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Prevention and treatment of steroid-induced osteoporosis – recommendations vs clinical practice

Profilaktyka i leczenie osteoporozy posteroidowej – zalecenia vs praktyka kliniczna

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Keywords

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Słowa kluczowe

osteoporoza posteroidowa, reumatoidalne zapalenie stawów, cukrzyca posteroidowa, przewlekła steroidoterapia

S u m m a r y

Introduction. Patients with inflammatory connective tissue diseases chronically treated with glucocorticoids are susceptible to many adverse events of this kind of treatment. One of the most serious ones is osteoporosis. Up to 50% of patients with glucocorticoid-induced osteoporosis can suffer from fractures what in consequence can lead to disability.

Aim. The aim of the study was to evaluate if patients chronically treated with glucocorticoids receive an adequate prevention and treatment of glucocorticoid-induced osteoporosis according to current polish recommendations. The second aim was to investigate the vitamin D deficiency status in the studied population.

Material and methods. 80 patients diagnosed with connective tissue diseases treated with glucocorticoids for more than 3 months were enrolled into the study. All participants underwent biochemical (vitamin D serum concentrations) and clinical evaluation (densitometry, medical history of fractures). Statistical analysis was performed with STATA13 software.

Results. 60% of all patients and 50% of patients treated with bisphosphonates had vitamin D serum levels below recommended values (< 30 ng/ml). 46 patients (57.5%) had 88 indications for treatment. Only 16 (34.8%) participants who required treatment received pharmaceutical therapy.

Conclusions. The results of the study clearly show that patients chronically treated with glucocorticoids require more strict controls in terms of osteoporosis prevention (especially vitamin D supplementation) and treatment in order to prevent fractures and disability.

S t r e s z c z e n i e

Wstęp. Pacjenci z rozpoznaniem układowej choroby tkanki łącznej przewlekle leczeni glikokortykosteroidami są narażeni na liczne działania niepożądane tego rodzaju terapii. Jednym z najpoważniejszych jest osteoporoza. Nawet u 50% pacjentów z osteoporozą indukowaną steroidami dochodzi do złamań, co w konsekwencji może prowadzić do niepełnosprawności.

Cel pracy. Celem badania było sprawdzenie, czy pacjenci przewlekle przyjmujący glikokortykosteroidy otrzymują profilaktykę i leczenie osteoporozy posteroidowej zgodnie z aktualnymi polskimi wytycznymi. Drugim celem projektu była ocena stopnia niedoboru witaminy D w badanej populacji.

Materiał i metody. Do badania włączono 80 pacjentów z układową chorobą tkanki łącznej, którzy byli leczeni glikokortykosteroidami przez więcej niż 3 miesiące. U wszystkich uczestników badania oznaczono stężenie witaminy D oraz dokonano oceny klinicznej (m.in. historia złamań, densytometria). Analizę statystyczną wykonano przy użyciu programu STATA13.

Wyniki. Stężenia 25(OH)D < 30 ng/ml stwierdzono u 60% wszystkich badanych i u połowy pacjentów leczonych bisfosfonianami. U 46 pacjentów (57,5%) stwierdzono

Conflict of interest
Konflikt interesów

None
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88 wskazań do farmakoterapii osteoporozy. Odpowiednie leczenie wdrożono jedynie u 16 osób (34,8%) wymagających takiej terapii.

Wnioski. Wyniki badania pokazują, że pacjenci przewlekle leczeni glikokortykosteroidami wymagają ściślejszej kontroli w zakresie prewencji (szczególnie uzupełniania niedoboru witaminy D) oraz leczenia osteoporozy posteroidowej w celu uniknięcia złamań i ewentualnej niepełnosprawności z tego powodu.

INTRODUCTION

Systemic glucocorticoids (GCS) have unquestionable place in treatment of autoimmune and inflammatory disorders. Unfortunately despite their positive effects, GCS can cause serious adverse events such as osteopenia and glucocorticoid-induced osteoporosis (GIO) (1). The use of GCS is the most common cause of iatrogenic and secondary osteoporosis, as well as the early-onset osteoporosis (before 50 years of age) (2). The mechanisms of GCS impact on bone loss are as follows (3, 4):

- increase of calcium excretion and decrease in gastrointestinal calcium resorption which lead to increase of PTH concentration,
- decrease of production of osteoblast precursors, osteoblast proliferation and activity (plus premature apoptosis),
- loss of function and increased apoptosis of osteocytes (5),
- prolonged osteoclast lifespan (4),
- suppressive effect on TGF-β, insulin-like growth factor-1 (IGF-1) and growth hormone (GH),
- increased bone resorption (in some cases) caused by hypogonadism and secondary hyperparathyroidism,
- reduction in collagen type 1 synthesis,
- decrease of muscle mass (which cause also increased risk of falls).

Additionally, the underlying rheumatic inflammatory disease can contribute in bone remodeling leading to decrease in formation and increase in resorption (2). In rheumatoid arthritis there is a two-fold increase in risk of hip and vertebral fractures, even regardless of the GCS use (6). The increased risk of bone loss is observed immediately after GCS admission and is the highest in first 3-6 months of treatment (7), afterwards the decline of bone mineral density is slower. There is also an increased risk of fractures, especially vertebral fractures (or ribs) as the use of GCS affects more trabecular bone than cortical bone (i.e. femur) (8). Of note, due to low bone quality in patients treated with GCS, fractures occur more often than it results from a decrease in bone mineral density (BMD), more often within the same BMD as in postmenopausal osteoporosis and even in high BMD values (9). The negative effect of GCS is potentially reversible after cessation of therapy which also includes the decrease in fracture risk (10). High cumulative and daily dose of GCS increase risk of fracture (5). However, data suggest that there is no "safe dose" of GCS in terms of osteoporosis prevention (5). Thus, all patients treated chronically should be properly managed (8, 11-13). The main goal is to prevent fractures and if they occur – to reduce the risk of further fractures.

AIM

The aim of the study was to investigate if and to what extent patients chronically treated with GCS receive optimal prevention and treatment of osteoporosis according to current polish recommendations (11-13). The second objective was to evaluate the vitamin D deficiency status in patients with inflammatory connective tissue diseases treated chronically with GCS.

MATERIAL AND METHODS

Eighty patients, treated with glucocorticoids for at least three months, referred to the Department of Endocrinology of Centre of Postgraduate Medical Education in Warsaw underwent clinical evaluation including: medical history of the daily, cumulative dose and type of GCS, daily dose of calcium and vitamin D intake, history of fractures, family history of osteoporosis. All patients were evaluated for serum vitamin D and calcium levels. BMD was assessed by dual-energy X-ray absorptiometry (g/cm^2) at the femoral neck and lumbar spine (L1-L4) using the General Electric Healthcare Lunar Prodigy Advance densitometer.

The exclusion criteria were as follows: pregnancy, corticoid treatment for less than three months, diagnosed hypercortisolemia before corticoid treatment, cancer, liver or renal failure.

The study was approved by the Bioethics Committee and all patients gave their written consent to participate in the study.

Patients were divided into two groups: group 1 < 40 years of age and group 2 ≥ 40 years of age. The 10-year risk of major osteoporotic fracture was calculated for group 2 using the polish version of FRAX tool: https://www.sheffield.ac.uk/FRAX/tool.jsp.

Statistical analysis was performed with STATA13 software. The measured continuous parameters were described by the minimum and maximum value, mean and standard deviation (SD). Compatibility with a normal distribution was checked with test of Shapiro-Wilk and equality of variance with Bartlett's test. Next, the obtained mean of the two groups was compared using Student's t test for two variables. In the absence of normal distribution of one of the variables, the nonparametric U-Mann-Whitney-Wilcoxon test was used. When inequality of variances of normally distributed variables was found the Welch test was performed.

Definitions of vitamin D serum concentrations (14): sufficient level ≥ 30 ng/ml, insufficiency 20-30 ng/ml, deficiency < 20 ng/ml and overt hypovitaminosis < 10 ng/ml (15). Definitions of reduced bone mineral density based on densitometry (11):

- > -1 SD: normal value,
- ≤ -1 SD to > -2.5 SD: osteopenia,
- ≤ -2.5 SD: osteoporosis,
- ≤ -2.5 SD and fracture: advanced osteoporosis.

Indications for treatment in patients chronically treated with GCS according to current polish recommendations (11-13):

1. Any low-energy fracture (treatment should be started even without performing densitometry).
2. High risk of fracture (≥ 10%) assessed using FRAX calculator.
3. Moderate risk of fracture (5-10%) assessed using FRAX calculator.
4. BMD T-score (in femur neck) ≤ -1.5 SD (in patients older than 50 years) and Z-score ≤ -1.5 in younger patients (for relevant age and sex).
5. BMD T-score (in lumbar spine L1-L4) ≤ -2.5 SD – irrespective of age.
6. Patients (> 65 years of age) at the beginning of GCS therapy when they are scheduled to receive ≥ 7.5 mg of prednisone (or equivalent) for more than 3 months (obligatory preventive osteoporosis treatment) (12, 13).
7. Postmenopausal women with accelerated bone metabolism (elevated concentration of bone turnover markers, CTX, collagen type 1 crosslinked C-telopeptide or P1NP, procollagen 1 aminoterminal propeptide) which increase their fracture risk (i.e. assessed by FRAX tool) from low to moderate or from moderate to high.

In 2017 the new recommendation was given: in patients ≥ 50 years of age treated with > 5 mg of prednisone/day (or equivalent) for more than 3 months with additional risk factors of fracture, preventive bisphosphonate treatment should be considered (12, 13).

RESULTS

The study included 80 patients during chronic glucocorticoid therapy. Seventeen patients suffered from systemic lupus erythematosus (SLE), 35 were diagnosed with rheumatoid arthritis, 8 with polymyalgia rheumatica, 6 with polymyositis, 5 with mixed connective tissue disease, 3 with unclassified arthritis, 1 with Wegener granulomatosis and 3 with Sjogren's syndrome. The basic characteristic of patients were presented in table 1.

Tab. 1. Basic characteristic of patients

Characteristic of patients Total	Group 1 66	Group 2 14
Age (yr) mean ± SD	40-77 58.6 ± 9.6	20-38 30.2 ± 5.5
Women Men	54 12	10 4
Time of steroid treatment (in months) mean ± SD	5.9-363.7 98.2 ± 94.9	2.75-174.4 54 ± 52.2
Daily dose (in miligrams) (equivalent of prednisone) mean ± SD	1.25-37.5 6.9 ± 6.5	2.5-50 14.55 ± 14.8
Cumulative dose (in grams) (equivalent of prednisone) mean ± SD	0.345-135.05 25.32 ± 30.9	1.66-101.86 21.06 ± 24.94
BMI (kg/m^2) mean ± SD	14.7-46.34 26.4 ± 25.6	16.4-42.4 24.7 ± 6.8
25(OH)D level (ng/ml) mean ± SD	7.66-76.6 32.14 ± 12.5	7.6-33.92 21.78 ± 7.46
Vitamin D dose (IU) (N = 56) mean ± SD	200-6000 2047 ± 1096	400-2000 1430 ± 676.6

Results for group 1 (≥ 40 years of age, 66 patients)

55 patients (out of 66) were ≥ 50 years of age. Two patients had osteopenia (treated with zoledronate and ibandronate) and 1 had advanced osteoporosis with fracture treated with denosumab before GC treatment.

Bone mineral density assessment

T-score for femoral neck:
- ≤ -2.5 SD – 6 patients (9%),
- ≤ -1.5 SD and > -2.5 SD – 24 patients (36.5%),
- > -1.5 SD and < 0 SD – 30 patients (45.5%),
- ≥ 0 SD – 6 patients (9%).

T-score for lumbar spine (L2-L4):
- ≤ -2.5 SD – 6 patients (9%),
- ≤ -1.5 SD and > -2.5 SD – 18 patients (27.4%),
- > -1.5 SD and < 0 SD – 23 patients (34.8%),
- ≥ 0 SD – 19 patients (28.8%).

Vitamin D

9 participant have not received vitamin D supplementation. Their serum 25(OH)D level was 16.8-34.8 ng/ml. Vitamin D serum concentrations of patients who received vitamin D supplementation (200-6000 IU/day, mean 2047 ± 1096 SD) was 7.66-76.6 ng/ml. The detailed results are presented in table 2.

In general 33 (50%) patients had vitamin D levels < 30 ng/ml, for 5 patients data were lacking. Detailed results are presented in table 3.

Tab. 2. Mean 25(OH)D levels in patients with and without vitamin D supplementation

Age (yrs)	Vitamin D supplementation N(%)	25(OH)D ng/ml Mean ± SD	Vitamin D supplementation N(%)	25(OH)D ng/ml Mean ± SD	P
< 40	10 (71,5)	21 ± 7	4 (28,5)	24,2 ± 9,8	0,53
≥ 40	57 (86,4)	33 ± 12,9	9 (13,6)	25,7 ± 7	0,13
All patients	67 (83,75)	31,2 ± 12,9	13 (16,25)	25,3 ± 7,3	0,15

Tab. 3. 25(OH)D deficiency status in the studied population

25(OH)D ng/ml	Group 1 (>40 yr) 61 patients N (%)	Group 2 (<40 yr) 14 patients N (%)	All patients N (%)
< 10	1 (1,6)	1 (7,1)	2 (2,7)
< 20	5 (8,2)	2 (14,3)	7 (9,3)
20-30	27 (44,3)	9 (64,3)	36 (48)
≥ 30	28 (45,9)	2 (14,3)	30 (40)

5 patients suffered from low-trauma fractures during GC treatment. 3 of them had vitamin D insufficiency and 2 had optimal 25(OH) D serum concentrations.

Calcium intake

23 patients did not take any calcium supplementation. 6 patients received 500 mg/day, 36 patients 1000 mg/day and 1 patient 4000 mg/day.

Risk of fracture (FRAX tool)

The 10-year fracture risk was estimated using FRAX calculator for polish population:

- low risk (FRAX < 5%) – 28 patients (42.4%),
- moderate risk (FRAX 5-10%) – 27 patients (40.9%),
- high risk (FRAX ≥ 10%) – 11 patients (16.7%).

Treatment

18 patients received treatment – 15 were treated with bisphosphonates and 3 with denosumab (only 1 female participant treated with bisphosphonates was < 50 years of age):

- 14 of them had indications for treatment as described in "Material and methods" section (including patient number 1 presented below),
- 3 patients with FRAX < 5% (number 2, 3 and 4 described below) received bisphosphonates by the treating physician decision,
- interestingly, 1 participant (the patient number 5 described below) had normal BMD in femoral neck and lumbar spine and low fracture risk (< 5% in FRAX calculator).

Five participants (17.8%) with FRAX < 5% were treated with bisphosphonates:

1. Patient number 1: 68-year-old female treated with 20 mg of prednisone/day diagnosed with osteopenia before GC treatment (7th indication for treatment presented in "Material and methods" section).
2. Patient number 2: a female ≥ 50 years of age diagnosed with osteopenia before GC treatment (BMD T-score in L1-L4 -2.4 and 0.7 in femur neck).
3. Patient number 3: a 57-year-old male with BMD T-score in L1-L4 -1.0 and -0.9 in femur neck.
4. Patient number 4: a female ≥ 50 years of age with BMD T-score in L1-L4 -1.7 and -1.3 in femur neck.
5. Patient number 5: a premenopausal woman with BMD T-score in L1-L4 -1.0 and -0.6 in femur neck. Indications for treatment in this case remains unclear.

34.8% of patients (23 participants out of 66) did not have indications for pharmaceutical treatment (as described in "Material and methods" section). The indications for treatment were found in 43 participants (65.2%). As mentioned above, only 14 of them (32.6%) received an adequate therapy.

The indications for treatment were found in:

1. 5 patients (100%) with low-energy fracture during GC treatment (4 patient were treated with bisphosphonates and 1 with denosumab).
2. 8 patients (72.7%) with FRAX > 10% (6 patients were treated with bisphosphonates and 2 with denosumab).
3. 5 patients (18.5%) with FRAX 5-10% (4 were treated with bisphosphonates and 1 with denosumab).
4. 9 patients (37.5%) with T-score in femoral neck ≤ -1.5 to > -2.5 SD. All of them were ≥ 50 years of age.
5. 4 patients (66.6%) with T-score ≤ -2.5 SD in femoral neck.
6. 4 patients (66.6%) with T-score ≤ -2.5 SD in lumbar spine (L2-L4).
7. 3 patients (80%) ≥ 65 years of age with dose of GCs ≥ 7.5 of prednisone (or equivalent). In none of them was the bisphosphonates initiated as the obligatory osteoporosis preventive treatment.

Summary

There were 84 indications for treatment in 43 patients. In 14 patients (32,6%) who received treatment 38 indications were found. There were 46 indications for treatment in 29 patients (67,4%) in whom pharmacotherapy have not been initiated. It means that in some cases one patient had multiple indications for treatment but nevertheless none of these participants were managed according to current recommendations. In 3 patients – out of 23 in whom indications for treatment were not found – the treating physician initiated therapy for other additional reasons (described above, patient 2, 3 and 4). For 1 treated patient, indications for therapy remains unclear (patient number 5).

Results for group 2 (< 40 years of age, 14 patients)

None of the participants was diagnosed with osteoporosis or osteopenia before GC treatment.

Vitamin D

4 participant (28.5%) have not received vitamin D supplementation. Their serum 25(OH)D level was 14.3-33.92 ng/ml. 8 participants received between 400-2000 IU of vitamin D/day (mean 1430 ± 676.6). Their vitamin D serum concentration was 7.6-32.7 ng/ml. The detailed results are presented in table 2. In group 2 – 12 (85.7%) patients had their vitamin D levels < 30 ng/ml. More detailed results (for both groups as well) are presented in table 3 and figure 1. One male patient had multiple low-trauma fractures of

lumbar spine during GC treatment. His 25(OH)D serum concentration was 21.6 ng/ml, despite this insufficiency, he was treated with bisphosphonates.

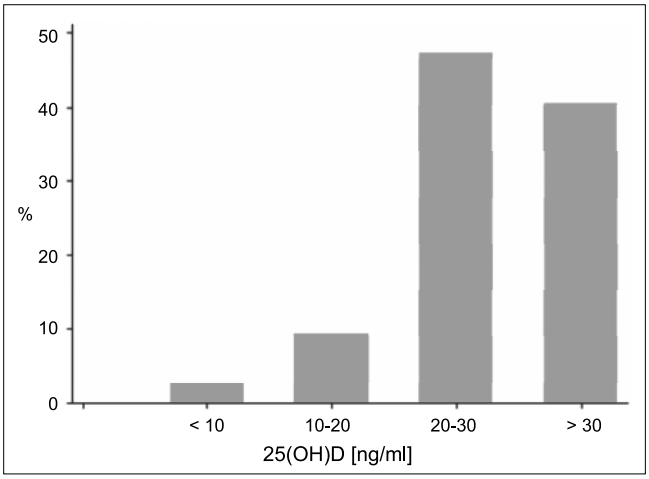

Fig. 1. Vitamin D status in all participants (N = 80)

Calcium intake

2 patients (14.3%) did not take calcium supplementation. 1 patient received 500 mg/day, 10 patients 1000 mg/day and 1 patient 1500 mg/day.

Bone mineral density assessment

Z-score for femoral neck:
- ≤ -2.5 SD – 0 patients,
- ≤ -1.5 SD and > -2.5 SD – 2 patients (14.3%),
- > -1.5 SD and < 0 SD – 7 patients (50%),
- ≥ 0 SD – 5 patients (35.7%).

Z-score for lumbar spine (L2-L4):
- ≤ -2.5 SD – 1 patient,
- ≤ -1.5 SD and > -2.5 SD – 1 patient (7.1%),
- > -1.5 SD and < 0 SD – 7 patients (50%),
- ≥ 0 SD – 6 patients (42.9%).

Risk of fracture (FRAX tool)

Risk of fracture (FRAX tool) was not measured as it is only designed for patients ≥ 40 years of age.

Treatment

Two patients (14.3%) were treated with bisphosphonates. One 23-year-old male after low-energy fracture of the thoracic spine (Z-score of the femur neck and lumbar spine -0.8 and -0.1 SD, respectively) and one 20-year-old female (BMI 16.5 kg/m^2) with BMD Z-score of the femoral neck and lumbar spine -1.9 and 2.7 SD, respectively. Their 25(OH)D serum concentrations were 33.92 and 21.6 ng/ml, respectively.

One 38-year-old female with BMD Z-score of the femoral neck and lumbar spine -1.7 and -1.7 SD, respectively have not received any specific treatment (apart from 1000 mg calcium and 2000 IU/day of vitamin D). Her 25(OH)D serum level was 20.4 ng/ml.

In general 4 indications for treatment were found in 3 patients (2 of them received pharmaceutical therapy).

Results for both groups

When analyzing both groups together (N = 80):
- 66 participants received vitamin D supplementation between 200-6000 IU/day (mean 2000 IU ± 1063),
- the serum 25(OH)D levels were between 7.6-76.6 ng/ml (mean 28.8 ± 12.4 SD),
- 60% of patients had 25(OH)D levels < 30 ng/ml,
- 9 patients (50%) treated with bisphosphonates had 25(OH)D serum concentrations < 30 ng/ml,
- 88 indications for treatment were found in 46 patients (57.5%). Only 16 (34.8%) participants received pharmaceutical therapy.

DISCUSSION

Polish recommendation are based on the polish version of FRAX tool and specificity of polish population therefore we compared them to clinical practice (11-13).

The results of our study show that 31.25% of participants have not received any additional calcium supplementation. The recommended calcium intake is 1000-1200 mg/day (8, 12, 13, 16) while its daily intake in Poland rarely exceeds 700 mg (17). Taking into consideration that diet in Poland is rather poor in calcium, it is a good practice to recommend at least 500 mg/day of additional calcium intake to every patient.

The American College of Rheumatology recommends the vitamin D supply (600-800 IU/day) and the serum 25(OH)D level ≥ 2 ng/ml even when initializing treatment with bisphosphonates (8). According to polish recommendations the adequate dose of vitamin D supplementation is 800-2000 IU/day (11-14) and the serum 25(OH)D level should exceed 30 ng/ml (11, 14, 16). Patients with vitamin D deficiency (< 20 ng/ml) should be treated with therapeutic doses of 25(OH)D – 7000-10 000 IU/day or 50 000 IU/week optimally for 1-3 months till the optimal concentration is reached (≥ 30 ng/ml) (12-14, 16). Starting treatment with bisphosphonates is contraindicated in vitamin D deficiency (16) as they may cause or potentiate hypocalcemia (i.e. myasthenia, tetany attacks) through their effect of blocking calcium release from bones (17). In the present study 13 patients (16.25%) have not received any vitamin D supplementation. 60% of all participants and 50% of patients treated with bisphosphonates had serum 25(OH)D concentrations < 30 ng/ml (but ≥ 20 ng/ml). 9.3% of all patients had vitamin D serum level < 20 ng/ml but none of them have received the therapeutic doses of 25(OH)D.

Glucocorticoid-induced osteoporosis may lead to fractures in almost 30-50% of patients (18) and in consequence to disability. In the present study all patients after low-energy fracture and 72.7% of patients with FRAX > 10% have received treatment. Among patients with FRAX 5-10% the percentage of treated patients was very low (only 18.5%). In general 65.2% (30 out of 46) of patients with indications for treatment have

not received pharmaceutical therapy. What is even more surprising some of these patients had multiple indications for treatment nevertheless none of them was properly managed. This may be due to the fact that criteria for treatment of postmenopausal osteoporosis are used rather than criteria specifically designed for patients on chronic glucocorticoid therapy. According to polish data only 10% of patients with osteoporosis are treated (19). Taking that into consideration comforting is the fact that percentage of patients who required treatment in our study reached higher values – 34.8%.

CONCLUSIONS

In conclusion, less than half of patients treated with glucocorticoids for connective tissue diseases have vitamin D serum levels in recommended ranges (> 30 ng/ml). Only one third of patients on prolonged corticotherapy with obvious indications for antifracture treatment received an adequate pharmacotherapy. These results indicate the necessity for better surveillance of patients in terms of 25(OH)D serum concentrations (especially during bisphosphonates treatment), prevention and osteoporosis treatment.

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