Will Statin Use Prevent Fracture of Type 2 Diabetes Associated with Thiazolidinedione Treatment? A Mini-Review and a Hypothesis

Chiung-Huei Peng[a], Yi-Sun Yang[b], Kuan-Chou Chen[c], Chiung-Chi Peng[d] and Chien-Ning Huang[*,b]

[a]*Department of Nursing, Hungkuang University, Sha Lu, Taichung Hsien, Taiwan*

[b]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Chung-Shan Medical University Hospital, Taichung City, Taiwan*

[c]*Department of Urology, Taipei Medical University, Wu-Xin Street, Taipei City, Taiwan*

[d]*Department of Nursing, Cardinal Tien's College of Nursing, Taipei Hsien, Taiwan*

Abstract: Thiazolidinediones (TZDs) are a multi-effective anti-glycemic drug for type 2 diabetes. Recent clinical trials suggest TZDs are associated with bone loss or fracture in older diabetic women. Diabetic women exhibit more rapid bone loss despite the higher baseline bone mineral density. The higher fracture risk of type 2 diabetes may be associated with neural and vascular complications, or the fragile bone structure.

Statins were found to exert protective effects on bone through their anti-oxidative effect on vascular and advanced glycation end product-related disorders. The impact of combination use of statins and TZDs on bone however has never been addressed. Whereas considering the advantages of statins and TZDs in treating type 2 diabetes regarding their cardiovascular protection and glycemic control improvement, we hypothesize that the concomitant use of statins and TZDs might also prevent against bone complications of type 2 diabetes or induced by TZDs, especially for older diabetic women.

Keywords: Type 2 diabetes, bone fracture, thiazolidinediones, statins.

INTRODUCTION

Thiazolidinediones (TZDs) are one kind of effective oral anti-glycemic drugs (OAD) for type 2 diabetes. They promote insulin sensitivity *via* activating peroxisome proliferator activated receptor γ (PPARγ) and the subsequent regulation on adipocyte differentiation and fatty acid metabolism [1]. However, in A Diabetes Outcomes Progression Trial (ADOPT), rosiglitazone, one of the TZDs, is reported to be associated with bone loss and fracture in type 2 diabetic patients [2]. The chronic complications of diabetes are well known including the vasculopathy and neuropathy, whether osteo-dysregulation is induced by TZDs or by diabetes per se still remains unclear.

Among all the complications, coronary heart disease is the major cause of mortality in diabetic individuals. It is reported that the statin drug simvastatin effectively lowers the concentrations of low density lipoprotein C (LDL-C) and apoprotein B (apoB) in TZDs-treated type 2 diabetic patients [3]. Combinations of atorvastatin and rosiglitazone further decrease high sensitivity C reactive protein (hsCRP) level and increase adiponectin, and exert their effect on other biomarkers compared with the group treated with rosiglitazone alone [4]. Statins are recently suggested to have bone-protective effect [5]. However, the impact of combination use of statins and TZDs on bone has never been addressed.

In the present report, we review the evidence in association with diabetes, TZDs, statin and fracture, and hypothesize that a combination use of statins and TZDs might be beneficial to prevent bone loss or fracture in TZDs-treated type 2 diabetic patients.

DIABETES ASSOCIATED WITH OSTEOPOROSIS OR BONE FRACTURE

In the previous reports, both cross-sectional and prospective studies showed that type 1 diabetic patients were associated with the decrease in bone mineral density (BMD) and the increased risk of osteoporosis and bone fracture [6]. However, there exist controversies in the investigations of type 2 diabetes. Most studies demonstrated that type 2 diabetic patients had higher BMD, probably due to increased body weight, but others reported non-significant differences [7-9]. The cross-sectional studies reported decreased risk of fracture in type 2 diabetic patients, whereas prospective studies demonstrated that type 2 diabetes was associated with increased osteoporotic fracture, despite the higher BMD [10,11]. When compared diabetic individuals with or without fractures, the former were found to have lower hip BMD and lean mass, and were more likely to have peripheral neuropathy, ischemic stroke and falls, implying that other factors such as diabetic complications could be involved in the fracture risk [12].

Some reports demonstrated that there existed sex difference with osteoporosis in type 2 diabetic patient. Older women with type 2 diabetes had better BMD, whereas no differences were observed in men [13]. Schwartz *et al.* indicated that diabetic white women, but not men or black women, had the more rapid bone loss despite having the higher baseline BMD [14]. In Women's Health Initiative Observational Study (WHI-OS), women with type 2 diabetes showed to be at increased risk for fractures even after adjust-

*Address correspondence to this author at the Division of Endocrinology and Metabolism, Department of Internal Medicine, Chung-Shan Medical University Hospital, No. 110, Section 1, Chien-Kuo N. Road, Taichung City, Taiwan; Tel: 886-4-24739595, Ext. 34708; Fax: 886-4-24739220; E-mail: cshy049@csh.org.tw

ing the visual problems and frequency of falls [15]. Although the bone density seems to be greater in diabetes, the bone structure could be more fragile caused by the formation of advanced glycation end (AGE) products, the lower levels of IGF-I, and hypercalciuria or inflammation [15].

TZDs THERAPY AND BONE COMPLICATION

TZDs have been permitted in clinical use since 1997. Since the hepatotoxicity induced by troglitazone, currently, only rosiglitazone and pioglitazone are used to treat type 2 diabetic patients [1]. TZDs bind to and activate PPARγ, a member of steroid nuclear receptor family observed in adipose and other insulin target tissues, thus mediating adipogenesis and the expression of relating markers [16]. PPARγ is also expressed in bone marrow, where the mesenchymal cells could differentiate into adipocytes and osteoblasts, indicating the potential effect of TZDs in regulating bone metabolism [17,18]. Actually, TZD was reported to inhibit osteoclast-like cell formation and bone resorption *in vitro*, which was not related to its adipogenic effect [19]. TZD was reported to decrease bone turnover markers in 33 Japanese type 2 diabetic patients before significant improvement of glucose metabolism, suggesting the direct effect of TZD on bone [20]. In addition, TZD was shown to decrease serum leptin, which could be associated with preventing bone loss of type 2 diabetes [21].

However, recently, many studies have demonstrated the negative impact of TZDs on bone. *In vitro* studies demonstrate that PPARγ2 activation in marrow stroma cells increases adipocyte differentiation while decreasing osteoblastogenesis [22]. PPARγ2 enhances the expression of aP2, a marker of differentiated adipocytes, but reduces Runx2, the main regulator of osteoblasts. In addition, the activation of PPARγ also suppresses other markers involved in osteoblast differentiation, such as α1(I)collagen alkaline phosphatase, osteocalcin and osteopontin [23]. These evidences suggest that PPARγ may act as a switch point between osteogenic and adipogenic pathways. It was reported TZD increased the amount of bone marrow adipose tissue [24]. In rosiglitazone-treated mice, TZD was demonstrated to promote osteogenic cell apoptosis and decrease the trabecular volume and BMD [25]. On the contrary, PPARγ deficient mice exhibited enhanced osteogenesis [26]. In addition to the osteogenesis pathway, by using a Tie2Cre/flox mouse model, PPARγ deletion is demonstrated to impair osteoclastogenesis, thus resulting in osteopetrosis and extramedullary hematopoiesis, whereas rosiglitazone promotes osteoclast differentiation in a receptor-dependent manner [27].

Clinically, some prospective observational studies suggest that TZDs cause bone loss in older diabetic women [28]. Results of recent ADOPT showed that rosiglitazone use increased fracture risk of diabetic patients, whereas the fracture usually occured at humerus, hand and foot [2]. In a randomized controlled trial, rosiglitazone exerted skeletal effects by decreasing bone formation and BMD in healthy postmenopausal women, especially at hip and lumber [29]. Another popularly used TZD pioglitazone, was also advised to cause fracture risk of diabetic female in 2007 [30]. As diabetic women may increase bone turnover per se, it is of great possibility that TZDs superimposed the bone loss. In addition, TZDs are known to inhibit aromatase pathway, the main

estrogen source of postmenopausal women, implicating another possible mechanism for TZDs to impact negatively on bone [28].

STATINS AND THE POSSIBLE EFFECT ON BONE

Statins are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which are wildly used to treat hypercholesteremia. Statins were demonstrated to prevent primary and secondary coronary artery disease in diabetic patients [31,32]. In recent years, statins were found to increase new bone formation in rodents and in human cells [5].

In vitro experiment of different cell lines showed that statins exerted their effects on stimulating osteoblast differentiation and bone formation *via* BMP-2 expression, and/ or inhibiting osteoclast differentiation and bone resorption [33-36]. *In vivo* animal studies also suggested that statins were effective to increase bone formation or decrease bone resorption [37,38]. However, discrepancies exist in humans. In Geelong cross-sectional study, statin use was associated with 60% reduction of fracture risk, which was greater than would be expected from the increase of BMD [39]. Statins seemed to reduce the risk of fracture among older women [40]. In a prospective cohort study of Netherland, statins use was associated with lower risk of vertebral fracture. The relative risk decreased on higher cumulative use [41]. A Danish case-control study also suggested that statin use decreased the hip fracture [42]. In the previous investigations, it was demonstrated statins, but not the other lipid-lowering drugs, reduced the fracture risk [43,44]. The anabolic and anti-resorptive effects of statins increased more BMD in post-menopausal women than those treated by hormone replacement alone [45]. However, results of recent WHI-OS suggested that statin use did not improve bone density and fracture risk [46]. Some systemic analysis reported that statins might be effective in improving hip BMD and lowering the risk of non-spine fractures [47]. Whereas in a randomized controlled trial, simvastatin showed no benefit on BMD for postmenopausal osteopenic women [48].

Although there still exist controversies about statin-mediated bone effect, some reports indicate that statin increase BMD and prevent bone loss in patients with type 2 diabetes [49,50]. In the clinical trials, lovastatin is shown to prevent bone loss in postmenopausal diabetic women, whereas atorvastatin has no effect on bone turnover in type 2 diabetic patients [51,52].

The possible mechanism of statins has been investigated in *in vitro* studies. Mevalonate abolished statin-induced mineralization, suggesting the direct regulating role of HMG-CoA on bone metabolism [53]. It was suggested that statins could integrate PI3K signal to Akt and MAPK thus mediate osteoblast differentiation *via* BMP-2 expression [54]. Furthermore, statins were reported to decrease the serum level of AGE [55,56]. In diabetic patients, the cross-linking and accumulation of AGE are associated with tissue damage such as vascular and neural complications. It was demonstrated that atorvastatin inhibited AGE-induced reaction by suppressing reactive oxygen species generation, which acted in a cholesterol-lowering independent manner, and could contribute to the early clinical benefit among diabetic patients [56]. In fact, the protective effect of statins on bone

could include their impact on vascular disturbance and AGE-related disorders.

HYPOTHESIS: COMBINATION USE OF STATINS WITH TZDs

Fracture and cardiovascular disease are the common morbidity or mortality for ageing people. According to the previous reports mentioned above, statins might be expected to exert protective effects against the bone complication associated with TZDs or type 2 diabetes. TZDs used in type 2 diabetic treatment exert their clinical effects not only on improving insulin sensitivity, β-cell preservation, but also on the elevation of adiponectin and anti-inflammation [57,58]. Although it was once considered to be associated with increased myocardial infarction recently [59], another recent meta-analysis found no significantly increased risk of cardiovascular mortality by using either rosiglitazone or pioglitazone [60]. Furthermore, the longterm clinical trial, PROactive study, as well as a meta-analysis regarding pioglitazone on cardiovascular disease risk has also suggested that the drug demonstrated a protective effect [61,62]. ADOPT study, apparently, showed that TZDs act more effective to control hyperglycemia, and consistently maintain HbA1C level below 7.0%. However, ADOPT also showed that TZDs increase the bone fracture risk of women [2].

It has been documented in the large scaled clinical trial such as HPS and CARDS that statin could reduce cardiovascular events for type 2 diabetic patients [31,32]. In addition, many previous reports suggested stain also prevent the risk of bone fracture. Hence we here hypothesize that combination therapy of TZD and statin for type 2 diabetic patients could improve glycemic control and protect cardiovascular system, as well as prevent potential bone loss or fracture induced by TZD or by diabetes per se. The important anti-inflammation effect could also be provided by both medication. While concerning poly-pharmacy as a treatment limitation for patients, premixed with TZD and statin as a single tablet might be an option to improve drug compliance.

In conclusion, combination use of TZDs and statins could be expected to be the best treatment choice for type 2 diabetic patients, especially among postmenopausal women. Further studies *in vitro*, *in vivo* or clinical trials are still necessary to see the bone effect by the concomitant use of TZDs and statins.

CONCLUSION

- Diabetes per se could result in bone fracture *via* rapid bone loss, fragile bone structure, or due to vascular complications and neuropathy.

- TZDs are effective OAD which exert their effects not only on increasing insulin sensitivity, but on the pleiotropic functions including changing lipid profile and anti-inflammation. However, recent ADOPT study demonstrated TZDs increase the bone fracture risk of diabetic women.

- Many studies have shown that statins might be beneficial in preventing bone loss or decrease fracture risk. In literature they were shown to increase the BMD of type 2 diabetic patients.

- Statins have been shown to reduce cardiovascular events for type 2 diabetic patients. Combination use of statins and TZDs effectively lower the concentrations of LDL-C, apoB and CRP, as well as increase adiponectin. Hence combination therapy with both statins and TZDs could be expected not only to improve glycemic control and protect cardiovascular system, but also to prevent potential bone loss or fracture induced by TZDs or by diabetes per se.

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