIN D IN PATIENTS WITH OSTEOPOROSIS AND VITAMIN D HYPOVITAMINOSIS IN PRIMARY HEALTH CARE

Abstract

Introduction: Vitamin D, its active metabolites and analogs, represent a group of compounds with numerous functions in the body. The activated receptor for vitamin D in the intestines stimulates the synthesis of the binding protein for calcium, bone stimulates the production of osteocalcin, osteoponin, alkaline phosphatase, increases the transport of calcium from vancellular to intracellular cells, can mobilize calcium from the intracellular calcium reservoir and enhance the metabolism of phosphatidylinositol.

Objective: The aim of this paper is to examine the possible cause-and-effect linkages between the therapeutic response and the use of vitamin D and additional diseases and therapies in primary health care patients with vitamin D deficiency and osteoporosis.

Material and method: Epidemiological survey of osteoporosis and hypovitaminosis D vitamins, was conducted as a retrospective study in patients in primary health care of the Health Kragujevac, after receiving the decision of the Ethics Committee of the Health Center Kragujevac. In the period from 01. 02. 2018. to 22. 10. 2019. an study was conducted, in which patients with various diseases, ages 30 to 65, were administered vitamin D (Detrical® 1000), and levels of serum D vitamins were measured before and after therapy.

Results: Statistically significant differences in the response to vitamin D (Detrical®1000) were observed in patients with hypertension, diabetes and

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thyroid disorders ($p < 0.05$). The results obtained also indicate, that there are statistically significant differences in patients with hypertension treated with combination therapy with ACE inhibitor and diuretic ($p < 0.05$). T-assay of samples showed a statistically significant increase in the level of vitamin D in the subjects after treatment with Detrical® ($p < 0.0001$).

Conclusion: Ensuring adequate vitamin D intake is a key ingredient in the treatment of osteoporosis. People at high risk of developing fractures benefit from taking vitamin D supplementation, at least 800 IJ per day. By entering one tablet daily, Detrical®1000, a better neuromuscular function is achieved.

Key words: vitamin D, Detrical®1000, osteoporosis, co / polymorbidities.

Introduction:

Vitamin D, it's active metabolites and analogues, represent a group of compounds with numerous functions in the body. The primary role of vitamin D is in the metabolism of calcium and phosphorus. Today, it is known that vitamin D reduces the physiological activity of parathyroid hormones in two ways: directly, by acting on the cells of the parathyroid glands, and indirectly, through hypercalcemia. Vitamin D is known to participate in the breakdown and formation of bones. By acting on osteoblasts, through vitamin D receptors, it increases the synthesis of osteocalcin, alkaline phosphatase and type 1 colleagues. The effect of vitamin D on osteoclasts is twofold: indirectly – through osteoblasts and directly – by suppressing the differentiation of promyelocytes into monocytes, which are precursors of osteoclasts.[1] The alarming data is that the number of the world's population with the existence of hypovitaminosis D is growing day by day, and that this phenomenon is currently on a pandemic scale.[2]

The incidence of osteoporosis increases with age and most often occurs in postmenopausal women. Due to the reduction in ovarian estrogen levels associated with menopause, bone loss accelerates and the possibility of bone remodeling decreases.[3] In the United States, one in three white women aged 60–70 has osteoporosis, while after the age of 80, the incidence of female disease increases to 70%. The expected risk of fracture in postmenopausal women by the end of life is 30–40% in Western European countries.[4] Pharmacotherapeutic protocols for the most common diseases and conditions in primary health care indicate the essential role of general practitioners in assessing the risk of osteoporosis which includes: female gender, early menopause before the age of 45 or perennial menopause, age, low body mass index, presence of previous fractures in minor trauma, positive family history of osteoporosis, presence of endocrine diseases.[6]

In Serbia, there is a silent epidemic of vitamin D deficiency, as well as the presence of an increasing number of diseases caused by it, which is why it is recommended to take additional vitamin D in concentrations that prevent conditions and diseases

caused by its deficiency.[7,8] By introducing the general public and its sources, and the professional public with adequate supplementary doses can influence the reduction of the number of deficient persons both in our country and in the world.[9]

The aim of this study was to examine the possible causal relationship between the therapeutic response to vitamin D and additional diseases and therapy in patients in primary care with vitamin D deficiency and osteoporosis by processing the collected data.

Material and method:

Study design

Epidemiological monitoring of osteoporosis and vitamin D hypovitaminosis was conducted as a retrospective study in patients in the primary health care of the Kragujevac Health Center, after receiving the decision of the Ethics Committee of the Kragujevac Health Center (01-1546/2). By analyzing the medical documentation of patients treated at the Kragujevac Health Center, Aerodrom branch, an study was conducted in the period from February 1, 2018. to 10/22/2019 years.

Study population

The study included a total of 250 patients of both sexes aged 30 to 65 years. Based on the insight into the medical documentation of the patient (electronic card in the department of the chosen doctor). Patients had serum vitamin D levels determined prior to the introduction of vitamin D (Detrical® 1000), and the study was repeated after three months of drug administration. In a sample of 250 patients diagnosed with osteoporosis and vitamin D hypovitaminosis, demographic indicators (age of patients, sex of patients), the presence of comorbidities and the most commonly used therapeutic procedures were monitored. Subjects with frequent changes in pharmacotherapy and patients who used other vitamin D preparations and drugs in the prevention and treatment of osteoporosis were excluded from the study.

Statistical data processing

For the influence of gender, age, additional diseases and therapy on vitamin D levels before and after the application of Detrical® 1000, the multiple regression method was used, while the effect of Detrical® 1000 therapy on serum vitamin D levels before and after therapy was examined by T-comparison test.

Results:

The study included 250 subjects, of which 115 (46%) were women and 135 (54%) men, statistical analysis showed that there was no statistically significant di-

fference between the sexes in vitamin D levels before and after therapy (p >0.005). The average age of the respondents was 49.34 ± 7.34 years, the youngest respondent was 30 years old, while the oldest was 68 years old.

112 (40.9%) subjects were diagnosed with vitamin D deficiency, 138 (59.1%) subjects were diagnosed with vitamin D deficiency associated with osteopenia. There was a statistically significant difference in vitamin D levels, before and after therapy between the group of subjects who had only vitamin D deficiency and a group of subjects who had osteopenia in addition to vitamin D deficiency (p < 0.005). Lower levels of serum vitamin D had a group of subjects who were in addition to vitamin D deficiency who also had osteopenia

The most common comorbidity among the subjects was arterial hypertension in 132 (62.9%) subjects, diabetes mellitus was also present in 65 (24.6%) subjects and thyroid disease in 53 (12.5%) subjects.

The influence of gender, age, comorbidity and additional therapy on the levels of vitamin D in the blood of the subjects before and after the therapy with vitamin D preparation (Detrical®) was examined by multiple regression analysis.

Preliminary analyzes proved that the assumptions of normality, linearity, multicollinearity and homogeneity of variance were not violated. Comorbidities accounted for 34.1% of the total variance, while adjunctive therapy gender and age accounted for 45.7% of the total variance.

Table 1. *Overview of multiple regression results on the effect of gender, age, comorbidity, and adjunctive therapy on vitamin D levels prior to taking Detrical® 1000*

Variable	B	SE B	β	t	p
Gender	-0,59	0,110	-0,035	-0,908	0,6
Age	-0,042	0,008	-0,456	-5,029	>0,000001*
Hypertension	-0,663	0,130	-0,367	-5,081	>0,00001*
Diabetes Melitus	-0,459	0,116	-0,316	-3,948	>0,00001*
Thyroid disease glands	-0,359	0,104	-0,243	-3,436	>0,00001*
Renal insufficiency	-0,253	0,189	-0,099	-1,341	0.182
Antihypertensives	0,160	0,172	0,100	0,930	0,354
Antihypertensives in combined with diuretics	0,659	0,240	0,248	2,750	0,007*
Medications for normalization thyroid hormone	0,291	0,192	0,168	1,513	0,133

*statistički značajno

Tabela 2. *Presentation of the results of multiple regressions on the influence of gender, age, comorbidity and additional therapy of vitamin D levels after taking Detrical® 1000.*

Variable	B	SE B	β	t	p
Gender	-0,55	0,122	-0,32	-0,449	0,6
Age	-0,042	0,009	-0,444	-4,828	>0,000001*
Hypertension	-0,515	0,138	-0,277	-3,725	>0,00001*
Diabetes Melitus	-0520	0,123	-0,348	-4,220	>0,00001*
Thyroid disease glands	-0,316	0,111	-0,209	-2,857	>0,000001*
Renal insufficiency	-0,322	0,200	-0,123	-1,512	0.109
Antihypertensives	0,109	0,233	0,066	0,466	0,682
Antihypertensives in combined with diuretics	0,051	0,361	0,030	0,141	0,888
Medications for normalization thyroid hormone	-0,104	0,402	-0,33	-0,258	0,796

* statistically significant

Tabela 3. *Vrednosti serumskog nivoa vitamina D pre i posle terapije, rezultati T-testa uparenih uzoraka*

Values of serum vitamin D [ng/ml]	Before therapy	After therapy	P
0–9,4	106(31,2%)	90(38,6%)	<0,0001
9,5–15,9	84(50,7%)	85(43,6%)	<0,0001
16–20	57(18,1%)	75(17,8%)	<0,0001

The effect of vitamin D therapy (Detrical® 1000) on serum vitamin D levels before and after therapy was examined by T-test of paired samples. There was a statistically significant increase in vitamin D levels in subjects after treatment with Detrical® ($p < 0.0001$). The presented tables show a statistically significant difference in the response to vitamin D, through serum levels of vitamin D, before and after the administration of vitamin D at a dose of 1000 IU. The tables also show the effect of associated diseases and adjunctive therapy on the therapeutic response to vitamin D.

Discussion:

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has been advising since 2013 that the minimum serum vitamin D concentration should be 50 nmol/l (20 ng/ml), to ensure optimal bone metabolism, in persons younger than 50 years, while in the elderly, due to the optimal impact on musculoskeletal system, these values should be over 75nmol/l. Estimation of optimal vitamin D intake with the aim of achieving the desired concentration can be determined based on serum vitamin D levels. Every 2.5 μg (1000 IU) of added vitamin D will increase the level of serum vitamin D by about 2.5 nmol/l.[10]

The results of the study showed that the frequency of co/polymorbidity is correlated with aging and reduced adaptive capacity of the organism, so it is necessary to use therapeutic guidelines for each patient and not for each disease separately.[11] Taking into account all medications and dietary supplements used by the patient, rational supplementation can be performed, all for the purpose of better quality of life of the patient. The results of this study indicate that arterial hypertension, diabetes and thyroid disease are among the three most common polymorbiditis experienced by subjects with osteoporosis and hypovitaminosis treated with Detrical® 1000. In the treatment of these diseases, thyroid hormone normalizing drugs, oral antidiabetic drugs and oral antidiabetics. Did not show a statistically significant effect on vitamin D levels in the blood before and after the application of Detrical® 1000 ($p > 0.05$). ACE inhibitors used in fixed combinations with duretics have a statistically significant effect on the level of vitamin D in the blood ($r = 0.007$). Epidemiological studies that have addressed this issue show that vitamin D supplementation can improve blood pressure control, which has been confirmed by this study. The mechanism by which vitamin D (Detrical® 1000) leads to the regulation of blood pressure in patients on therapy with ACE inhibitors and duretics is the inhibition of renin synthesis, which results in a drop in blood pressure.[12]

In recent years, researchers have paid great attention to studies that deal with therapeutic drug monitoring, because the relationship between serum concentration and therapeutic response to the drug is crucial for therapy. A study by the author *Luca Dalle Carbonare*[13] from 2018 indicates the importance of monitoring the levels of vitamin D in the blood, after oral vitamin D supplementation. Interestingly, this study explained the influence of waist circumference, risk bearers on metabolic and cardiovascular side effects of vitamin D, which may be one of the future hypotheses for research of this type.

In subjects with thyroid disease, thyroid disease was shown to be the most resistant to vitamin D therapy, with a statistical significance of $p < 0.000001$. Thyroid disease occurred in 30% of subjects in this study.

Multiple regression showed a statistically significant difference in the answer of vitamin D therapy, when it comes to patients with diabetes. In a study conducted in 2018, oral vitamin D supplementation at a dose of 500 mg, proved to be useful in patients with type 2 diabetes, precisely because it prevents bone loss. The therapeutically weaker response to administered vitamin D (Detrical® 1000) can be explained by the fact that people with DMT2 are at higher risk of bone fractures due to altered bone function and bone reshaping.[14] Vitamin D supplementation in this group of patients should be at an increased dose interval, due to the altered pharmacokinetics of vitamin D in the body, which is caused by this disease.[15]

Although the study was conducted on a large number of the studied population, in order to relevantly consider the impact of additional diseases and therapy on vitamin D supplementation (Detrical® 1000), it is necessary to determine the impact of serum vitamin D levels on bone density, which is of great importance for patients with vitamin D hypovitaminosis and osteoporosis.

Conclusion:

By taking one tablet a day, of the Detrical®1000 product, better neuromuscular function is achieved in patients with co-osteoporosis and vitamin D hypovitaminosis. Arterial hypertension, diabetes, and thyroid disease are the three most common polymorbidities experienced by subjects with osteoporosis and hypovitaminosis treated with Detrical® 1000, with treatment of these diseases showing no statistically significant effect on blood vitamin D levels before and after Detrical® 1000.

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