ORIGINAL ARTICLE

Effect of methylprednisolone pulse therapy with and without alendronate on biochemical markers of bone turnover in patients with Graves' ophthalmopathy

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KEY WORDS

bone turnover, Graves' ophthalmopathy, methylprednisolone

ABSTRACT

INTRODUCTION Immunosuppression with glucocorticoids is the method of choice in the treatment of active Graves' ophthalmopathy (GO). However, glucocorticoid therapy may have side effects, among others, it affects bone metabolism.

OBJECTIVES The aim of the study was to compare the effect of methylprednisolone pulse therapy (MPPT) with and without alendronate on bone turnover markers in patients with GO with normal and reduced bone mineral density (BMD).

PATIENTS AND METHODS The study included 53 patients with GO and 20 sex- and age-matched healthy controls. Twenty patients with normal BMD (17 women, 3 men, aged 45 ±1.0 years) received only MPPT (8 g intravenously during 4 weeks). The remaining patients, with reduced BMD, were randomly assigned either to MPPT without alendronate (10 women, 2 men, aged 47 ±1.0 years) or MPPT with alendronate (18 women, 3 men, aged 47 ±1.0 years). BMD of the lumbar spine and femoral neck was assessed using dual energy X-ray absorptiometry (DEXA) before treatment. The markers of bone formation (serum osteocalcin, carboxyterminal propeptide of type I collagen [PICP], alkaline phospatase) and the markers of bone resorption (serum carboxyterminal telopeptide of type I collagen [ICTP], cross-linked C-terminal telopeptide of type I collagen [CTX], serum calcium [Ca] and potassium [P], as well as urinary excretion of deoxypyridinoline, Ca, and P) were determined before and after treatment.

RESULTS MPPT caused a decrease in bone formation markers and an increase in some bone resorption markers. MPPT with alendronate decreased bone formation and bone resorption markers.

CONCLUSIONS A negative effect of MPPT on bone turnover is observed both in patients with GO with normal and with reduced BMD. Simultaneous use of MPPT and alendronate in patients with GO and reduced BMD suppresses bone resorption caused by methylprednisolone.

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INTRODUCTION Graves' ophthalmopathy (GO) is considered an autoimmune disorder.[1,2] Such concept is supported by histopathological changes associated with the disease. Increased volume of the orbital content is caused by edema, production of hydrophilic glycosaminoglycans, hypertrophy, and marked infiltration of immunocompetent cells. This process is intensified by locally synthesized cytokines and growth factors.[3,4] About 5% of the patients develop severe, vision-threatening ophthalmopathy. Immunosuppression with the use of glucocorticoids or orbital radiotherapy, or the combination of both,[5,6] is considered to be the treatment of choice during the active phase of severe GO. However, glucocorticoid therapy may cause multiple side effects, for example, it may negatively affect bone metabolism. This effect depends mostly on the total dose of glucocorticoids.[7] Recent studies have indicated that high-dose intravenous methylprednisolone

pulse therapy (MPPT) seems to be more effective than treatment with prednisone alone.[8,9] Hyperthyroidism, either associated with or preceding the development of GO, might adversely affect bone tissue.[10] Optimal ophthalmopathy treatment should not induce further bone resorption.

The aim of the current study was, first, to investigate the effect of high-dose MPPT on bone metabolism in patients with active and moderately severe GO; second, to determine whether the effect of MPPT on bone turnover is different in patients with normal and reduced bone mineral density (BMD); and, third, to determine whether the combination of MPPT and alendronate treatment could prevent the possible unfavorable effect of MPPT on bone metabolism in patients with reduced BMD.

PATIENTS AND METHODS Fifty-three euthyroid patients with active and moderately severe GO and 20 sex- and age-matched healthy controls were included in the study. Patients with GO were selected from among consecutive patients admitted between January 2006 and September 2010 to the Department of Internal Diseases, Meidcal University of Silesia, Katowice, Poland.

The diagnosis of ophthalmopathy was based on ophthalmological investigation and quantitative magnetic resonance imaging of the orbits and retro-orbital space. Activity of GO was defined with the clinical activity score of 4 or higher, based on the classification system proposed by Mourits et al.[11] Severity of GO was assessed using the NOSPECS classification by calculating the total eye score.[12] All patients were clinically euthyroid, with normal free triiodothyronine (FT_3) and free thyroxine (FT_4) levels during the study and within 4 months prior to the study. Subjects with hyperthyroidism were maintained euthyroid with thionamide therapy. All female subjects were premenopausal. The exclusion criteria were as follows: contraindications to glucocorticoid therapy, previous treatment with glucocorticoids, or any other current therapy known to affect bone or calcium metabolism. The study was approved by the Local Bioethics Committee and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all subjects.

BMD of the lumbar spine and femoral neck was assessed using dual energy X-ray absorptiometry (DEXA) before treatment. BMD values were expressed as g per cm^3. The obtained results were compared with those of sex-matched young controls at peak bone mass and expressed as T-scores. According to the definition of the World Health Organization,[13] osteopenia was diagnosed in patients with the T-score between <–1 to –2. 5 standard deviation (SD), osteoporosis in those with the T-score <–2. 5, and normal bone density in those with the T-score not exceeding 1 SD below the mean BMD value for young adults. Twenty consecutive patients with normal BMD (17 women, 3 men, aged 45 ±1 year, group A) were treated with high-dose intravenous MPPT (1 g per day for 2 successive days, repeated 4 times within 4 weeks). The remaining patients, with reduced BMD, were randomly assigned to either MPPT without alendronate (10 women, 2 men, aged 47 ±1.0 year, group B) or MPPT with concomitant alendronate 10 mg given orally every day within 4 weeks (18 women, 3 men, aged 47 ±1.0 year, group C). The characteristics of the patients are presented in TABLE 1.

In patients with GO, the biochemical markers of bone metabolism, serum calcium (Ca) and potassium (P) levels, and urinary Ca excretion were assessed twice: in groups A and B before and after MPPT; in group C before and after MPPT with concomitant alendronate therapy. In healthy controls, the tests were performed only once. In all subjects, thyroid-stimulating hormone (TSH), FT_3, and FT_4 levels were assessed once (in patients with GO before treatment).

The following markers of bone formation were determined: serum osteocalcin, carboxyterminal propeptide of type I collagen (PICP), total alkaline phosphatase (tAP), bone alkaline phosphatase (bAP). Moreover, the following markers of bone resorption were assessed: carboxyterminal telopeptide of type I collagen (ICTP) and urinary deoxypiridinoline (DPD) excretion. Another marker of bone resorption, serum cross-linked C-terminal telopeptide of type I collagen (CTX), was additionally measured in group C and in controls.

TSH was assessed by immunoradiometric assay (IRMA; Orion Diagnostica, Czech Republic); FT_4 and FT_3 by a radioimmunoassay (RIA; Immunotech, Czech Republic); serum TSH-receptor antibodies (TRAbs) by a radio receptor assay (B.R.A.H.M.S. Diagnostica, Germany); osteocalcin by RIA (B.R.A.H.M.S. Diagnostica); PICP and ICTP by RIA (Orion Diagnostica, Finland); bAP by IRMA (OSTASE Beckman Coulter kit, United States); urinary DPD excretion by an enzyme linked inmunosorbent assay (ELISA; Pyrilinks-D, Metra Biosystems, Inc., United States) and the final results were expressed as nmol DPD/ mmol creatinine [Cr]); CTX was determined by ELISA (Serum Cross laps TM kit Osteomer Biotech A/S, Denmark).

The normal ranges were as follows: FT_4, 11.5–23.0 pmol/l; FT_3, 2.5–5.8 pmol/l; serum TRAbs, <9.0 U/l; osteocalcin, 0.67–2.01 nmol/l; PICP: women, 50–170 µg/l; men, 38-202 µg/l; ICTP: women, 1.6–5.0 µg/l; men, 1.3–5.2 µg/l; bAP: women, 8.7 ±2.9 µg/l; men, 12.3 ±4.3 µg/l; urinary DPD excretion: women, 2.5–6.5 nmol/mmol Cr; men, 2.5–5.5 nmol/nmol/mmol Cr; CTX: women, 2304 ±110 pmol/l; men, 2382 ±1364 pmol/l.

Serum Ca, P, and tAP levels and urinary Ca excretion (mmol/10 mmol Cr/24 h) were assessed by standard methods in the Central Hospital Laboratory.

Statistical analysis All results were expressed as means ± standard error of the mean. The mean values were compared using the *t* test (for parameters

TABLE 1 Characteristics of patients with Graves' ophthalmopathy and controls

		Group A	Group B	Group C	Control group
n		20	12	21	20
sex, women/men		17/3	10/2	18/3	17/3
age, y		45.00 ±1.43	47.17 ±1.19	47.23 ±1.34	46.50 ±1.28
duration of hyperthyroidism	month	5.00 ±0.20	5.92 ±0.29	5.90 ±0.15[d]	0
	range	2–6	4–8	4–7	
duration of ophthalmopathy	month	4.8 ±0.22	5.37 ±0.28	5.33 ±0.23	0
	range	2–6	4–7	3–6	
smokers, yes/no		6/14	10/2[b]	18/3[c]	2/18
CAS		5.35 ±0.27	5.33 ±0.29[b]	5.72 ±0.34	0
TES		14.5 ±1.90	13.83 ±1.94	14.38 ±1.92	
TRAbs, U/l		47.70 ±9.86[a]	53.77 ±13.50[a]	51.26 ±10.20[a]	3.59 ±0.55
TSH, mIU/l		2.00 ±0.36	1.90 ±0.39	1.67 ±0.14	1.48 ±0.15
FT_3, pmol/l		3.78 ±0.13	3.80 ±0.27	3.54 ±0.16	3.39 ±0.07
FT_4, pmol/l		17.45 ±0.57	16.68 ±1.04	17.38 ±0.66	15.87 ±0.55
BMD L_2–L_4, g/cm ^{3}		1.17 ±0.01	0.96 ±0.03[a]	0.97 ±0.01[a]	1.18 ±0.02
BMD femoral neck, g/cm^3		1.00 ±0.02	0.83 ±0.02[a]	0.79 ±0.02[a]	1.00 ±0.01

Values are presented as means ± standard error of the mean.

Group A: patients with normal T-score (–1 to +1 SD) treated with methylprednisolone pulse therapy; group B: patients with T-score <–1 SDs treated with methylprednisolone pulse therapy; group C: patients with T-score < –1 SDs treated with methylprednisolone and alendronate.

a P <0.001 vs. controls; **b** P <0.05; **c** P <0.01; **d** P <0.001: groups B and C vs. group A

Abbreviations: BMD – bone mineral density, CAS – clinical activity score, FT_3 – free triiodothyronine, FT_4 – free thyroxine, TES – total eye score, SD – standard deviation, TRAbs – serum TSH-receptor antibodies, TSH – thyroid-stimulating hormone

with normal distribution) or the Mann-Whitney test (for parameters with distribution deviations). Differences in the number of smokers between groups B and C and group A were analyzed using the χ^2 test. The P value less than 0.05 was considered statistically significant.

RESULTS **Serum thyroid-stimulating hormone, free triiodothyronine, and free thyroxine levels** Patients with GO did not show any statistically significant differences in serum TSH, FT_3, and FT_4 levels compared with healthy subjects (TABLE 1).

Markers of bone formation Patients with GO had significantly higher serum osteocalcin, PICP, and bAP levels than controls (TABLE 2).

Markers of bone resorption Serum ICTP levels were significantly higher in groups A and B compared with control subjects. In group C, serum CTX concentration and urinary DPD excretion was significantly higher than in controls. Serum Ca and P levels as well as urinary Ca excretion did not differ significantly between GO patients and the control group (TABLE 3).

Effect of methylprednisolone pulse therapy on bone formation and resprption markers MPPT significantly reduced serum osteocalcin, PICP, and ICTP levels and increased urinary Ca excretion. In group B, MPTT significantly increased urinary DPD excretion compared with controls (TABLES 2 and 3).

Effect of simultaneous methylprednisolone pulse therapy and alendronate treatment on bone formation and resorption markers MPPT and concomitant alendronate therapy decreased the levels of bone formation markers (serum osteocalcin, PICP, bAP) and bone resorption markers (serum ICTP and CTX, DPD urinary excretion) (TABLES 2 and 3).

DISCUSSION The aim of the study was to estimate the effect of short-term intravenous MPPT with or without alendronate therapy on bone turnover markers in patients with an active and moderately severe form of GO and with normal or reduced BMD. In patients with GO, the BMD of the lumbar spine and femoral neck was measured by DEXA before therapy. This examination was not repeated after 4 weeks of MPPT because the precise estimation of BMD loss by DEXA is not possible in such a short period of time.[14]

In patients with GO, the levels of bone formation and resorption markers were higher than in control subjects. Increased levels of bone resorption and formation markers are considered to be an evidence of enhanced bone turnover. All study patients were euthyroid during the study and at least 4 months prior to MPPT. However, all patients had been treated for hyperthyroidism in the past. There were no differences between the groups in terms of sex and TSH, FT_4, and FT_3

TABLE 2 Serum markers of bone formation in patients with Graves' ophthalmopathy before and after methylprednisolone treatment (groups A and B) or methylprednisolone with alendronate treatment (group C) and in controls

		Group A	Group B	Group C	Control group
osteocalcin, nmol/l	before	1.65 ±0.22[a]	2.31 ±0.43[a]	1.73 ±0.21[a]	1.16 ±0.09
	after	0.89 ±0.15[a++]	1.11 ±0.29[+++]	0.79 ±0.15[++]	
PICP, ng/ml	before	175.03 ±20.62[a]	193.39 ±30.15[a]	145.94 ±15.06[a]	120.36 ±7.75
	after	74.69 ±6.02[b+++]	85.65 ±11.37[a+++]	72.47 ±15.13[++]	
tAP, nmol/l/s	before	1071.05 ±90.80	1118.92 ±119.60	1184.47 ±92.33	999.25 ±52.63
	after	997.45 ±74.45	1118.92 ±119.60	1016.76 ±77.70	
bAP, µg/l	before	15.52 ±1.70[b]	12.12 ±4.04[a]	15.56 ±2.35[a]	10.26 ±0.76
	after	14.12 ±1.54[a]	18.47 ±3.85	11.89 ±1.47[+]	

Values are presented as means ± standard error of the mean.

a P <0.05 vs. control; **+** P <0.05 before vs. after treatment
b P <0.001 vs. control; **++** P <0.01 before vs. after treatment; **+++** P <0.001 before vs. after treatment

Abbreviations: PICP – carboxyterminal propeptide of type I collagen, bAP – bone alkaline phosphatase, tAP – total alkaline phosphatase

TABLE 3 Markers of bone resorption, serum calcium and potassium levels, and urinary calcium excretion in patients with Graves' ophthalmopathy before and after methylprednisolone treatment (group A and B) or methylprednisolone with alendronate treatment (group C) and in controls

		Group A	Group B	Group C	Control group
serum ICTP, ng/ml	before	5.16 ±0.38[b]	6.66 ±1.08[a]	3.40 ±0.26	3.97 ±0.18
	after	3.27 ±0.27[a+++]	4.50 ±0.87[++]	3.40 ±0.26	
serum CTX, pmol/l	before	–	–	6515.90 ±919.01[a]	4272.00 ±347.59
	after	–	–	2561.61±463.77[++]	
urinary DPD excretion, nmol/mmol Cr	before	4.74 ±0.4	6.95 ±0.72	7.90 ±1.16[b]	5.36 ±0.32
	after	5.42 ±0.56	8.40 ±0.89[c]	3.81 ±0.64[+++]	
serum Ca, mmol/l	before	2.29 ±0.01	2.28 ±0.02	2.25 ±0.01	2.29 ±0.05
	after	2.31 ±0.01	2.27 ±0.07	2.17 ±0.02	
serum P, mmol/l	before	1.44 ±0.03	1.24 ±0.06	1.31 ±0.04	1.42 ±0.03
	after	1.39 ±0.03	1.20 ±0.04	1.19 ±0.04	
urine Ca, mmol/10 mmol Cr/24 h	before	2.97 ±0.13	3.56 ±0.44	2.97 ±0.31	3.19 ±0.18
	after	4.33 ±0.37[a+++]	3.56 ±0.44	2.91 ±0.31	

Values are presented as means ± standard error of the mean.

a P <0.05 vs. control; **+** P <0.05 before vs. after treatment
b P <0.01 vs. control; **++** P <0.01 before vs. after treatment
c P <0.001 vs. control; **+++** P <0.001 before vs. after treatment

Abbreviations: Ca – calcium, Cr – creatinine, CTX – cross-linked C-terminal telopeptide of type I collagen, DPD – deoxypyridinoline, ICTP – carboxyterminal telopeptide of type I collagen, P – potassium

levels. Outdoor activities and nutrition were similar in all patient groups, but in groups with decreased BMD (B and C), longer periods of hyperthyroidism and a greater number of smokers were found compared with group A with normal BMD. Decreased BMD in groups B and C could most likely be attributed to prolonged thyrotoxicosis and perhaps to smoking. It is known that thyroid hormones accelerate bone formation and resorption, with more influence on bone resprption.[15] Bone turnover can be enhanced even in subclinical hyperthyroidism.[16] In overt hyperthyroidism, a correlation between clinical symptoms, thyroid hormone levels, and bone turnover markers has been observed.[17] Moreover, increased bone turnover may persist for at least 2 to 8 months following the treatment of hyperthyroidism.[18] Thus, increased bone turnover in our study group might have been expected despite clinical and biochemical euthyreosis lasting at least 4 months.

In the present study, the assessment of bone turnover markers was repeated after MPPT (the cumulative dose was 8 g during 4 weeks). MPPT caused a decrease in some markers of bone formation (osteocalcin and PICP) in all patients. MPPT also increased some markers of bone resorption (urinary DPD excretion in group B and urinary Ca excretion in groups A and B). Osteocalcin and bAP levels are considered to reflect different aspects of osteoblastic function. The measurement of PICP provides direct information on the rate of synthesis of type I collagen. ICTP and DPD are considered to be the markers of different bone resorption phases. Urinary DPD excretion is thought to be a much more sensitive and reliable measure of bone resorption than

plasma ICTP concentrations. Serum ICTP may also be derived from newly synthesized collagen.[19] In our study, MPPT decreased the serum levels of ICTP both in patients with normal and reduced BMD. Impaired synthesis of type I collagen during MPPT might have caused a decrease in serum ICTP levels.

The decrease in some markers of bone formation and the increase in some markers of bone resorption observed in our study after MPPT confirm the already recognized harmful effect of glucocorticoids on bone metabolism. This effect depends mainly on their cumulative dose.[7] A dose of prednisone above 7. 5 mg daily given for at least 3 months (or equivalent doses of other steroids) was associated with an increased risk of bone loss.[20] The cumulative dose of methylprednisolone used in our study exceeded a corresponding prednisone dose of 7.5 mg daily. Although MPPT was administered only for 4 weeks, it caused significant disturbances in bone metabolism. Thus, our findings seem to be in line with other literature data on the limited safety of glucocorticoid use.[21]

Inhibition of bone formation is considered to be the most significant effect of glucocorticoids on the bone. Recent studies have shown that glucocorticoids act directly on osteoblasts via the upregulation of the OPG/RANKL/RANK system. Glucocorticoids decrease osteoblast differentiation, increase osteoblast and osteocyte apoptosis, and inhibit osteoprotegerin expression.[22] Moreover, bone loss observed in the first phase of glucocorticoid therapy is caused by extension of the lifespan of preexisting osteoclasts.[23] Biochemical markers of bone turnover reflect the rate of bone formation and bone resorption in the whole body. Our findings confirm the results of other authors.[24,25]

Simultaneous use of methylprednisolone and alendronate in patients with reduced BMD normalized urinary DPD excretion. Moreover, in patients treated with methylprednisolone and alendronate, urinary Ca excretion was not significantly increased, in contrast to patients treated only with methylprednisolone. In addition, methylprednisolone and alendronate therapy decreased bone resorption documented by a decrease in serum CTX levels. CTX is currently considered to be the most sensitive marker of bone resorption.[26] Our results indicate that alendronate is able to inhibit methylprednisolone-induced bone resorption in patients with GO and with reduced BMD. Alendronate inhibits osteoclast-mediated bone resorption, leading to osteoclast inactivity and apoptosis and bone turnover suppression.[27] The other mechanism of bisphosphonate action could be the stimulation of osteoblasts to produce osteoprotegerin,[28] which prevents osteoclastic bone resorption.[29] Since glucocorticoids inhibit osteoprotegerin production by osteoblasts,[30] it seems that alendronate could inhibit the unfavorable effect of glucocorticoids on the bone. Our results suggest that alendronate use during short-term MPPT could prevent an increase of bone resorption in patients with low initial bone mass and other risk factors for osteoporosis.

Finally, there is the question whether this short-term high-dose MPPT administration reduces BMD. BMD measurement after such a short treatment may be not insensitive enough to show significant differences.[14] Newer technologies, such as high resolution peripheral quantitative computed tomography or micromagnetic resonance imaging, could be more helpful in identifying individual fracture risk in patients on glucocorticoids.[31] Additionally, a direct relationship between BMD and fracture risk in glucocorticoid-induced osteoporosis has not been established[32] because fractures occur at higher BMD.[33] Repeated assessment of BMD after 6 months or 1 year was not possible in our study group because some of the patients were treated using different regimens, including short-term high-dose MPPT, chronic prednisone treatment, or a combination of prednisone treatment and radiotherapy.

In conclusion, a harmful effect of short-term MPPT on bone turnover (expressed as a decrease of bone formation and an increase of bone resorption) was observed in patients with GO and with normal or reduced BMD. Combined methylprednisolone and alendronate treatment in patients with decreased BMD may inhibit bone resorption caused by methylprednisolone.

REFERENCES

1 Smith TJ. Pathogenesis of Graves' orbitopathy: a 2010 update. J Endocrinol Invest. 2010; 33: 414-421.

2 Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010; 362: 726-738.

3 Ajjan RA, Weetman AP. New understanding of the role of cytokines in the pathogenesis of Graves' ophthalmopathy. J Endocrinol Invest. 2004; 27: 237-245.

4 Smith TJ. Novel aspects of orbital fibroblast pathology. J Endocrinol Invest. 2004; 27: 246-253.

5 Koshiyama H, Koh T, Fujiwara K, et al. Therapy of Graves' ophthalmopathy with intravenous high-dose steroid followed by orbital irradiation. Thyroid. 1994; 4: 409-413.

6 Marcocci C, Marinò M, Rocchi R, et al. Novel aspect of immunosupressive and radiotherapy management of Graves' opththalmopathy. J Endocrinol Invest. 2004; 27: 272-280.

7 Pearce G, Tabansky DA, Delmas PD, et al. Corticosteroid-induced bone loss in men. J Clin Endocrinol Metab. 1998; 83: 801-806.

8 Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid. 2008; 18: 333-346.

9 Zang S, Ponto KA, Kahaly GJ. Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab. 2011; 96: 320-332.

10 Allain TJ, McGregor A. Thyroid hormones and bone. J Endocrinol. 1993; 139: 9-18.

11 Mourtis M, Prummel WM, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol. 1997; 47: 9-14.

12 Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of American Thyroid Association. J Clin Endocrinol Metab. 1977; 44: 203-204.

13 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994; 843: 1-129.

14 Hassager C, Jensen SB, Gotfredsen A, Christiansen C. The impact of measurement errors on the diagnostic value of bone mass measurements: theoretical considerations. Osteoporos Int. 1991; 1: 250-256.

15 Mosekilde L, Eriksen EF, Charles P. Effects of thyroid hormones on bone and mineral metabolism. Endocrinol Metab Clin North Am. 1990; 19: 35-63.

16 Kisakol G, Kaya A, Gonen S, Tunc R. Bone and calcium metabolism in subclinical autoimmune hyperthyroidism and hypothyroidism. Endocr J. 2003; 50: 657-661.

17 Garnero P, Vassry U, Bertholin A, et. al. Markers of bone turnover in hyperthythyroidism and the effects of treatment. J Clin Endocrinol Metab. 1994; 78: 955-959.

18 Sabuncu T, Akson N, Arikan E, et al. Early changes in parameters of bone and mineral metabolism during therapy for hyper- and hypothyroidism. Endocr Res. 2001; 27: 203-213.

19 Seibel MJ. Molecular markers of bone turnover: biochemical, technical and analytical aspects. Osteoporos Int. 2000; 11: Suppl 6: S18-S29.

20 Rüegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol. 1983; 25: 615-620.

21 Heffernan MP, Saag KG, Robinson JK, Callen JP. Prevention of osteoporosis associated with chronic glucocorticoid therapy. JAMA. 2006; 295: 1300-1303.

22 Hofbauer LC, Gori F, Riggs BL, et al. Stimulation of osteoprotegerin ligand and inhibition ofosteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology. 1999; 140: 4382-4389.

23 Weinstein RS, Chen JR, Powers CC, et al. Promotion of osteoclast survival and antagonism of bisphosphonate-induced osteoclast apoptosis by glucocorticoids. J Clin Invest. 2002; 109: 1041-1048.

24 Dovio A, Perazzolo L, Osella G, et al. Immediate fall of bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. J Clin Endocrinol Metab. 2004; 89: 4923-4928.

25 Frediani B, Falsetti B, Bisogno S, et al. Effects of high dose methylprednisolone pulse therapy on bone mass and biochemical markers of bone metabolism in patients with active rheumatoid arthritis: a 12-month randomized prospective controlled study. J Rheumatol. 2004; 31: 1083-1087.

26 Christgau S, Bitsch-Jensen O, Hanover Bjarnason N, et al. Serum CrossLaps for monitoring the response in individuals undergoing antiresorptive therapy. Bone. 2000; 26: 501-511.

27 Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008; 83: 1032-1045.

28 Dobnig H, Hofbauer LC, Viereck U, et al. Changes in the RANK ligand/osteoprotegerin system are correlated to changes in bone mineral density in bisphosphonate-treated osteoporotic patients. Osteoporos Int. 2006; 17: 693-703.

29 Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998; 93: 165-176.

30 Vidal NO, Brändström H, Jonsson KB, Ohlsson C. Osteoprotegerin mRNA is expressed in primary human osteoblast-like cells: down-regulation by glucocorticoids. J Endocrinol. 1998; 159: 191-195.

31 Carballido-Gamio J, Majumdar S. Clinical utility of microarchitecture measurements of trabecular bone. Curr Osteoporos Rep. 2006; 4: 64-70.

32 Khan AA, Hanley DA, Bilezikian JP, et al.; Canadian Panel of the International Society for Clinical Densitometry. Standards for performing DXA in individuals with secondary causes of osteoporosis. J Clin Densitom. 2006; 9: 47-57.

33 Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum. 2003; 48: 3224-3229.

Wpływ pulsacyjnego leczenia metyloprednizolonem z alendronianem i bez alendronianu na biochemiczne wskaźniki obrotu tkanki kostnej u chorych z oftalmopatią w przebiegu choroby Gravesa

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metyloprednizolon, obrót kostny, oftalmopatia Gravesa

STRESZCZENIE

WPROWADZENIE Metodą z wyboru leczenia aktywnej oftalmopatii towarzyszącej chorobie Gravesa (*Graves' ophthalmopathy* – GO) jest immunosupresja za pomocą kortykosterydoterapii. Metoda ta może jednak wywołać skutki uboczne, między innymi wpływa na metabolizm tkanki kostnej.

CELE Celem pracy było porównanie wpływu leczenia pulsacyjnego metyloprednizolonem (*methylprednisolone pulse therapy* – MPPT) łącznie i bez alendronianu na zachowanie się wskaźników obrotu kostnego u chorych z GO z normalną i obniżoną gęstością mineralną kości (*bone mineral density* – BMD).

PACJENCI I METODY W badaniu wzięło udział 53 chorych z GO oraz 20 osób zdrowych dobranych pod względem płci i wieku. Dwudziestu chorych z prawidłową masa kostną (17 kobiet i 3 mężczyzn w wieku 45 ±1,0 lat) otrzymywało wyłącznie MPPT (dożylnie 8 g w ciągu 4 tygodni). Pozostali chorzy z obniżoną BMD otrzymywali MPPT bez alendronianu (10 kobiet i 2 mężczyzn w wieku 47 ±1,0 lat) lub MP łącznie z alendronianem (18 kobiet i 3 mężczyzn w wieku 47 ±1,0 lat). BMD kręgosłupa i kości udowej oceniano przed leczeniem przy użyciu przy użyciu densytometrii kostnej (*dual energy X-ray absorptiometry* – DEXA). Przed i po MPPT oznaczano wskaźniki tworzenia tkanki kostnej (stężenie w surowicy osteokalcyny, C-końcowego propeptydu prokolagenu typu I [PICP], fosfatazy zasadowej) oraz wskaźniki resorpcji kostnej (stężenie w surowicy C-końcowego telopeptydu kolagenu typu I [ICTP], C-końcowego usieciowanego telopeptydu kolagenu typu 1 [CTX], wapnia [Ca] i potasu [P] oraz wydalanie z moczem deoksypirydynoliny, Ca i P).

WYNIKI MPPT spowodowało obniżenie wskaźników tworzenia tkanki kostnej oraz wzrost niektórych wskaźników resorpcji tkanki kostnej. MPPT z dodatkiem alendronianu obniżyło zarówno wskaźniki tworzenia, jak i resorpcji tkanki kostnej.

WNIOSKI Niekorzystny wpływ leczenia MP na tkankę kostną występuje u chorych z GO zarówno z prawidłową, jak i z obniżoną BMD. Równoczesne stosowanie MPPT i alendronianu u chorych z GO i z obniżoną BMD hamuje resorpcję kostną wywołaną podaniem metyloprednizolonu.

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