

# LONG-TERM COMPLIANCE OF PATIENTS WITH OSTEOPOROSIS TREATMENT AND ITS EFFECT TO FRACTURE OCCURRENCE

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## SUMMARY

**Objectives:** The objective of this study was to evaluate the effect of long-term treatment of patients with osteoporosis being actively managed by medical staff and following the therapeutic methods and principles of treatment of osteoporosis.

**Methods:** The medical records of patients which were examined in an osteological outpatient office first time in the year 2009 were reviewed. The results of densitometry examinations were compared with the results from the year 2019. Patients regularly absolved densitometry, properly and regularly took prescribed medicaments for either anti-osteoporotic treatment or for supplementation of vitamin D and calcium. The cohort consisted of 100 patients. Next, we split the group into 3 categories – less than 65 years of age, 65–75 years of age and lastly over 75 years of age. By default, we assessed and compared the T-scores (deviation from the average value of bone density of 30 years old healthy person) in the area of the proximal femur and in the area of the lumbar spine. The bone mineral density (BMD) values in g/cm<sup>2</sup> and their relation to corresponding T-score from set area were also reviewed.

**Results:** Based on the results of densitometry, osteoporosis was diagnosed in 41 patients, manifest osteoporosis in 14 and osteopenia in 36, nine patients had their bone density value within the normal range. The average T-score values of “total hip” were –1.42, “neck” –2.08, BMD values of “total hip” were 0.802 g/cm<sup>2</sup>, “L1-L4” –2.05, “L total” –1.45, and BMD of “L total” was 0.886 g/cm<sup>2</sup>. In the time of the last examination, the T-score (disregarding the type of treatment) raised from the initial value by 40.16% in the area of lumbar spine, by 56.69% in the area of “total hip”, and by 40.16% in the area of “neck”. While sorting the cohort based on age, we detected a similar effect of active management of treatment in each of the 3 categories.

**Conclusion:** Cooperation of the patients during the treatment of a chronic disease requiring long-term usage of medicaments is often problematic and it is necessary to devote adequate attention to it. The solution to improve the treatment can be active management of the patient by the medical facility or by the medical staff.

**Key words:** osteoporosis, osteoporosis treatment, compliance

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## INTRODUCTION

Osteoporosis is a metabolic affection of the skeleton with its characteristic sign being the decrease of bone mass and deterioration of the microarchitecture of bone tissue, which causes higher fragility of bones and higher predisposition to fractures. Worldwide, osteoporosis affects more than 200 million patients and about 30% of all menopausal women suffered from it. The most serious complication of osteoporosis are fractures. Lifetime risk of a fracture of a proximal femur, a vertebra, or a forearm is estimated to be about 40%, which is similar to the risk of a coronary disease. In Europe, the incidence of osteoporotic fractures is rising not only in the hip area but also in other anatomical

locations. Approximately 3/4 million new osteoporotic fractures were recorded in the EU in the year 2010. The risk of death after a hip fracture of a 65-year old woman is the same as the one of breast cancer and 4-times higher than the one of uterus cancer (1).

The current definition of osteoporosis allows us to observe the epidemiology of osteoporosis based on the occurrence of fractures or based on the occurrence of densitometrically defined osteoporosis. This disease does not have any symptoms and can occur as an osteoporotic fracture which forms after the impact of minimal violence (2, 3). Because of that, prevention and early treatment is essential. The reasonable compliance of a patient has a significant role in the treatment of osteoporosis and is also an important factor in the prevention of fractures. It is essential

for the treatment effect that patients take medicaments regularly and on a long-term basis. It is proven that long-term treatment of osteoporosis (more than 6 months) significantly decreases the risk of fractures. On the other side, weak adherence and compliance of patients lowers the effect of treatment and so does not lead to the wanted result – reduction of risk of a fracture. It results in the increase of hospitalizations caused by osteoporotic fractures and to pointless (unindicated) changes of therapeutic methods (4).

Even though it was proved that there is a positive effect from long-term treatment of osteoporosis, the adherence of patients to treatment is not optimal (5). There is a high amount of data saying that many patients with an osteoporotic fracture are underdiagnosed and the majority of them is not treated at all for up to a year from the fracture. The effectivity of treatment of osteoporosis is highly dependent on the effectivity of medicaments (effect of the medicament showed in evidence-based medicine studies, with compliance being over 80% and are selected in a different way than patients in common practices), safety, tolerance (absence of unwanted effects), and adherence (how accurately the patient uses the prescribed medicaments).

Adherence consists of 2 components – persistence (time span from the beginning to the end or discontinuation of treatment, in other words whether the patient will be taking the medicaments long-term); and compliance (accuracy and correctness of using medicaments).

According to literary sources it is estimated that about 45–50% of patients terminate the treatment up to 12 months from its initiation. Talking about treatment of osteoporosis by bisphosphonates in usual practice, more than 50% of all patients do not follow the long-term treatment, 20% of them do not even take the prescribed medicaments from the pharmacy (6, 7).

Some of the most common causes and factors of bad adherence to treatment, e.g., by bisphosphonates, are said to be frequent dosing (once or more times per day), gastrointestinal unwanted effects or problems with application. Based on released information, the pharmaceutical companies are trying to create medicaments, which are applied once a week, once a month, half-year, or once a year. Nevertheless, it is important to point out that the treatment of osteoporosis is, even when using such medicaments, effective only when it is complex, and that adequate life regime measurements and daily regular intake of calcium and vitamin D are in place (6, 7).

The goal of this study was to evaluate the effect of long-term treatment of osteoporosis. It was focused on a section of patients that followed pre-determined therapeutic methods and principles of treatment during its entirety. They regularly underwent densitometry, correctly and regularly took prescribed medicaments, either for anti-osteoporotic treatment or for supplementation of vitamin D and calcium.

## MATERIALS AND METHODS

The cohort of patients was created from metabolic bone unit managing patients with observing them and regularly forecalling them for examinations.

Medical documentation of patients, which were first examined in metabolic bone unit in the year 2009 and subsequently absolved a densitometry were evaluated retrospectively. Results

of densitometry were statistically compared with results of controls from 2019. During the entire observing, patients absolved regular controls, laboratory examinations, followed prescribed treatment, and it is effect was frequently observed by densitometry in accordance with current recommendations of osteological society and the Official Bulletin of the Ministry of Health of the Slovak Republic (8). Outpatient controls were executed in 6-month intervals at minimum. The patients underwent a control examination on the whole-body densitometer Hologic once a year. Laboratory examinations aimed at observing the metabolism of calcium and bone turnover were executed at the start of treatment and then in regular controls once a year. Effect and effectivity of treatment were evaluated based on values gained from densitometrical examinations from 2009 and 2019, the occurrence of fractures was also observed. During the treatment, methods recommended by the Official Bulletin of the Ministry of Health were used (8). In respect of 10-year period of observations and treatment, the treatment was updated regularly based on medicaments availability, course of treatment and most recent medical knowledge. The medicamentous treatment consisted, in the case of osteopenia, of supplementation of calcium and vitamin D. In the case of osteoporosis, the core treatment consisted of regular usage of medicaments from the group of bisphosphonates, denosumab, strontium ranelate together with supplementation of calcium and vitamin D.

The cohort overall contained 100 patients (females). The average age at the time of first examination was 69.25 years (the youngest patient was 43 years old, the oldest 88 years old). The average body mass index (BMI) value was 27.30. Table 1 shows the most frequent comorbidities in the observed groups.

Aiming to gain a more detailed look on the impact of active management of each age group of patients we split the whole cohort into 3 age groups – patients 65 years old or under in the time of first examinations; patients aged 65–75; patients aged over 75. Number of patients in each group were 23 patients, 47 patients, and 30 patients, respectively.

We rated and compared the values of T-score (deviation of the average value of bone density of 30-years old healthy persons) in the area of proximal femur and lumbar spine as usual. Next,

**Table 1. Most frequent comorbidities of our patients**

Disease	Number
Arterial hypertension	42
Hysterectomy in past	19
Ischaemic heart disease	12
Hypothyroidism	12
Dyspeptic syndrome	7
Hypercholesterolemia	6
Chronic pancreatitis	5
Thyroiditis	4
Hepatopathy	4
Varices of lower extremity	4
Depression	3
Heart arrhythmia	3
Rheumatoid arthritis	3

bone mineral density (BMD) values in g/cm<sup>2</sup> and their relation to associated T-score from set area were observed.

## RESULTS

Based on the results of densitometry from the first examination from 2009, 41 patients were diagnosed with osteoporosis, 14 with manifest osteoporosis, 36 with osteopenia, and 9 patients had their BMD inside of the norms. Average T-score values of “total hip” were –1.42, “neck” –2.08, BMD values of “total hip” were 0.802 g/cm<sup>2</sup>, “L1-L4” –2.05, “L total” –1.45 and BMD of “L total” was 0.886 g/cm<sup>2</sup> (Table 2).

In time of the first examination in 2009, 20 patients suffered a fracture in their history, caused by a micro-injury or randomly found during RTG examination. In 10 cases it was a distal forearm fracture, in 4 cases a fracture of proximal humerus, in 5 cases a vertebral fracture, and in 1 case a fracture of pubic bone.

In 2019, the average T-score value of “total hip” was –0.62 (maximum 1.9, minimum –2.5), average T-score in the area of femoral neck –1.33 (maximum 0.9, minimum –2.9), and average BMD value in the area of proximal femur was 0.870 g/cm<sup>2</sup> (maximum 1.17, minimum 0.63).

In the area of L (lumbar) spine in 2019, the average T-score in area of the worst spondyle was –1.39 (maximum 1.7, minimum –3.8), average T-score of “L total” was –0.87 (maximum 2.7, minimum –3.3), and average BMD value of “L total” was 0.943 g/cm<sup>2</sup> (maximum 1.34, minimum 0.64).

With good adherence (caused by active management of patients by medical staff based on most recent medical knowledge) to treatment of osteoporosis and correct compliance of patients, T-score after 10 years increased in the area of femoral neck by 0.75 SD (standard deviation) on average, in the area of “total hip” by 0.8 SD and in the area of “L spine” increased by 0.58 SD on average.

The BMD values in grams of minerals/cm<sup>2</sup> increase in the area of “total hip” where it changed by 0.068 on average, in the area of lumbar spine it raised by 0.057 on average. We however did not record rise of BMD value in correlation with T-score values in associated areas.

Fractures occurred during the treatment – 6 patients suffered an osteoporotic fracture during the monitored treatment period.

In 2 cases, it was a fracture of distal radius and in the remaining 4 cases, there were vertebral fractures; 2 patients suffered a fracture of 2 vertebrae (in both cases Th11 and Th12 – thoracic), in the remaining 2 cases it was a fracture of L2 or L3. Only 1 patient had an osteoporotic fracture in their history before the start of treatment. All fractures were treated conservatively.

Based on the results of densitometrical examinations in 2019, 1 patient was diagnosed with severe osteoporosis, 10 patients with osteoporosis, 81 patients with osteopenia, and 8 patients had their bone density value in the normal range. It means, that the number of patients with osteoporosis decreased significantly (from 55 to 11%) in the observed groups (Table 3).

With good adherence and correct compliance, the T-score (irrespective of type of treatment) increased from the original value by 41.16% in the area of lumbar spine, by 56.69% in the area of “total hip”, and by 40.16% in the area of femoral neck.

While sorting the different groups, we found a comparable effect of active management of treatment in all 3 groups (Table 4, 5).

## DISCUSSION

Because of its possible consequences the osteoporosis is a severe disease, and its occurrence is rising exponentially within the population. It has become a huge medical, social and economic problem. That is one of the reasons why osteoporosis is often called the epidemic of the third millennium. Its highest influence is within the population 75 years old and higher (9). The expenses of diagnostics and treatment of osteoporosis including the treatment of fractures are climbing to huge amounts and are constantly rising (10). Annually, European Union’s expenses on osteoporosis are

**Table 3. Comparison of DEXA results in 2009 and 2019**

T-score	2009	2019
Normal	9	8
Osteopenia	36	81
Osteoporosis	41	10
Severe osteoporosis	14	1

DEXA – dual-energy X-ray absorptiometry

**Table 2. Results of densitometry examination in 2009 and 2019**

	DEXA at first examination 2009	DEXA at last examination 2019
Average T-score “total hip”	–1.42 (max. 1.6, min. –3.5)	–0.62 (max. 1.9, min. –2.5)
Average T-score “neck”	–2.08 (max. 1, min. –4.03)	–1.33 (max. 0.9, min. –2.9)
Average BMD “total hip”	0.802 g/cm <sup>2</sup> (max. 1.133, min. 0.549)	0.870 g/cm <sup>2</sup> (max. 1.17, min. 0.63)
Average T-score “L1-L4” (evaluation of vertebra with lowest T-score)	–2.05 (max. 0.61, min. –4.48)	–1.39 (max. 1.7, min. –3.8)
Average T-score “L total”	–1.45 (max. 0.98, min. –4.03)	–0.87 (max. 2.7, min. –3.3)
Average BMD “L total”	0.886 g/cm <sup>2</sup> (max. 1.154, min. 0.604)	0.943 g/cm <sup>2</sup> (max. 1.34, min. 0.64)

Total hip – evaluation of bone density in whole proximal femur region; neck – evaluation of bone density in femoral neck region only; L – lumbar vertebra and its number; DEXA – dual-energy X-ray absorptiometry

**Table 4.** State of patients divided based on age categories in the first examination in 2009

First examination 2009	Group 1 (age under 65 years) Total 23 patients n (%)	Group 2 (age 65–75 years) Total 47 patients n (%)	Group 3 (age over 75 years) Total 30 patients n (%)
Normal	2 (8.7)	4 (8.5)	3 (10.0)
Osteopenia	10 (43.5)	18 (38.3)	8 (26.7)
Osteoporosis	8 (34.8)	20 (42.6)	13 (43.3)
Severe osteoporosis	3 (13.0)	5 (10.6)	6 (20.0)

**Table 5.** State of patients divided based on age categories in the last examination in 2019

Last examination 2019	Group 1 (age under 65 years) Total 23 patients n (%)	Group 2 (age 65–75 years) Total 47 patients n (%)	Group 3 (age over 75 years) Total 30 patients n (%)
Normal	1 (4.3)	2 (4.3)	5 (16.7)
Osteopenia	20 (87.0)	39 (83.0)	22 (73.3)
Osteoporosis	1 (4.3)	6 (12.8)	3 (10.0)
Severe osteoporosis	1 (4.3)	0	0

estimated to be about 37 billion euros; 66% of that are expenses on treatment of fractures, 29% on long-term aftercare. The main problem remains the fact that only 5% of all expenses are spent on prevention (1, 11). Complex supportive programmes which have a significant positive influence on the status and quality of the skeleton and lead to decrease of expenses on subsequent treatment and resolving consequences should be an integral part of the treatment of osteoporosis in the system of public health care (12). The effectivity and rationality of treatment of osteoporosis is dependent on correct indication (choice of an appropriate patient) and on sufficient duration of dosing. Multiple studies documented that adherence of patient to treatment of osteoporosis is suboptimal (13, 14). Kothawala et al. published a meta-analysis of worldwide adherence of patients to treatment of osteoporosis. The results show that the rate of adherence decreased from 53% in the case of treatment lasting from 1–6 months, in the case of treatment from 7–12 months or 13–24 months to 43%. The correct compliance was 62% for treatment from 1–6 months and 66% for the treatment from 7–12 months (6). The values released by McCombs et al. are even lower. They evaluated the compliance during the treatment of osteoporosis with 58,109 patients overall. The rate of right compliance during treatment lasting more than a year was lower than 25% for all types of treatment of osteoporosis (15). In the retrospective cohort study, which rated 24-month persistence in treatment by denosumab dosed every 6-months to postmenopausal women in the US and Canada the persistence was 58% (16). All these data confirm the importance of active management of patients with osteoporosis for reaching the effect of long-term treatment with themselves being interested in the management of treatment (17, 18).

In our cohort, the results of 100 patients were rated, with long-term (in the followed period of 10 years) and correctly used prescribed medicaments and followed recommendation of their doctor referring to the supplementation of vitamin D and calcium. They were also regularly densitometrically examined in order

to evaluate the effectivity of treatment. From 2009 to 2019 the T-score value in the area of femoral neck increased from  $-2.08$  to  $-1.33$ , which is an average increase by 0.75 SD. T-score of “total hip” increased from  $-1.42$  to  $-0.62$ , which is an average increase by 0.8 SD. In the area of “L spine” the T-score increased from  $-1.45$  to  $-0.87$ , which is an average increase by 0.58 SD. In the beginning of treatment, 41% of patients were diagnosed with osteoporosis, 14% were diagnosed with manifest osteoporosis. After 10 years, the number of patients with osteoporosis decreased to 10% and the number of patients with manifest osteoporosis decreased to 1%. In a randomized study FREEDOM, which presents the results of 10-year treatment by denosumab in post-menopausal women with osteoporosis, the T-score in the area of lumbar spine increased by 30.9%, by 15.2% in the area of “total hip” and by 13.8% in the area of femoral neck. The rise of T-scores in our cohort was by 40.16% in the area of “L spine”, by 56.69% in the area of “total hip” and by 40.16% in the area of femoral neck. The higher increase in the file could be caused by non-unified type of treatment of each patient or by composition of followed groups. In the FREEDOM study, in the beginning of observations all the patients had their densitometrical values in the range of osteoporosis (19). Silverman et al. claim that with treatment by denosumab dosed every 6 months and right compliance during 24 months was the average rise of BMD in the area of “L spine” by 7.8%, in the area of femoral neck by 2.1% (16).

Long-term compliance also significantly affects the occurrence of fractures. Freemantle et al. claim that patients with compliance higher than 80% in treatment by bisphosphonates had 16% lower relative risk of fractures than patients with lower compliance (20). Silverman et al. published 5.8% occurrence of fracture within 24-month treatment by denosumab with good compliance (16). In our file, at the beginning of treatment, the occurrence of osteoporotic fractures was 20% with decrease to 6% in 2019. Halpern et al. observed the relation between following the treatment of osteoporosis and the occurrence of fractures on 21,655 patients,

who began the treatment by alendronate, risedronate, ibandronate, or raloxifene. They published results saying that patients with low adherence to treatment had a 37% higher risk of suffering a fracture. They did not record any significant difference between different medicines (11).

## CONCLUSION

Osteoporosis is an important medical and socioeconomic problem in the present time. Its occurrence keeps rising, which is caused by higher life expectancy, but also by the modern lifestyle. Nowadays, it is no problem to diagnose and cure this disease. There are many different medicaments available whose effectivity is confirmed by many studies. The algorithm of treatment and prevention is also known. Even then, the treatment fails many times, which can be seen at the number of cases of osteoporotic fractures rising each year. In many cases, the failure is caused by insufficient adherence and compliance of the patient to treatment. Correct long-term treatment has a significant effect on the increase of bone density in all surveilled areas and also significantly decreases the risk of osteoporotic fractures, which was confirmed by our work as well. The cooperation of patients during the treatment of a chronic disease requiring long-term dosing of medicaments is often challenging and it is necessary to devote sufficient attention to it. Solution to this problem can be active management of patients by the medical facilities or doctors and calling patients for examinations, simplifying the dosing schemes, but also informing the patient about the importance of correct, regular and long-term usage of medicaments and also about the consequences of not following these methods.

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## Conflict of Interests

None declared

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