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Original Article / Оригинални рад

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The evaluation of the adherence to calcium, vitamin D and drugs for osteoporosis in patients with low bone mineral density

Евалуација адхеренције калцијума, витамина Д и лекова за остеопорозу код пацијената са сниженом коштаном густином

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SUMMARY

Introduction/Objective Osteoporosis is a systemic disease of bone tissue, which leads to an increase in the bone fragility and higher risk of fractures.
To determine adherence to calcium, vitamin D and drugs for osteoporosis in patients with reduced bone mineral density as well as to analyze reasons for low adherence.
Methods The study involved 80 postmenopausal women with reduced bone mineral density measured by dual-energy X-ray absorptiometry. Each patient filled in a specially designed questionnaire. Assessment of adherence to calcium, vitamin D and drugs for osteoporosis was done by Morisky scale. In the statistical analysis we used the SPSS programme v. 20.
Results All patients were female. 67.5% had osteoporosis and 32.5% had osteopenia. 62.5% of women said that they use calcium supplementation, 81.3% vitamin D and 62.3% drugs. 81.2% of women who used supplementation had low adherence to calcium, 82.8% low adherence to vitamin D and 65.8% low adherence to drugs for osteoporosis. Adherence to medication for osteoporosis is better in relation to the adherence of vitamin D and calcium ($p<0.05$, χ^2-test). Patients who recieved drug intravenously had better adherence than patients who received drug subcutaneously or orally.
Conclusion Adherence to vitamin D, calcium and drugs for osteoporosis is presently low in investigated population and the understanding of the causes of low adherence is still insufficiently explored.
Keywords: osteoporosis; patient adherence; calcium; vitamin D

САЖЕТАК

Увод/Циљ Остеопороза је системска болест коштаног ткива, која доводи до пораста фрагилности кости и тиме до већег ризика од прелома.
Циљ рада је евалуација адхеренције калцијума, витамина Д и лекова за остеопорозу код пацијената са сниженом коштаном густином и анализа разлога за ниску адхеренцију.
Методе У ову студију је укључено 80 постменопаузалних жена са сниженом коштаном густином измереном двоструком апсорпциометријом *X* зрака. Сви пацијенти су попуњавали исти, специјално дизајнирани упитник. Процена адхеренције калцијума, витамина Д и лекова за остеопорозу је рађена Мориски скалом. Обрада података рађена је у СПСС програм верзија 20.
Резултати Сви испитаници су били женског пола. Остеопорозу је имало 67,5%, а 32,5% остеопенију. Суплементацију калцијума користило је 62,5% жена, 81,3% витамин Д, а 62,3% лекове. Ниску адхеренцију калцијума је имало 81,2% жена које користе суплементацију, 82,8% ниску адхеренцију витамина Д и 65,8% ниску адхеренцију на лекове. Адхеренција на лекове за остеопорозу је боља у односу на адхеренцију калцијума и витамина Д ($p<0.05$, χ^2-тест). Пацијенти који примају лекове интравенски имају бољу адхеренцију него они који лек узимају супкутано или орално.
Закључци Адхеренција на витамин Д, калцијум и лекове за остеопорозу је ниска у испитиваној популацији са нејасним разлозима.
Кључне речи: остеопороза; адхеренција пацијента; калцијум, витамин Д

INTRODUCTION

Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to an increase in the bone fragility and therefore a higher risk of fractures [1]. World Health Organisation (WHO) definition of osteoporosis is based on the measurements of bone mineral density (BMD) [2]. In the treatment of osteoporosis, calcium and vitamin D supplementation is used, as well as drugs with different mechanisms of action. Calcium and vitamin D are required for normal bone metabolism. Deficit of vitamin D in organism leads to secondary hyperparathyroidism and bone resorption [3, 4]. Supplementation of vitamin D reduces the bone fragility and increases BMD. According to recommendations physician should initiate pharmacologic treatment when patient had hip or vertebral (clinical or asymptomatic) fractures, when

T-scores is ≤−2.5 SD at the femoral neck, total hip, or lumbar spine by dual-energy X-ray absorptiometry (DXA), in postmenopausal women and men age 50 and older with low bone mass (T-score between −1.0 SD and −2.5 SD, osteopenia) at the femoral neck, total hip, or lumbar spine by DXA and a 10-year hip fracture probability ≥3 % or a 10-year major osteoporosis-related fracture probability ≥20 % based on the USA-adapted WHO absolute fracture risk model (Fracture Risk Algorithm (FRAX®)) [5]. Drugs approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis are: bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy (HT), tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone 1–34 (teriparatide), and receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor (denosumab) [6, 7]. Bisphosphonates are prescribed most often for the treatment of osteoporosis. Patients can use them weekly, monthly, once in three months and once per year. They are efficious and well tolerated [8]. Estrogen/hormone therapy is approved by the FDA for the prevention of osteoporosis, relief of vasomotor symptoms, and vulvovaginal atrophy associated with menopause [9].

For optimal treatment it is necessary not only to recognize persons at risk, make appropriate diagnosis and treatment decisions, but also to ensure patient adherence. Adherence to medication is defined as the cooperation of the patient with the physician in relation to the dose, frequency and timing of medication during the recommended period of treatment [10, 11, 12]. Medication adherence can be divided into three major components: persistence, initiation adherence and execution adherence. Perisistance is defined as the length of time a patient fills his/her prescriptions [13]. Initiation adherence gives answer at question does the patient start with the indented pharmacotherapy [13]. Execution adherence is the comparison between the prescribed drug dosing regimen and the real patient's drug-taking behavior and includes dose omissions (missed doses) and the so-called 'drug holidays' (3 or more days without drug intake) [13]. There are objective and subjective ways of measuring adherence. Objective measures, including measurement of clinical outcomes, dose counts, pharmacy records, electronic monitoring of medication administration (e.g. the Medication Event Monitoring System, MEMS) and drug concentrations, seemingly provide the best measure of a patient's medication-taking behaviour. Subjective measures of adherence include physician or family reports, patient interviews and self-report adherence scales. These measures have the potential to identify the specific reasons for a patient's non-adherence. Subjective measures can be relatively simple to use and are less expensive [14]. Morisky scale is the often used metric to assess adherence. This scale can evaluate reliably, easily and efficiently the cooperation of the patient with physician [15, 16, 17]. With this scale, our study tried to analyze and evaluate the effects of therapy for osteoporosis in our patients, and compare them with the results in the related work, as there is no such data for our country.

The purpose of this pilot study was to determine adherence to calcium, vitamin D and drugs for osteoporosis in patients with reduced bone mineral density as well as to analyze reasons for low adherence.

METHODS

This prospective cross-sectional study is a pilot project at the Special Hospital for Rheumatic Diseases in Novi Sad, including the sample of 80 postmenopausal women with low bone mineral density, measured by dual-energy X-ray absorptiometry. Women were treated with supplementation of calcium, vitamin D and/or drugs for osteoporosis (bisphosphates or teriparatide). None of the women used hormone replacement therapy. All patients signed informed consent to participate in this study. The study was approved by the Ethics Committee of Special Hospital for Rheumatic Diseases in Novi Sad. Each patient filled in a specially designed questionaire . The assessment of the adherence to calcium, vitamin D and drugs for osteoporosis was done by Morisky scale, which contains eight items. In first seven questions patient can answer with yes or no, while in one last question patient can answer choosing one of five options offered. Answers are marked for first 7 questions with 1 point for „yes“ and 0 points for „no“. In the five-options question, answers „never“ and „rarely“ scored 0 points, while other options („from time to time“/“sometimes“/“often“/“all the time“) scored 1 point. A total score for each subject is obtained by adding up the points for all questions. Score ≥3 was considered as low adherence, 1-2 was medium adherence and score 0 was high adherence.

Statistical analysis In this study the SPSS programme v.20 was used, as well as the measures of central tendency, the ANOVA test and the Chi2 (χ^2) test.

RESULTS

Demographic data for all study subjects is presented in Table 1. All patients were female. The average age for all subjects was 65.52 ± 8.29. Most of the subjects live in the city and have a high-school. 67.5% had osteoporosis with a duration of M 4.29 ± 3.36 years and 32.5% had osteopenia with a duration of M 3.54 ± 2.42 years. The subjects had entered the menopause earliest with 35 years, and latest with 55 years. The average enterence in the menopause was 47.5 years (M = 47.5).

Table 1. Patients characteristics.

Variables		
Gender (frequency/percent)	Female	80/100
Age (x̄±SD)		65,52±8,29
Place for living (frequency/%)	City	52/65
	Village	28/35
Education (frequency/%)	Primary school	23/28,8
	High school	44/55
	Faculty	13/16,3
Osteporosis (frequency/%)		54/67,5
Osteopenia (frequency/%)		26/32,5
Duration of osteoporosis (x̄±SD)		4,29±3,36
Duration of osteoenia (x̄±SD)		3,54±2,42
The average enterance in the menopause (x̄±SD)		47,5±4,8

62.5% of women involved in this study, used calcium supplementation. Using Morisky scale, our results showed that they in 81.2% had the low adherence (Table 2). Vitamin D supplementation used 81.3% of women, but adherence to vitamin D was also in 82.8% low. There

Table 2. Adherence to calcium, vitamin D and drugs for osteoporosis

	Calcium		Vitamin D		Drugs for osteoporosis	
	n	%	n	%	n	%
Middle adherence	9	18,8	11	17,2	13	34,2
Low Adherence	39	81,2	53	82,8	25	65,8

$p<0,05$

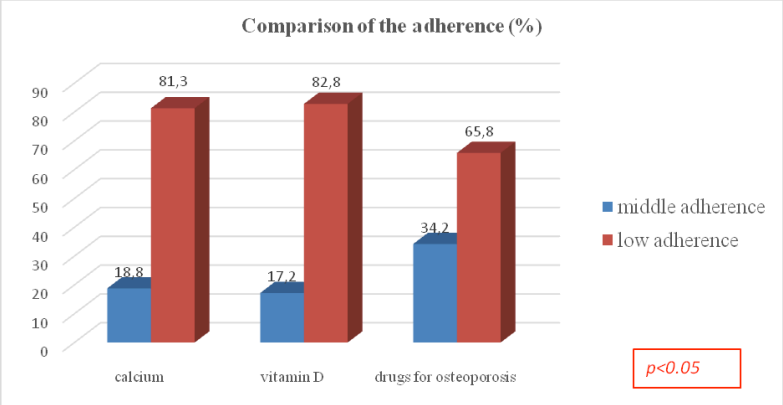

Figure 1. Comparison of the adherence to calcium, vitamin D and drugs for osteoporosis.

Table 3. Reasons for low adherence to calcium

		Forget-fulness	Price	Many other drugs	Low tolerance/ Side effects	Total
Middle adherence	n	7	1	1	0	9
	%	33,3	8,3	14,3	0,0	20,5
Low adherence	n	14	11	6	4	35
	%	66,7	91,7	85,7	100,0	79,5
Total	n	21	12	7	4	44
	%	100,0	100,0	100,0	100,0	100,0

χ^2=4,41 , df=3, p=0,220; Likelihood Ratio=5,22, df=3, p=0,156

Table 4. Reasons for low adherence to vitamin D

		Forget-fulness	Price	Many other drugs	Low tolerance/ Side effects	Total
Middle adherence	n	5	1	4	1	11
	%	20,0	9,1	57,1	100,0	25,0
Low adherence	n	20	10	3	0	33
	%	800,0	90,9	42,9	0,0	75,0
Total	n	25	11	7	1	44
	%	100,0	100,0	100,0	100,0	100,0

χ^2=8,67 , df=3, p=0,034; Likelihood Ratio=8,20, df=3, p=0,042

was no high adherence in the study population. 62.3% of women said that they take some medication for osteoporosis. Results of the adherence to drugs for osteoporosis (Table 2) showed that in the study population, there was no high adherence. Most of the subjects had a low adherence.

Comparison of the adherence to calcium, vitamin D and drugs for osteoporosis are shown in Figure 1. Adherence to drugs for osteoporosis was higher in comparison to vitamin D and calcium ($p<0.05$, χ^2-test). However, there was no statistically significant difference in adherence to vitamin D and calcium ($p> 0.05$, χ^2-test).

Reasons for the low adherence to calcium, vitamin D and medications for osteoporosis were also analized, based on data obtained from questionnaires. The results showed that there was no statistically significant correlation between the level of adherence and reasons for not taking calcium supplementation (Likelihood Ratio = 5.22, df = 3, p = 0.156). Results are shown in Table 3. Regarding the reasons for low adherence to vitamin D supplementation, results showed that there was a statistically significant correlation (Likelihood Ratio = 8.20, df = 3, p = 0.042) with low adherence. Main reason for the low adherence to vitamin D is the price of preparation (90.9% of all patients) as shown in Table 4. Results of the low adherence and reasons for not taking medication

showed that there is no statistically significant correlation between these factors (Likelihood Ratio = 7.33, df = 3, p = 0.063). Low adherence had those patients who forget to take the medicine (84.6%), and high adherence had those where the price of medication was problematic (66.7%). The results are shown in Table 5.

Table 5. Reasons for low adherence to drugs for osteoporosis.

		Forget-fulness	Price	Many other drugs	Low tolerance/ Side effects	Total
Middle adherence	n	2	2	1	1	6
	%	15,4	66,7	100,0	100,0	33,3
Low adherence	n	11	1	0	0	12
	%	84,6	33,3	0,0	0,0	66,7
Total	n	13	3	1	1	18
	%	100,0	100,0	100,0	100,0	100,0

χ^2=7,38 , df=3, p=0,061; Likelihood Ratio=7,33, df=3, *p*=0,063

In relation to the drug application options and their effect on the adherence to drugs for osteoporosis, there was no statistically significant difference (Likelihood Ratio = 4.83, df = 2, p = 0.089). All participants (100%) who took medication for osteoporosis intravenous had a middle level of adherence. Most of those who took medicine for osteoporosis through tablets and subcutaneous had a low adherence. The results are shown in Table 6.

Table 6. Adherence to drugs for osteoporosis and drug consumption.

		Oral	Intra venous	Subcuta neous	Total
Middle adherence	n	10	2	1	13
	%	32,3	100,0	20,0	34,2
Low adherence	n	21	0	4	25
	%	67,7	0,0	80,0	65,8
Total	n	31	2	5	38
	%	100,0	100,0	100,0	100,0

χ^2=4,34 , df=2, p=0,114; Likelihood Ratio=4,83, df=2, *p*=0,089

DISCUSSION

Like in other chronic diseases, adherence to medications for osteoporosis is low. The reasons are numerous, but the most common are fear of side effects, cost of the treatment and lack of motivation to take the drug for a disease that is clinically "silent". Lack of pain until fracture happens contributes to low adherence. Also, several social and economic factors are involved, esspecially in developing countries. Every physician have to think about this factors when makes a treatment decision. Low adherence leads to poor results in the treatment, increased risk of fractures and therefore increases the costs of the treatment [18].

Most important novelity of this study is consideration that this is one of the first studies of the adherence to calcium, vitamin D and drugs for osteoporosis conducted in our country, Republic of Serbia. Until now, all our knowledge on the subject was relied on foreign studies. This study was conducted prospectively using Morisky scale as subjective measure of the adherence because it has benefits of being cheap, acceptable to patients, valid, reliable, has the ability to distinguish between different types of non-adherence, easy to administer, and able to provide information on attitudes and beliefs about medication [19]. The study was designed to be very close to common clinical practice.

Supplementation with calcium and vitamin D is required not just to treat patients with osteopenia, but also in patients with osteoporosis and continues after the start of osteoporosis

treatment. The results of our study indicated a low adherence to calcium and slightly better adherence to vitamin D. Similar results were recorded also by the authors of a large study ADVICE [20]. This study, which was performed in the leading centers for the treatment of osteoporosis in Italy, analyzed adherence to calcium and vitamin D and factors affecting it. It was concluded that adherence was low, and it is necessary to increase it by frequent contact with the doctor which showed an increase in the patients' motivation for the treatment [20]. On contrary, an observational study which was carried out in three osteocenters in the Czech Republic, reported good adherence, but with a fixed combination of Ca–vitamin D which was observed in 60% of persistent participants [21].

The main reason for low adherence to vitamin D in our study was the price of preparation. The use of drugs every day, every month, for years, could be an economic burden for the patient. Results of one study condacted in Canada suggested that about 1 in 10 Canadians, who receive a prescription, report costrelated nonadherence [22]. Education of the patients was probably not the reason of low adherence, while all patients had at least medium level of education.

A number of options for the treatment of osteoporosis is increasing. The most commonly used bisphosphonates that can be given per week, or per month, or every three months, or per year. Besides these medications, there are: calcitonin, hormonal therapy, selective estrogen receptor modulators and teriparatide. Despite having many options for the treatment, drug adherence is low. The assumption was that the estrogen hormone therapy would have better adherence since it eliminates the symptoms of menopause [23]. However, studies did not confirm this. Contrary to our expectations, the study confirmed that adherence to bisphosphonate therapy is better than adherence to the hormones and calcitonin [23]. Our results align with the results of the meta-analysis of 24 observational studies on large populations, where it was confirmed that adherence to medications for osteoporosis is low [23]. Results from a recently condacted cohort in Bologna, Italy which used administrative databases as a reliable source of data for “prescription continuity” showed that adherence to the fixed-dose combination (alendronate with colecalciferol) was higher than to plain alendronate throughout the follow-up period [24].

Also, our study considered the reasons for low adherence. It was found that the price concerned the patients, but does not have a statistically significant effect on the adherence to drugs for osteoporosis, similar to other studies [25]. Our results indicate that patients often forget to take the medicine and that fear of the side effects or intolerance to the preparation was not the cause of low adherence, while other authors on the contrary did conclude that the fear of side effects was a significant cause of low adherence [25, 26]. Also, one American recently condacted study concluded that barriers to prescription treatment include a preference for alternative, non-prescription treatments and not just a fear of possible side effects [26]. Another study which was also conducted in USA, reveals undertreatment of women diagnosed with osteoporosis. This study showed that in 41% of the patients, the physician did not recommend treatment, and in 38%, the patient choose not to initiate

treatment. Among patients who did not initiate recommended treatment, the predominant reason was concern over side effects, cost of medication, and pre-existing stomach or digestion problems [27].

The results of our study suggestes that patients who recieved the drug intravenously had better adherence, in comparison with the patients who recieved the drug orraly or subcutaneously.

There were also some limitations in our study. We used just subjective measures for the adherence. Also, adherence to fixed combinations of Ca-Vitamin D, fixed doses of bisphosphonates-Vitamin D and hormonal therapy was not explored. Nevertheless, we believe that the results provided by our survey contain valuable information for the adherence to calcium, vitamin D and drugs for osteoporosis among Serbian people.

CONCLUSIONS

Adherence to vitamin D, calcium and drugs for osteoporosis is presently low in investigated population and the understanding of the causes of low adherence is still insufficiently explored. We believe that better patient education, more therapy possibilities and frequent visits to the doctor, can significantly help the patient to understand the importance of this problem and increase the adherence.

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