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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, its 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-

ference 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	-0,520	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 polymorbidities 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 diuretics 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 diuretics 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 DM2 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 poly-morbidities 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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