

BISPHOSPHONATES – A GOOD CHOICE FOR WOMEN WITH TYPE 2 DIABETES AND POSTMENOPAUSAL OSTEOPOROSIS?

RALUCA NAN¹, DANIEL GRIGORIE^{2,3*}, ADRIAN CURSARU⁴, ALINA ȘUCALIUC^{2,3},
RAMONA DRĂGUȚ¹, EMILIA RUSU¹, MĂDĂLINA MUȘAT^{2,3}, GABRIELA RADULIAN^{1,5}

¹Department of Diabetes 2, "Prof. Dr. N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, 5-7 Ion Movilă Street, Bucharest, Romania

²"C. I. Parhon" National Institute of Endocrinology, 34-36 Aviatorilor Boulevard, Bucharest, Romania

³Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, 34-36 Aviatorilor Boulevard, Bucharest, Romania

⁴Department of Orthopaedics and Traumatology, "Carol Davila" University of Medicine and Pharmacy, 169 Splaiul Independenței, Bucharest, Romania

⁵Department of Hygiene and Diabetes, "Carol Davila" University of Medicine and Pharmacy, 17-23 Calea Plevnei, Bucharest, Romania

*corresponding author: grigorie_d@yahoo.com

Manuscript received: November 2015

Abstract

The aim of the study was to assess the levels of biochemical markers of bone turnover (BTMs) and the effects of bisphosphonates therapy (BT) on BTMs and bone mineral density (BMD) in women with type 2 diabetes (T2D) and recently diagnosed postmenopausal osteoporosis. Two groups of women have been evaluated at baseline and one year later: a group of 35 women diagnosed with T2D and newly postmenopausal osteoporosis (diabetic group) and a group of 35 women only with postmenopausal osteoporosis (control group). Consistent with other studies, we found that bone turnover was reduced in T2D patients, as both serum osteocalcin and C-terminal crosslink of collagen (CTX) were significantly lower than controls. After a year of BT, both osteocalcin and CTX did not change in the diabetic group and decreased in the control group. Significant increases in BMD, especially at the lumbar spine, were noted in both groups. In diabetic women, bone turnover is low and does not change after one year of BT, but there is a significant benefit at lumbar spine BMD.

Rezumat

Scopul acestui studiu a fost de a evalua markerii *turnover*-ului osos (MTO) și efectele terapiei cu bifosfonați (TB) asupra MTO și densității minerale osoase (DMO) la femeile cu diabet zaharat tip 2 (DZ2) și osteoporoză postmenopauză recent diagnosticată. Au fost evaluate două grupuri de femei, la includerea în studiu și un an mai târziu: un grup cu DZ2 și osteoporoză postmenopauză recent diagnosticată (grupul diabetic) și un grup doar cu osteoporoză postmenopauză (grupul control). În concordanță cu alte studii, s-a observat că *turnover*-ul osos a fost redus la paciențele cu DZ2, atât osteocalcina, cât și colagenul *crosslink*-at (CTX) fiind semnificativ mai mici decât în grupul control. După un an de TB, atât osteocalcina cât și CTX nu s-au modificat în grupul diabetic, dar au scăzut în grupul control. O creștere semnificativă a DMO, în special la nivel lombar, a fost observată în ambele grupuri. Femeile diabetice prezintă un *turnover* osos scăzut care nu se modifică după un an de TB, dar apare o îmbunătățire semnificativă a DMO lombară.

Keywords: bisphosphonates, type 2 diabetes, bone mineral density (BMD), markers of bone turnover (BTMs)

Introduction

Diabetes and osteoporosis are two very common diseases with a great socio-economic impact. The westernization of lifestyle accelerates growth of diabetes and osteoporosis [2]. The prevalence of diabetes is 9.28% in Romania [14] and the prevalence of osteoporosis in women and men over the age of 50 years in Romania is 20.5% and 6.2% respectively [9]. The relationship between diabetes and bone tissue has been investigated for a long time. Type 2 diabetes (T2D) is characterized by hyperinsulinemia in the early stages of the disease. The hyperinsulinemia might contribute to the increased

bone mass and hyperglycaemia might accelerate bone resorption [11, 20]. Patients with T2D have higher bone mineral density (BMD) at the femoral neck and lumbar spine and a 69% higher risk of non-vertebral fractures than those without diabetes [5, 16]. Therefore routine assessment of BMD by Dual energy X-ray absorptiometry (DXA) may lack sensitivity in diagnosis of osteoporosis in diabetic patients. Abundant evidence exists that subsets of fracture risk factors are either exacerbated in T2D (poor balance, reduced muscle quality, and falls) or are T2D-specific (poor glycaemic control, T2D duration, antidiabetic drugs and complications) [7].

Bisphosphonates (BP) therapy reduces bone loss by decreasing osteoclastic bone resorption and represents the first-line of osteoporosis treatment in Romania. The efficacy of osteoporosis treatment is usually assessed by DXA measurement, which is limited and controversial in patients with diabetes.

The recent evidence suggesting that fracture risk is higher for a given femoral neck BMD T-score and age or for a given FRAX probability in patients with T2D compared to non-diabetic control has led to the suggestion that fragility fractures in T2D may result from underlying skeletal abnormalities of bone quality. FRAX is a computed algorithm, also available for Romania [9], which includes in the calculation of the absolute risk of fracture factors independent of BMD. The use of bone turnover markers (BTM) may offer clinical potential to predict fracture risk and to monitor therapeutic response independent of BMD [24].

In diabetic patients bone turnover is low and BP administration is associated with low turnover also; therefore the question of the benefit of BP treatment in diabetic women with osteoporosis is appropriate. The aim of this study was to assess the levels of biochemical markers of bone turnover and the effects of bisphosphonates therapy on markers of bone turnover and BMD in women with T2D and recently diagnosed postmenopausal osteoporosis and one year after initiation osteoporosis therapy with bisphosphonates.

Materials and Methods

Study design

We performed a retrospective study using the patients' database of the "C. I. Parhon" National Institute of Endocrinology, Bucharest, Romania, over a 3-year period, from January 2012 to January 2015. We included in the study 70 women with newly diagnosed postmenopausal osteoporosis, divided in two groups: 35 women with postmenopausal osteoporosis and type 2 diabetes (diabetic group) and 35 non-diabetic women with postmenopausal osteoporosis (control group, age and hip T-score matched) who were assessed at baseline and one year, after beginning the osteoporosis treatment. The study has been approved by the "C. I. Parhon" National Institute of Endocrinology, Ethical Committee.

Inclusion criteria were newly diagnosed women with postmenopausal osteoporosis, aged between 50 and 80 years. Women were matched in terms of age and hip T-score.

Exclusion criteria were early onset hypogonadism, growth hormone deficiency, thyroid gland disease, primary hyperparathyroidism, cirrhosis, reduced glomerular filtration rate (GFR < 60 mL/min/1.73 m²), corticosteroid therapy, neoplasms, total or partial

hysterectomy, systemic lupus erythematosus, rheumatoid arthritis, malabsorption or any bone-active medication, menopause hormone replacement therapy at the time of bone assessment.

The treatment for osteoporosis were bisphosphonates (mostly alendronate), vitamin D and calcium and the treatment for diabetes was represented by diet or oral agents such as metformin (up to 2500 mg/day), sulfonylurea (gliclazide up to 120 mg/day, glimepiride up to 6 mg/day) or dipeptidyl peptidase-4 inhibitors (100 mg/day). Thiazolidinediones have been excluded although they decrease the glucose plasma level by increasing insulin sensitivity in the liver, adipose tissue and skeletal muscle [8]. They are associated with an increased risk of fractures in women [29]. Optimal treatment regimens must address both improvements of bone mass and glycaemic control. As this ideal treatment is presently unknown, BP are the most used therapy. Other experimental treatments are those with anabolic mechanisms, like parathyroid hormone (PTH). Recently, it has been shown that PTH therapy could only partially reversed the adverse skeletal effects of T2D on the skeleton, indicating that the presence of diabetes blunted the bone-anabolic effects of PTH [12].

Body mass index (BMI - a person's weight in kilograms divided by the square of height in meters) was calculated according to World Health Organisation [27].

Biochemical parameters

Bone turnover markers (osteocalcin and C-terminal crosslink of collagen (CTX)), 25-hydroxyvitamin D (25(OH)D) and PTH were measured by electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas e 601 analyser (Roche, Hitachi Corporation Japan). The assessment of fasting blood glucose (FPG), alkaline phosphatase (ALP), total calcium (photometric method) and glycosylated haemoglobin (HbA1c) (immunoturbidimetric method) concentrations was performed using a Roche Cobas C501 analyser (Roche, Hitachi Corporation Japan). The blood tests kits were provided by Roche and all parameters were assessed at baseline and after one year.

Evaluation of BMD

All studied women underwent measurement of BMD at lumbar spine and femoral neck using GE-iDXA machine (General Electric Company – Lunar iDXA, United States) at baseline and one year later; the DXA instrument is calibrated to measure within a precision error of 1% for spine and 1.5% for hip. Postmenopausal osteoporosis was assessed based on T-score from BMD measurements as defined by the World Health Organization (WHO): T-score < -2.5 [26].

Statistical analysis

The Statistical Package (SPSS) version 17 was used for collection, analysis and interpretation of the results. Variables in control and study groups are

shown as elements of descriptive statistics (mean $\pm$ standard deviation). Comparisons between groups were performed using ANOVA for quantitative variables and independence chi square test for categorical variables. Correlation analysis was performed using Spearman's correlation coefficient. Two-tailed, $p < 0.05$ was considered statistically significant.

Results and Discussion

Serum levels of osteocalcin and CTX in women with T2D were significantly lower than in women without diabetes confirming that bone turnover is low in diabetic patients (Table I). A recent meta-analysis that evaluated bone turnover markers in patients with diabetes also reported decreased osteocalcin and cross-laps compared to controls [24]. According to these results, we observed that bone formation and bone resorption are altered in T2D. ALP, another marker of bone formation which reflects different stages of osteoblastic differentiation was also lower in the diabetic group at baseline (Table I). The reason for low bone turnover and especially reduced bone formation in T2D is not fully understood. Studies in rodents have shown that metabolic dysfunction in T2D seems to be related to an accelerated onset of aging. Although hyperglycaemia acts on skeletal homeostasis by suppressing osteoblast differentiation and enhancing osteoblast apoptosis. Current data show that T2D is

associated with low bone turnover probably due to the disproportionate reduction in bone formation relative to bone resorption [7].

As expected, after one year of BP treatment both markers of formation (osteocalcin ($p < 0.001$), ALP) and resorption (CTX ($p < 0.047$)), were significantly reduced in the non-diabetic, control group. In contrast, osteocalcin and CTX changes in the diabetic group were non-significant after BP treatment and also non-significant compared with control group values (Table I). These results are consistent with those reported by Malecha-Jędraszek *et al.* [20]. After one year of bis-phosphonate treatment, osteocalcin did not change in the diabetic group but a decreased level of osteocalcin was found in the control group, suggesting an imbalance between bone synthesis and bone resorption in this patients. In another study that evaluated non-diabetic women with post-menopausal osteoporosis, the level of osteocalcin was also lower after one year of antiresorptive therapy [22]. CTX was decreased in both studied groups, proving good therapy compliance. In contrast with our observations, the study conducted by Ikeda *et al.* [13] which investigated the effect of alendronate on BMD in postmenopausal osteoporotic diabetic women showed that alendronate treatment significantly decreased urinary N-terminal telopeptides of type I collagen (NTX), which is a resorption marker similar to CTX.

Table I

Bone mineral density, markers of bone turnover and 25(OH)D in the study groups at baseline and at one year later

Parameters	Diabetic group (n = 35)	Non-diabetic group (n = 35)	p-value	Diabetic group (n = 35)	Non-diabetic group (n = 35)	p-value
	At baseline			At one year		
Osteocalcin (ng/mL)	18.8 $\pm$ 10.1	30.9 $\pm$ 15.6	0.001*	19.5 $\pm$ 20.4	20.65 $\pm$ 11.5	0.778†
Crosslaps (ng/mL)	0.3 $\pm$ 0.2	0.55 $\pm$ 0.3	0.001*	0.25 $\pm$ 0.1	0.3 $\pm$ 0.2	0.181†
ALP (U/L)	73.9 $\pm$ 20.6	90.5 $\pm$ 59.8	0.125†	69.4 $\pm$ 15.5	72.6 $\pm$ 30.2	0.578†
25(OH)D (ng/mL)	17.1 $\pm$ 9.6	18.2 $\pm$ 7.7	0.585†	23.9 $\pm$ 9.4	24.4 $\pm$ 7.9	0.837†
PTH (pg/mL)	50.5 $\pm$ 15.9	44.1 $\pm$ 13.6	0.077†	46.1 $\pm$ 14.9	47.5 $\pm$ 16.6	0.714†
BMD hip (T-score)	-2.3 $\pm$ 0.75	-2.35 $\pm$ 0.7	0.859†	-2.1 $\pm$ 0.9	-2.3 $\pm$ 0.7	0.377†
BMD lumbar (T-score)	-2.9 $\pm$ 0.4	-3.35 $\pm$ 0.8	0.014*	-2.5 $\pm$ 0.45	-3.0 $\pm$ 0.8	0.003*

*statistically significant ($p < 0.05$), †not statistically significant

ALP - alkaline phosphatase, 25(OH)D - 25-hydroxyvitamin D, PTH - parathyroid hormone, BMD - bone mineral density

It is classically thought that overweight women are protected from osteoporosis, but there is an increasing evidence in conflict with this observation, suggesting that obesity interferes with bone health [21, 28]. All women included in our study were overweight, but women with T2D had a significantly higher BMI than women without diabetes throughout the study (Table II). Obviously, FPG levels were higher in the diabetic group than the control group (Table II). Levels of HbA1c suggest a poor glycaemic control. There was no

improvement in glycaemic values at one year after starting osteoporosis treatment.

An important outcome of our study is the significant increase of the T-score, considering the spine BMD ($p < 0.001$) after one year of BP treatment in the diabetic group. This was somewhat unexpected as BP treatment didn't produce an extra suppression over baseline resorption, as assessed by serum CTX. A study that followed the effect of alendronate treatment for three years in postmenopausal osteoporotic Japanese with or

without type 2 diabetes concluded that the alkaline phosphatase (ALP) and urinary NTX were decreased and BMD at lumbar spine level was

increased in postmenopausal Japanese women with osteoporosis [15]. The same results were obtained by Kushida *et al.* and Uchida *et al.* [18, 25].

Table II

Anthropometric and biochemical parameters of the study groups at baseline and one year later

Variables	Diabetic group (n = 35)	Non-diabetic group (n = 35)	p-value	Diabetic group (n = 35)	Non-diabetic group (n = 35)	p-value
	At baseline			At one year		
Age (years)	64.2 ± 8.1	63.6 ± 9.1	0.761 [†]	65.2 ± 8.1	64.6 ± 9.1	0.761 [†]
BMI (kg/m ²)	29.85 ± 4.1	25.0 ± 3.9	0.001*	29.8 ± 3.8	25.2 ± 3.7	0.001*
Ca (mg/dL)	9.6 ± 0.45	9.5 ± 0.4	0.674 [†]	9.7 ± 0.5	9.6 ± 0.4	0.241 [†]
FPG (mg/dL)	135.9 ± 52.7	88.05 ± 8.9	0.001*	132.1 ± 36.4	88.9 ± 15.5	0.001*
HbA1c (%)	7.1 ± 0.85	-	-	7.0 ± 0.8	-	-

*statistically significant (p < 0.05), [†]not statistically significant

BMI - body mass index, Ca - calcium, FPG - fasting plasma glucose, HbA1c - glycosylated haemoglobin

The effect of hyperglycaemia on the BMD is controversial. Some studies, shown that people with T2D, have reduced [1], unchanged [3] or increased [6, 16] bone mass in comparison to healthy control subjects. In our study BMD at the lumbar spine (T-score) was significantly higher in the diabetic group than the control group and this difference was maintained throughout the study period (Table I). BMD at the hip (T-score) did not differ between the two groups at baseline and one year later (Table I). A meta-analysis conducted by Ma *et al.* analysed the association between BMD and T2D and found that BMD was significantly higher in the diabetic population [19]. In our study, after a year of BP treatment, there was no increase in the hip BMD, but there was an increase in lumbar BMD in both groups (Table I). The study conducted by Sachmechi *et al.* [23] mainly on African American, South Asian and Hispanic women has shown a significant increase in BMD at the spine and hip in alendronate treated late postmenopausal osteoporotic women with T2D. Another study conducted mainly on Caucasian women demonstrated that alendronate increases BMD at both sites in older women with low BMD and T2D [17]. On the contrary, a study conducted by Dagdelen *et al.* on 26 postmenopausal, osteoporotic women with T2D shown that they were unresponsive to bisphosphonates therapy compared with 26 non-diabetic women [4].

In the diabetic group, baseline serum 25(OH)D levels were lower than in control group, however not reaching statistical significance (Table I). This is somewhat surprising as our diabetic patients had significantly higher BMIs than the control group. Considering D vitamin serum concentration, both groups were insufficient at baseline, with mean levels below 20 ng/mL. This confirms the high prevalence of vitamin D insufficiency described in Romania for women with postmenopausal osteoporosis [10]. After one year of vitamin D supplementation both groups become sufficient, reaching similar concentrations (Table I). A study conducted by Farr

et al. [6] also showed that 25(OH)D serum levels did not differ between diabetic and non-diabetic women. Though this is a small retrospective study this is a valuable one, as, there is a limited number of studies assessing the effects of bisphosphonates on bone turnover markers and BMD (T-score) in women with recently diagnosed postmenopausal osteoporosis and T2D.

Conclusions

The present study showed that bone turnover is low in T2D women and that bisphosphonates therapy for 1 year significantly increases lumbar spine BMD, even if there is no extra suppression of resorption, as assessed by serum CTX. These results suggest that bisphosphonates have a clinical significance in the treatment of women with T2D and osteoporosis and represent a good choice for these patients.

Acknowledgements

"This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013".

References

1. Adil C., Aydin T., Taşpinar Ö., Kiziltan H., Eriş A.H., Hocaoglu I.T., Poşul S., Kepekci M., Denizli E., Guler M., Bone mineral density evaluation of patients with type 2 diabetes mellitus. *J. Phys. Ther. Sci.*, 2015; 27: 179-182.
2. Brown S.A., Sharpless J.L., Osteoporosis: an under-appreciated complication of diabetes. *Clinical Diabetes*, 2004; 22: 10-20.
3. Caglayan E.K., Engin-Ustun Y., Sari N., Karacavus S., Seckin L., Kara M., Evaluation of bone density measurement in type 2 diabetic postmenopausal women with hypertension and hyperlipidemia. *J. Menopausal Med.*, 2015; 21(1): 36-40.

4. Dagdelen S., Sener D., Bayraktar M., Influence of type 2 diabetes mellitus on bone mineral density response to bisphosphonates in late postmenopausal osteoporosis. *Adv. Ther.*, 2007; 24(6): 1314-1320.
5. de Liefde I.I., van der Klift M., de Laet C.E., van Daele P.L., Hofman A., Pols H.A., Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos. Int.*, 2005; 16(12): 1713-1720.
6. Farr J.N., Drake M.T., Amin S., Melton L.J.^{3rd}, McCready L.K., Khosla S., *In vivo* assessment of bone quality in postmenopausal women with type 2 diabetes. *J. Bone Miner. Res.*, 2014; 29(4): 787-795.
7. Farr J.N., Khosla S., Determinants of bone strength and quality in diabetes mellitus in humans. *Bone*, 2016; 82: 28-34.
8. Gales C., Zamfir C., Stoica B., Nechifor M., Zinc and pioglitazone effects on ovaries and endometrium in diabetes. *Farmacia*, 2015; 63(1): 52-56.
9. Grigorie D., Șucaliuc A., Johansson H., Kanis J.A., McCloskey E., FRAX-based intervention and assessment thresholds for osteoporosis in Romania. *Arch. Osteoporos.*, 2013; 8: 164.
10. Grigorie D., Șucaliuc A., Ivan M., Neacșu E., Popa O., Diaconescu A., High prevalence of vitamin D deficiency in 1048 Romanian women with postmenopausal osteoporosis. *Acta Endo. (Buc.)*, 2008; 4(1): 33-45.
11. Hamann C., Kirschner S., Günther K.P., Hofbauer L.C., Bone, sweet bone - osteoporotic fractures in diabetes mellitus. *Nat. Rev. Endocrinol.*, 2012; 8(5): 297-305.
12. Hamann C., Picke A.K., Campbell G.M., Balyura M., Rauner M., Bernhardt R., Huber G., Morlock M.M., Günther K.P., Bornstein S.R., Glüer C.C., Ludwig B., Hofbauer L.C., Effects of parathyroid hormone on bone mass, bone strength, and bone regeneration in male rats with type 2 diabetes mellitus. *Endocrinology*, 2014; 155(4): 1197-1206.
13. Ikeda T., Iwata K., Long-term effect of alendronate on bone mineral density in postmenopausal type 2 diabetes mellitus. *J. of Diabetes & Metabolism*, 2011; S1: 002.
14. International Diabetes Federation. IDF Diabetes Atlas, 6th Edition, 2014 UPDATE.
15. Iwamoto J., Sato Y., Uzawa M., Takeda T., Matsumoto H., Three-year experience with alendronate treatment in postmenopausal osteoporotic Japanese women with or without type 2 diabetes. *Diabetes Research and Clinical Practice*, 2011; 93(2): 166-173.
16. Jackuliak P., Payer J., Osteoporosis, fractures, and diabetes. *Int. J. Endocrinol.*, 2014; 2014: 820615.
17. Keegan T.H., Schwartz A.V., Bauer D.C., Sellmeyer D.E., Kelsey J.L., Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the fracture intervention trial. *Diabetes Care*, 2004; 27(7): 1547-1553.
18. Kushida K., Shiraki M., Nakamura T., Kishimoto H., Morii H., Yamamoto K., Kaneda K., Fukunaga M., Inoue T., Nakashima M., Orimo H., Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. *J. Bone Miner Metab.*, 2004; 22(5): 462-468.
19. Ma L., Oei L., Jiang L., Estrada K., Chen H., Wang Z., Yu Q., Zillikens M.C., Gao X., Rivadeneira F., Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur. J. Epidemiol.*, 2012; 27(5): 319-332.
20. Malecha-Jędraszek A., Burska A., Donica H., Matuszek B., Korpysz M., Wojtysiak-Duma B., Nowakowski A., Selected markers of bone turnover in type 2 diabetic patients. *Current Issues in Pharmacy and Medical Sciences*, 2012; 25(4): 367-372.
21. Migliaccio S., Greco E.A., Fornari R., Donini L.M., Lenzi A., Is obesity in women protective against osteoporosis? *Diabetes Metab. Syndr. Obes.*, 2011; 4: 273-282.
22. Wael Rasheed N., Barbu C.G., Florea S., Branceanu G., Fica S., Mitrea N., Dragoi C.M., Nicolae A.C., Arsene A.L., Biochemical markers of calcium and bone metabolism in the monitoring of osteoporosis treatment. *Farmacia*, 2014; 62(4): 728-736.
23. Sachmechi I., Ahmed S., Joseph J., Reich D., Cardinal L., Kim P., Effect of alendronate on bone mineral density in post menopausal women with type 2 diabetes mellitus. *Int. J. of Endocrin. and Metabolic Disorders*, 2015; 1(1): 1-6.
24. Starup-Linde J., Vestergaard P., Biochemical bone turnover markers in diabetes mellitus - A systematic review. *Bone*, 2016; 82: 69-78.
25. Uchida S., Taniguchi T., Shimizu T., Kakikawa T., Okuyama K., Okaniwa M., Arizono H., Nagata K., Santora A.C., Shiraki M., Fukunaga M., Tomomitsu T., Ohashi Y., Nakamura T., Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. *J. Bone Miner. Metab.*, 2005; 23(5): 382-388.
26. World Health Organisation. Assessment of fracture risk and its implication to screening for postmenopausal osteoporosis. Technical report series 843. Geneva: WHO, 1994.
27. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: WHO, 2000.
28. Zhao L.J., Jiang H., Papasian C.J., Maulik D., Drees B., Hamilton J., Deng H.W., Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis. *J. Bone Miner. Res.*, 2008; 23: 17-29.
29. Zhu Z.N., Jiang Y.F., Ding T., Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. *Bone*, 2014; 68: 115-123.