Editorial
Clinical Diabetes & Therapeutics
Diabetes Metab J 2017;41:374-376
https://doi.org/10.4093/dmj.2017.41.5.374
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Changes in the Bone Mineral Density of Femur Neck and Total Hip Over a 52-Week Treatment with Lobeglitazone

Da Young Lee, Ji A Seo

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

Individuals with diabetes are at a high risk of both hip and non-hip fractures, regardless of the type of diabetes [1], and tend to be at a higher fracture risk at a given bone mineral density (BMD) than individuals without diabetes [2]. This could be because diabetes increases bone fragility by increasing the cortical porosity and decreasing the cortical area and bone material strength [3], in addition to causing bone loss. In addition to the classical risk factors for fracture, there are several others that are specific to diabetes, such as presence of diabetes for more than 10 years, treatment with thiazolidinedione (TZD) anti-diabetic agents, and the presence of diabetes-related complications [4].

TZDs act as ligands for peroxisome proliferator-activated receptor γ (PPAR-γ), which is expressed widely in the stromal cells of bone marrow, adipocytes, osteoblasts, and osteoclasts [5], and directly regulate the expression of genes involved in glucose homeostasis and adipogenesis; thereby, acting as insulin sensitizers. Although TZDs have better glycemic durability than sulfonylureas without increasing the risk of hypoglycemia [6], several clinically observed adverse effects, such as weight gain, edema, heart failure, and bone damage, reduce the prescription preference for TZDs [7]. In a recent meta-analysis of 22 randomized control trials, the risk of fracture in women using TZDs was approximately twice of that in women not using TZDs [8].

The reported mechanisms of action of TZDs on bones include increase in adipocyte formation [9], suppression of pro-osteoblast differentiation in mesenchymal stem cells [10], and promotion of osteoclast differentiation and activity [11,12]. In addition, TZDs activate adipokines and inflammatory cytokines [13,14], and regulate the energy metabolism affecting the skeleton [15].

Lobeglitazone is a novel PPAR-γ agonist with a substituted pyrimidine ring and a TZD moiety. Compared to other TZDs, its glucose-lowering effect is observed at a lower dose with fewer adverse reactions common to TZDs, such as weight gain, peripheral edema, and heart failure [7,16].

Lim et al. [17] evaluated the effects of a 52-week treatment with lobeglitazone on BMD, which is well-known to be adversely affected by TZDs. Compared to baseline, no statistically significant differences in the femur neck and total hip BMD were observed between lobeglitazone and placebo groups.

In this study, only the BMD of the femur was measured because the femur bone has a substantial proportion of cortical bone [18]. Among the diabetic population, this measurement may be more relevant than the measurement of the BMD of the lumbar spine because fractures in individuals treated with TZDs typically occur at cortical skeletal sites [19]. Therefore, the results of this study are meaningful.

Due to the small sample size and short study duration, the findings of this study can neither definitively define clinical risks nor generalize the conclusions to non-Asian individuals.

Corresponding author: Ji A Seo https://orcid.org/0000-0002-1927-2618
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
E-mail: seo-ji-a@hanmail.net

Another study at a larger scale with a longer duration is needed to establish the long-term clinical benefits and risks of lobeglitazone. Moreover, considering that TZDs reduced the strength of the radius and tibia in women [20], the effects of lobeglitazone on peripheral bones should also be evaluated in future studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Fan Y, Wei F, Lang Y, Liu Y. Diabetes mellitus and risk of hip fractures: a meta-analysis. Osteoporos Int 2016;27:219-28.
2. Ahmad OS, Leong A, Miller JA, Morris JA, Forgetta V, Mujammami M, Richards JB. A mendelian randomization study of the effect of type-2 diabetes and glycemic traits on bone mineral density. J Bone Miner Res 2017;32:1072-81.
3. Farr JN, Drake MT, Amin S, Melton LJ 3rd, McCready LK, Khosla S. In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. J Bone Miner Res 2014;29:787-95.
4. Viegas M, Costa C, Lopes A, Griz L, Medeiro MA, Bandeira F. Prevalence of osteoporosis and vertebral fractures in postmenopausal women with type 2 diabetes mellitus and their relationship with duration of the disease and chronic complications. J Diabetes Complications 2011;25:216-21.
5. Gimble JM, Robinson CE, Wu X, Kelly KA, Rodriguez BR, Kliewer SA, Lehmann JM, Morris DC. Peroxisome proliferator-activated receptor-gamma activation by thiazolidinediones induces adipogenesis in bone marrow stromal cells. Mol Pharmacol 1996;50:1087-94.
6. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
7. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106-18.
8. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014;68:115-23.
9. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology 2004;145:401-6.
10. Bruedigam C, Driel M, Koedam M, Peppel J, van der Eerden BC, Eijken M, van Leeuwen JP. Basic techniques in human mesenchymal stem cell cultures: differentiation into osteogenic and adipogenic lineages, genetic perturbations, and phenotypic analyses. Curr Protoc Stem Cell Biol 2011;Chapter 1:Unit1H.3.
11. Gruntmanis U, Fordan S, Ghayee HK, Abdullah SM, See R, Ayers CR, McGuire DK. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone increases bone resorption in women with type 2 diabetes: a randomized, controlled trial. Calcif Tissue Int 2010;86:343-9.
12. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. Nat Med 2007;13:1496-503.
13. Rosen CJ, Bouxsein ML. Mechanisms of disease: is osteoporosis the obesity of bone? Nat Clin Pract Rheumatol 2006;2:35-43.
14. Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Yano S, Sugimoto T. Relationships between serum adiponectin levels versus bone mineral density, bone metabolic markers, and vertebral fractures in type 2 diabetes mellitus. Eur J Endocrinol 2009;160:265-73.
15. Jeyabalan J, Shah M, Viollet B, Chenu C. AMP-activated protein kinase pathway and bone metabolism. J Endocrinol 2012;212:277-90.
16. Kim SG, Kim DM, Woo JT, Jang HC, Chung CH, Ko KS, Park JH, Park YS, Kim SJ, Choi DS. Efficacy and safety of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 24-weeks: a multicenter, randomized, double-blind, parallel-group, placebo controlled trial. PLoS One 2014;9:e92843.
17. Lim S, Kim KM, Kim SG, Kim DM, Woo JT, Chung CH, Ko KS, Park JH, Park Y, Kim SJ, Jang HC, Choi DS. Effects of lobeglitazone, a novel thiazolidinedione, on bone mineral density in patients with type 2 diabetes mellitus over 52 weeks. Diabetes Metab J 2017;41:377-85.
18. Favus MJ. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed. Washington, DC: American Society for Bone and Mineral Research; 2006. Chapter 2, Anatomy and functions of the adult skeleton; p7-11.
19. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, Heise MA, Aftring RP, Viberti G; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care 2008;31:845-51.

20. Schwartz AV, Vittinghoff E, Margolis KL, Scibora LM, Palermo L, Ambrosius WT, Hue TF, Ensrud KE. Intensive glycemic control and thiazolidinedione use: effects on cortical and trabecular bone at the radius and tibia. Calcif Tissue Int 2013; 92:477-86.