

THE EFFECTS OF THIAZOLIDINEDIONES ON BONE MINERAL DENSITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Rucsandra Dănciulescu Miulescu¹, Suzana Danoiu², Cătălina Poiană¹, Madalina Musat¹,
Denisa Margină¹, Liviu Serb³

¹ UMF Carol Davila București

² UMF Craiova

³ Hospital of Mulhouse France

Abstract

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. Certain medications have been associated with an increased osteoporosis risk. Thiazolidinediones, have been linked with an increased risk of osteoporosis and fracture. The aim of the present study is to evaluate the effects of thiazolidinediones on bone mineral density in the patients with type 2 diabetes mellitus. 54 patients (36 women and 18 men) with type 2 diabetes mellitus were recruited for this study. The subjects were between 53 and 68 years. The bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA). 26 patients followed thiazolidinediones therapy and 28 patients followed sulfonylurea and metformin treatment. The mean (\pm SD) T-score on hip was 2.20 ± 0.36 in patients using thiazolidinediones therapy, and on lumbar spine was 2.22 ± 0.24 . In patients using sulfonylurea and metformin treatment the mean (\pm SD) T-score on hip was 2.18 ± 0.22 and on lumbar spine was 2.18 ± 0.28 . No changes have been observed in the average values of BMD on hip and lumbar spine in patients using thiazolidinediones therapy compared with patients using sulfonylurea and metformin treatment.

Key words: diabetes mellitus, thiazolidinediones, bone mineral density.

Introduction

Osteoporosis, or porous bone is a disease characterized by low bone mass and structural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk on the vertebral column, rib, hip and wrist. Osteoporosis is defined by the World Health Organization (WHO) in women as a bone mineral density (BMD) 2.5 standard deviations below peak bone mass (20-year-old healthy female

average) as measured by dual energy X-ray absorptiometry (DXA). The World Health Organization has established the following diagnostic guidelines [1,2]: T-score -1.0 or greater is "normal", T-score between -1.0 and -2.5 is "low bone mass" (or osteopenia), T-score -2.5 or below is osteoporosis.

Osteoporosis is most common in women after menopause but may also develop in men, and may occur in the presence of particular hormonal disorders and other chronic diseases or as a result of medications. The World

Health Organization classification should not be applied to children, men.

The mechanism of osteoporosis is an imbalance between bone resorption and bone formation. Bone is resorbed by osteoclast cells, after which is deposited by osteoblast cells. The three main mechanisms by which osteoporosis develops are an inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth), excessive bone resorption and inadequate formation of new bone during remodeling [3].

Risk factors for osteoporotic fracture can be split between non-modifiable and (potentially) modifiable. The most important risk factors for osteoporosis are advanced age and female sex; estrogen deficiency following menopause is correlated with a rapid reduction in bone mineral density. In men a decrease in testosterone levels has a comparable effect, but less pronounced. Certain medications have been associated with an increase in osteoporosis risk. Thiazolidinediones have been linked with an increased risk of osteoporosis and fracture. Thiazolidinediones act by binding peroxisome proliferator-activated receptor (PPAR), specifically gamma, a group of receptor molecules inside the cell nucleus. When activated, the receptor migrates to the DNA (deoxyribonucleic acid), activating transcription of a number of specific genes. By activating PPAR γ : insulin resistance is decreased, adipocyte differentiation is modified, leptin levels decrease, adiponectin levels rise. The thiazolidinediones appear to trigger preferential differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts, leading to decreased bone formation and increased adipogenesis. Although only a few small, randomized

studies have examined the effects of thiazolidinediones on bone in humans, the available data suggest that these agents contribute to bone loss in postmenopausal women; the relationship is less clear in men [4].

The aim of the present study is to evaluate the effects of thiazolidinediones on bone mineral density in the patients with type 2 diabetes mellitus.

Materials and Methods

54 patients (36 women and 18 men) with type 2 diabetes mellitus were recruited for this study. The subjects were between 53 and 68 years. The women did not use hormone replacement therapy. The lumbar and hip BMD were measured by dual-energy X-ray absorptiometry (DXA). Anthropometric and biochemical parameters were assessed. The anthropometric measurement included waist circumference (WC) and body mass index (BMI). BMI was computed as a ratio of weight to the square of height (kg/m²). Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Serum osteocalcin and urinary cross-linked N-terminal telopeptides of type I collagen (NTX) levels were measured. Human bone is continuously remodeled through a coupled process of bone resorption by osteoclasts followed by bone formation by osteoblasts. This process is necessary for normal development and bone growth as well as skeletal integrity. Osteocalcin is a noncollagenous protein found in bone and dentin. It is secreted by osteoblasts and thought to play a role in mineralization and calcium ion homeostasis. It has been stipulated that osteocalcin may also function

as a negative regulator of bone formation. Approximately 90% of the bone organic matrix is made of type 1 collagen. This helical protein is stabilized by cross-links at its N-terminal and C-terminal ends. The identification of urinary collagen type 1 cross-linked N-telopeptides (NTX) has provided a specific biochemical marker of bone resorption. The utilization of markers of bone formation and resorption is that these indexes represent an average of turnover from all skeletal sites in the body. It is important to note that while these markers are fairly new and have certain limitations, they are much more descriptive of the dynamic nature of bone than a DEXA scan, which provides a more static representation. Serum osteocalcin was measured with a two-site immunoradiometric assay. NTX was analyzed by a commercially available ELISA (enzyme-linked immunosorbent assay) kit. In addition, they completed several questionnaires regarding their current and past medical history (macro- and microvascular complications), lifestyle factors (smoking, physical activity, and socioeconomic status). 26 patients followed thiazolidinediones

therapy and 28 patients followed sulfonylurea and metformin treatment.

Results

According the World Health Organization diagnostic guidelines, 16 women have osteopenia and 6 women have osteoporosis (Table 1). The mean (\pm SD) T-score on hip was 2.20 ± 0.36 and on lumbar spine was 2.22 ± 0.24 in patients using thiazolidinediones therapy. In patients using sulfonylurea and metformin treatment the mean (\pm SD) T-score on hip was 2.18 ± 0.22 and on lumbar spine was 2.108 ± 0.28 . The serum osteocalcin (mean SD) was 28 ± 6 ng/dl and the urinary NTX (mean SD) was 35 ± 8 BCE/nM in patients using thiazolidinediones therapy. In patients using sulfonylurea and metformin treatment the serum osteocalcin (mean SD) was 29 ± 3 ng/dl and the urinary NTX (mean SD) was 34 ± 86 BCE/nM. 14 patients were overweight (BMI between 25 kg/m² and 30 kg/m²) and 8 patients were obese (BMI over 30 kg/m²). 10 patients have central obesity (waist circumference ≥ 80 cm for women and ≥ 94 cm for men), according to the International Diabetes Federation definition [5].

Table 1. Characteristics of patients

	Characteristics of subjects using thiazolidinediones	Characteristics of subjects using sulfonylurea and metformin	p
BMI (kg/m ²)	28.34 ± 8.14	26.11 ± 3.22	$p < 0.05$
Waist circumference (cm)	89.22 ± 11.12	82.64 ± 9.32	$p < 0.05$
T-score on hip	2.20 ± 0.36	2.18 ± 0.22	NS
T-score on lumbar spine	2.22 ± 0.24	2.18 ± 0.28	NS
Serum osteocalcin (ng/ml)	28 ± 6	29 ± 3	NS
Urinary NTX (BCE/nM)	35 ± 8	34 ± 6	NS

Comparison is significant at the 0.05 level: $p < 0.05$

Discussion

The metabolic and endocrine alterations of diabetes adversely affect bone quantity and/or quality and may increase fracture risk. A recent meta-analysis, involving 836 000 subjects and 139 000 incident cases of fracture, found that type 2 diabetes was associated with significantly increased risks of non-vertebral, hip and foot fracture. Insulin has an anabolic effect on bone. However, the existence of an elevated fracture risk in type 2 diabetes, despite the underlying hyperinsulinaemia, suggests the involvement of other potential pathogenic influences (hyperglycaemia, diabetic complications and lifestyle factors) on bone [6].

Clinical trial findings, supported by bone marker and bone density data, suggest that the oral antidiabetic agents metformin and glibenclamide significantly lower fracture risk, whereas the thiazolidinediones slightly increase fracture risk in patients, with type 2 diabetes [6]. Studies available suggest that treatment with thiazolidinediones, contributes to bone loss in postmenopausal women; the relationship is less clear in men [7, 8]. More studies are needed to better understand the effects of thiazolidinediones on bone and fracture rates.

Our results differ from those of several previous studies. There were no statistically significant differences in the recorded parameters in patients using thiazolidinediones therapy and patients using sulfonylurea and metformin treatment. The mean T-score on hip and on lumbar spine, the serum osteocalcin and the urinary collagen type 1 cross-linked N-telopeptides was similar in both groups, but waist circumference, BMI, were higher in patients using thiazolidinediones therapy compared with patients using sulfonylurea and metformin treatment.

In patients using thiazolidinediones therapy 9 patients (34.61%) were overweight (BMI: 25-29.9 kg/m²) and 5 patients (19.23%) were obese (BMI over 30 kg/m²). In control group 5 subjects were overweight (17.85%) and 3 subjects were obese (10.71%).

Conclusion

No changes have been observed in the average values of BMD on hip and lumbar spine in patients using thiazolidinediones therapy compared with patients using sulfonylurea and metformin treatment.

The study of limited numbers of patients, thus requiring further validation.

REFERENCES

1. WHO (1994). "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group". World Health Organization technical report series 843: 1–129.

2. WHO Scientific Group on the Prevention and Management of Osteoporosis (2000: Geneva, Switzerland) (2003). Prevention and Management of osteoporosis: report of a WHO scientific group (pdf). <http://whqlibdoc.who.int/trs/WHO>.

3. **Raisz L** Pathogenesis of osteoporosis: concepts, conflict and prospects. J Clin Invest, 2005, 115 (12): 3318–25.

4. **McDonough AK, Rosenthal RS, Saag KG.** The effect of thiazolidindiones on BMD and osteoprosis. Nat Clin Pract Endocrinol Metab. 2008 Nov;4(11):643.

5. **Alberti KG, Zimmet P, Show J.** IDF Epidemiology Task Force Consensus Group. The metabolic Syndrome-a new worldwide definition et al. Lancet 2005;366:1059–62.

6. **Adami S.** Bone health in diabetes: considerations for clinical management. Curr Med Res Opin 2009 25(5): 1057-72.

7. **Meier C., Kraenzlin ME., Bodmer M., et al,** Use of thiazolidindiones and fracture risk. Arch Intern Med 2008 Apr 28;168(8):820-5.

8. **Loke YK., Singh S., Furberg CD.** Long-term use of thiazolidinediones and fracture in type 2 diabetes : a meta-analysis. CMAJ 2009 Jan 6;180(1):32-9.

Correspondence Data:

email: rucsandra_m@yahoo.com; Tel 0740199929 ; Fax 021 2105575
UMF Carol Davila București