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

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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 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.
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.

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