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

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INTRODUCTION

Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to an increase in bone fragility and therefore a higher risk of fractures [1]. The World Health Organization definition of osteoporosis is based on the measurements of bone mineral density [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. Vitamin D deficiency leads to secondary hyperparathyroidism and bone resorption [3, 4]. Supplementation of vitamin D reduces bone fragility and increases bone mineral density. According to recommendations, a physician should initiate pharmacologic treatment after a patient has had hip or vertebral (clinical or asymptomatic) fractures, when T-score is ≤ -2.5 SD at the femoral neck, total hip, or lumbar spine by dual-energy X-ray absorptiometry and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the USA-adapted World Health Organization absolute fracture risk model (Fracture Risk Algorithm (FRAX®)) [5]. Drugs approved by the US Food and Drug Administration for the treatment of osteoporosis are bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone 1-34 (teriparatide), and receptor activator of the 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 efficacious and well tolerated [8]. Estrogen/hormone therapy is approved by the Food and Drug Administration 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 app-
propriate 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. Persistence 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 intended 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’ (three 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, and 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 the 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 the 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. The 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 the patients signed informed consent to participate in this study. The study was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases in Novi Sad. Each patient filled out a specially designed questionnaire. The assessment of the adherence to calcium, vitamin D and drugs for osteoporosis was done by Morisky scale, which contains eight items. In the first seven questions the patient can answer with “yes” or “no,” while in one last question the patient can answer choosing one of five options offered. The answers for the first seven questions are marked 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 the questions. Score ≥ 3 was considered to be low adherence, 1–2 was medium adherence, and score 0 was high adherence.

IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis in this study, as well as the measures of central tendency, the ANOVA test, and the χ² test.

RESULTS

Demographic data for all study subjects is presented in Table 1. All the patients were female. The average age for all subjects was 65.52 ± 8.29. Most of the subjects lived in the city and had secondary school education; 67.5% of them 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 menopause with 35 years at the earliest, and with 55 years at the latest. The average entrance in the menopause was 47.5 years (M = 47.5).

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

| Table 1. Patient characteristics |
| Variables                  | Gender (frequency/percent) | Female 80/100 |
| Age (M ± SD)               | 65.52 ± 8.29               |
| Place of living (frequency/percent) | Urban 52/65 | Rural 28/35 |
| Education (frequency/percent) | Primary school 23/28.8 | Secondary school 44/55 | University 13/16.3 |
| Osteoporosis (frequency/percent) | 54/67.5                |
| Osteopenia (frequency/percent) | 26/32.5                |
| Duration of osteoporosis (M ± SD) | 4.29 ± 3.36         |
| Duration of osteopenia (M ± SD) | 3.54 ± 2.42           |
| The average age when entering menopause (M ± SD) | 47.5 ± 4.8 |

M – arithmetic mean; SD – standard deviation

| Table 2. Adherence to calcium, vitamin D, and drugs for osteoporosis |
| Adherence | Calcium | Vitamin D | Drugs for osteoporosis |
| Frequency | %      | Frequency | %      | Frequency | %      |
| Medium adherence | 9 | 18.8 | 11 | 17.2 | 13 | 34.2 |
| Low adherence | 39 | 81.2 | 53 | 82.8 | 25 | 65.8 |

p < 0.05
82.8% of them (Table 2). There was no high adherence in the study population. Some medication for osteoporosis was being taken by 62.3% of the women. Results of the adherence to drugs for osteoporosis showed that there was no high adherence that in the study population (Table 2). Most of the subjects had low adherence.

Comparison of 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 ($p < 0.05$, χ² test). However, there was no statistically significant difference in adherence to vitamin D and calcium ($p > 0.05$, χ² test).

Reasons for the low adherence to calcium, vitamin D, and medications for osteoporosis were also analyzed, based on the data obtained from questionnaires. The results showed that there was no statistically significant correlation between the level of adherence and the reasons for not taking calcium supplementation (likelihood ratio = 5.22, distribution function (df) = 3, $p = 0.156$), as shown in Table 3. Regarding the reasons for low adherence to vitamin D supplementation, the results showed that there was a statistically significant correlation (likelihood ratio = 8.20, df = 3, $p = 0.042$) with low adherence. The main reason for low adherence to vitamin D is the price of preparation (90.9% of all patients), as shown in Table 4. Results of 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 was present in patients who forgot to take the medicine (84.6%), and high adherence where the price of medication was problematic (66.7%), as shown in Table 5.

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, $p = 0.089$). Middle level of adherence was present...
in all the participants (100%) who took medications for osteoporosis intravenously. Low adherence was present in most of the patients who took the medicine for osteoporosis through tablets and subcutaneously, as shown in Table 6.

### DISCUSSION

Like in other chronic diseases, adherence to medications for osteoporosis is low. The reasons are numerous, but the most common are the fear of side effects, the cost of 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, especially in developing countries. Every physician has to think about these factors when he makes a treatment decision. Low adherence leads to poor treatment results, increased risk of fractures, and therefore increases treatment costs [18].

The most important characteristic of this study is that this is one of the first studies of adherence to calcium, vitamin D, and drugs for osteoporosis conducted in our country, the Republic of Serbia. Until now, all our knowledge on the subject relied on foreign studies. This study was conducted prospectively using the Morisky scale as a subjective measure of the adherence because it has benefits of being inexpensive, 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 ADVANCE study [20]. This study, 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]. In contrast, an observational study 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. Daily use of drugs, for years, could be an economic burden for the patient. Results of one study conducted in Canada suggested that about 1 in 10 Canadians who receive a prescription report cost-related nonadherence [22]. Education of the patients was probably not the reason of low adherence, while all patients had at least medium level of education.

The number of options for the treatment of osteoporosis is increasing. The most commonly used medications are bisphosphonates, which can be given per week, per month, every three months, or per year. In addition to these medications there are also 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 menopause symptoms [23]. However, studies do not confirm this. Contrary to our expectations, the present study confirmed that adherence to bisphosphonate therapy is better than adherence to 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 conducted 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 cholecalciferol) was higher than that to plain alendronate throughout the follow-up period [24].

Also, our study considered the reasons for low adherence. It was found that the price did worry the patients, but it did 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, in contrast, other authors did conclude that the fear of side effects was a significant cause of low adherence [25, 26]. Also, in one study recently conducted by American authors it was 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 also conducted in the USA reveals under-treatment of women diagnosed with osteoporosis. This study showed that in 41% of patients the physician did not recommend any treatment, and in 38%, the patient chose not to initiate the treatment. Among patients who did not initiate the 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 suggest that patients who received the drug intravenously had better adherence, in comparison with patients who received the drug orally or subcutaneously.

| Table 6. Adherence to drugs for osteoporosis and drug consumption |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Adherence                  | Drug administration         | Total                       |
|                            | Oral                        | Intravenous                 | Subcutaneous                |
| Low adherence              | Frequency 21                | 0                           | 4                           | 25                          |
|                            | % 67.7                      | 0                           | 80                          | 65.8                        |
| Medium adherence           | Frequency 10                | 2                           | 1                           | 13                          |
|                            | % 32.3                      | 100                         | 20                          | 34.2                        |
| Total                      | Frequency 31                | 2                           | 5                           | 38                          |
|                            | % 100                       | 100                         | 100                         | 100                         |

χ² = 4.34, df = 2, p = 0.114; likelihood ratio = 4.83, df = 2, p = 0.089
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 population.

REFERENCES


CONCLUSIONS

Adherence to vitamin D, calcium, and drugs for osteoporosis is presently low in investigated population and 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.
Процена адхеренције калцијума, витамина Д и лекова за остеопорозу код болесника са сниженом коштаном густином

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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 процена адхеренције калцијума, витамина Д и лекова за остеопорозу код болесника са сниженом коштаном густином и анализа разлога за ниску адхеренцију.

Методе У ову студију је укључено 80 постменопаузалних жена са сниженом коштаном густином измереном двоструким апсорпцијом зрака. Сви болесници су попуњавали исти, специјално дизајнирани упитник. Процена адхеренције калцијума, витамина Д и лекова за остеопорозу је рађена скалом Мориски. Обрада података рађена је у програму SPSS, у верзији 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% витамина Д, а 62,3% лекове. Ниску адхеренцију калцијума имало је 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 (р < 0,05, χ² тест). Болесници који примају лекове интравенски имају бољу адхеренцију него они који лек узимају субкутано или орално.

Закључци Адхеренција на витамин Д, калцијум и лекове за остеопорозу је ниска у испитаној популацији, из нејасних разлога.

Кључне речи: остеопороза; адхеренција болесника; калцијум, витамин Д

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