Use of thiazolidinediones and risk of hip fracture in old people in a case–control study in Taiwan

Hsien-Feng Lin, MD, MS[a,b], Kuan-Fu Liao, MD, PhD[c,d,e], Ching-Mei Chang, RN, MSN[f], Cheng-Li Lin, MS[g,h], Chih-Hsueh Lin, MD, PhD[b,g], Shih-Wei Lai, MD[b,g,*]

Abstract

Little research is available on the association between use of thiazolidinediones and hip fracture in old people in Taiwan. We conducted a population-based case–control study to examine this issue.

Using the database of the Taiwan National Health Insurance Program, we identified 603 type 2 diabetic subjects 65 years or older in age with newly diagnosed hip fracture in 2000 to 2013 as cases. We randomly selected 603 type 2 diabetic subjects 65 years or older without hip fracture as the controls. Both cases and controls were matched with sex, age, comorbidities, and index year of diagnosing hip fracture. Current use of thiazolidinediones was defined as subjects whose last remaining one tablet of thiazolidinediones was noted ≤30 days before the date of diagnosing hip fracture. Never use of thiazolidinediones was defined as subjects who never had a prescription of thiazolidinediones. The odds ratio (OR) and 95% confidence interval (CI) for hip fracture associated with thiazolidinediones use was estimated by the multivariable unconditional logistic regression analysis.

After adjustment for covariables, the multivariable logistic regression analysis revealed that the adjusted OR of hip fracture was 1.64 for subjects with current use of thiazolidinediones (95% CI 1.01, 2.67), when compared with subjects with never use of thiazolidinediones.

Our findings suggest that current use of thiazolidinediones is associated with a 64% higher risk of hip fracture in type 2 diabetic old people in Taiwan. Clinicians should consider the possibility of thiazolidinediones-associated hip fracture among type 2 diabetic old people currently using thiazolidinediones.

Abbreviation: ICD-9 code = International Classification of Diseases Ninth Revision Clinical Modification.

Keywords: hip fracture, old people, thiazolidinediones

[a] School of Chinese Medicine, [b] Department of Family Medicine, China Medical University Hospital, Taichung, [c] Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung, [d] College of Medicine, Tzu Chi University, Hualien, [e] Graduate Institute of Integrated Medicine, China Medical University Hospital, Taichung, [f] Department of Nursing, Tungs' Taichung Metro Harbor Hospital, Taichung, [g] College of Medicine, China Medical University, Taichung, [h] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan.

* Correspondence: Shih-Wei Lai, Department of Family Medicine, China Medical University Hospital, No 2, Yuh-Der Road, Taichung City, 404, Taiwan (e-mail: wei@mail.cmuh.org.tw).

1. Introduction

The prevalence of diabetes mellitus and type 2 diabetes mellitus, in particular, has been increasing worldwide because of the high rates of obesity. Many studies have investigated methods for reducing the incidence of type 2 diabetes, with primary recommendations including improved diet and increased exercise.[1,2] Oral hypoglycemics are first-line drugs against type 2 diabetes mellitus when diet and exercise fail to control blood glucose levels. Patients with type 2 diabetes mellitus have been shown to have higher bone densities[3–6] and possibly lower fracture risks than general population.[7] However, many studies have shown an association between type 2 diabetes mellitus and fracture risk.[8,9] The increased risk might be related to other factors such as complications of diabetes, risk of falling, and use of antidiabetic medications. Thiazolidinediones, including pioglitazone and rosiglitazone, are a relatively new and effective class of oral antidiabetic agents that have gained wide use in clinical conditions characterized by insulin resistance. Thiazolidinediones are ligands of the peroxisome proliferator-activated receptor gamma nuclear transcription factor. Various studies have shown that thiazolidinedione use decreases bone mineral density and elevates fracture risk.[10–13] A meta-analysis showed that rosiglitazone and pioglitazone are associated with a significantly increased fracture risk.[14]

Hip fractures, which constitute a common health problem with many proposed and established risk factors,[15] are associated with significant morbidity and mortality rates and reduction in the quality of life of older individuals. Patients with type 2 diabetes mellitus and hip fractures have a significantly longer mean duration of hospitalization, pressure sores, and cardiovascular complications.[16]

Given the paucity of information regarding the association between thiazolidinedione use and hip fracture risk in Asian

countries, the present population-based case–control study was conducted to investigate this particular association among the elderly in Taiwan.

2. Methods

2.1. Data source

Taiwan is an independent country with more than 23 million residents.[17–24] A population-based case–control study was conducted using the database of the Taiwan National Health Insurance Program. This insurance program began in March 1995 and has covered 99% of the 23 million residents of Taiwan.[25] Details of the program can be found in previous studies.[26–30] The present study was approved by the Research Ethics Committee of China Medical University (CMUH-104-REC2–115).

2.2. Sampled participants and comorbidities

Subjects with type 2 diabetes, ≥65 years of age and who were newly diagnosed with hip fractures (ICD-9 code 820) in 2000 to 2013 were included as cases. The diagnosis date of the hip fracture was defined as the index date. Subjects with type 2 diabetes who were not diagnosed with hip fractures were randomly selected as controls from the same database. Both cases and controls were matched for sex, age (per 5 years), comorbidities, and index date. Comorbidities potentially related to hip fractures before the index date included alcohol-related, cardiovascular, chronic kidney, and chronic obstructive pulmonary diseases; hyperlipidemia; hypertension; and osteoporosis. The diagnostic accuracy of comorbidities based on ICD-9 codes has been well examined in previous studies.[31–35]

2.3. Use of thiazolidinediones and other hypoglycemic agents

Thiazolidinediones available in Taiwan include pioglitazone and rosiglitazone, whereas other antidiabetic agents available in Taiwan include sulfonylurea, metformin, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and insulin. The definition of medication use was adapted from previous studies.[36–41] To decrease biased results, subjects whose last thiazolidinedione tablet was noted to be scheduled at ≥31 days before the index date were excluded from the study. Therefore, the current use of thiazolidinedione was defined as subjects whose last thiazolidinedione tablet was noted to be scheduled at ≤30 days before the index date or those still taking thiazolidinedione tablets upon the diagnosis of a hip fracture diagnosis. Nonuse of thiazolidinediones was defined as the lack of a thiazolidinedione prescription. Medication history regarding the use of other hypoglycemic agents was also included.

2.4. Statistical analysis

First, the distribution of demographic status, use of thiazolidinediones and other hypoglycemic agents, and comorbidities between the cases and controls were compared using the chi-square test and Fisher exact test for categorized variables. Student t test was performed to examine the differences in mean age and mean duration of type 2 diabetes between the cases and controls. Univariable and multivariable unconditional logistic regression analyses were performed to calculate the odds ratio (OR) and 95% confidence interval (CI) to determine the association between thiazolidinedione use and hip fracture risk. A multivariable analysis with adjustments for the duration of type 2 diabetes mellitus was performed. The dose-dependent effects of thiazolidinedione were analyzed among current users. The average daily dose of thiazolidinedione was calculated by dividing the total quantity of thiazolidinedione by the total number of days for which it was administered. The average daily dose was divided into 2 levels according to median doses of <15 and ≥15 mg. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC), and results showing 2-tailed P values of < .05 were considered statistically significant.

3. Results

3.1. Descriptive characteristics of the study population

In total, 603 cases with newly diagnosed hip fractures in 2000 to 2013 and 603 controls without hip fractures (Table 1) were included. Both cases and controls had similar sex and age distributions. The mean ages (standard deviation) of the cases and controls were 76.8 (6.5) and 76.7 (6.2) years, respectively, without a statistical significance (t test, $P = .8$). The cases were more likely to have higher proportions of current thiazolidinedione use (9.0% vs 4.6%; chi-square test, $P = .003$) and longer durations of type 2 diabetes mellitus (4.8 vs 3.9 years; t test, $P = .001$) than the controls. No significant differences in other comorbidities and the use of other hypoglycemic agents were observed between the cases and controls (chi-square test, $P > .05$).

3.2. Association between hip fracture risk and thiazolidinedione use

After adjusting for covariables, multivariable logistic regression analysis revealed that the adjusted OR for hip fracture risk was 1.64 in subjects currently using thiazolidinediones (95% CI, 1.01–2.67) compared with that in those who never used the drug (Table 2). The duration of type 2 diabetes was another factor significantly associated with hip fracture risk (annually; adjusted OR: 1.08; 95% CI, 1.04–1.12).

3.3. Association between hip fracture risk and average daily dose in current users of thiazolidinediones

Further analysis on the dose-dependent effect of thiazolidinediones was conducted among current users. After adjusting for covariables, the adjusted OR for hip fracture risk was 1.46 in subjects with an average daily thiazolidinedione dose of <15 mg (95% CI, 0.80–2.66) and 6.22 in those with an average daily thiazolidinedione dose of ≥15 mg (95% CI, 2.32–16.7) compared with that in those who never used thiazolidinediones (Table 3). These results suggest that thiazolidinedione use has a dose-dependent effect on hip fracture risk.

4. Discussion

The most significant findings of the present study included the association between the current use of thiazolidinediones and a 1.64-fold increase in the hip fracture risk in older Taiwanese individuals with type 2 diabetes. A meta-analysis showed that patients using rosiglitazone and pioglitazone had a 1.5-fold increase in fracture risk compared with those using other

Table 1

Characteristics of cases with hip fracture and controls in older people.

| Variable | Hip fracture | | | | P value* |
| | No, N = 603 | | Yes, N = 603 | | |
	n	%	n	%	
Sex					.9
Female	398	66.0	399	66.2	
Male	205	34.0	204	33.8	
Age group, y					.8
65–74	248	41.1	250	41.5	
75–84	299	49.6	290	48.1	
≥85	56	9.3	63	10.4	
Age, y; mean, standard deviation†	76.7	6.2	76.8	6.5	
Duration of type 2 diabetes, y; mean, standard deviation†	3.9	2.9	4.8	3.6	.001
Thiazolidinediones use					.003
Never use	575	95.4	549	91.0	
Current use	28	4.6	54	9.0	
Other hypoglycemic agents use					.8
Never use	168	27.9	171	28.4	
Ever use	435	72.1	432	71.6	
Comorbidities before index date					
Alcohol-related disease‡	6	1.0	5	0.8	.2
Cardiovascular disease	480	79.6	469	77.8	.4
Chronic kidney disease	34	5.6	26	4.3	.3
Chronic obstructive pulmonary disease	162	26.9	158	26.2	.8
Hyperlipidemia	221	36.7	226	37.5	.8
Hypertension	566	93.9	570	94.5	.6
Osteoporosis	130	21.6	126	20.9	.8

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

* Chi-square test.

† t test comparing subjects with and without hip fracture.

‡ Fisher-exact test.

antidiabetic drugs.[14] Habib et al[42] conducted a cohort study in which thiazolidinedione use was observed to be associated with a 1.4-fold increase in fracture risk compared with other antidiabetic medication use. Another cohort study[43] that compared thiazolidinedione use with metformin use reported a 1.3-fold increase in fracture risk. Using a self-controlled case series design to compare periods of exposure and nonexposure to thiazolidinediones, Douglas et al[44] found a within-person rate ratio of 1.43 for fracture risk. Several studies have conducted that thiazolidinediones may exert unwanted effects on bone, resulting in attenuated osteoblast number and increased osteoclastogenesis.[12,45–48] The peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a DNA-binding nuclear hormone receptor that regulates glucose metabolism and bone

Table 2

OR and 95% CI of hip fracture associated with thiazolidinediones use and comorbidities in older people.

| Variable | Crude | | Adjusted* | |
	OR	95% CI	OR	95% CI
Sex (male vs female)	0.99	(0.78, 1.26)		
Age, per 1 y	1.00	(0.99, 1.02)		
Duration of type 2 diabetes, per 1 y	1.09	(1.05, 1.13)	1.08	(1.04, 1.12)
Thiazolidinediones use (never use as a reference)				
Current use	2.02	(1.26, 3.24)	1.64	(1.01, 2.67)
Other hypoglycemic agents use (never use as a reference)				
Ever use	0.98	(0.76, 1.25)		
Comorbidities before index date (yes vs no)				
Alcohol-related disease	0.83	(0.25, 2.74)		
Cardiovascular disease	0.90	(0.68, 1.18)		
Chronic kidney disease	0.75	(0.45, 1.27)		
Chronic obstructive pulmonary disease	0.97	(0.75, 1.25)		
Hyperlipidemia	1.04	(0.82, 1.31)		
Hypertension	1.13	(0.70, 1.83)		
Osteoporosis	0.96	(0.73, 1.27)		

CI = confidence intervals, OR = odds ratio.

* Covariables found to be significantly associated with hip fracture in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model. Adjusted for duration of type 2 diabetes (per 1 year).

Table 3

Average daily dose of current use of thiazolidinediones and risk of hip fracture in older people.

Variable	Case number/control number	Crude odds ratio	95% CI	Adjusted odds ratio*	95% CI
Never use of thiazolidinediones as a reference	549/575	1.00	Reference	1.00	Reference
Current use of thiazolidinediones					
Average daily dose					
<15 mg	28/23	1.28 (0.73, 2.24)	1.46 (0.80, 2.66)		
≥15 mg	26/5	5.45 (2.08, 14.3)	6.22 (2.32, 16.7)		

* Adjusted for duration of type 2 diabetes (per 1 year).

mass. PPAR-γ receptors are most abundant in adipocytes and regulate their differentiation and function. The increased expression of PPAR-γ led to changes in marrow structure and function, such as decrease in osteoblast number, increase in marrow fat cells and osteoclast number, and loss of the multipotential character of bone marrow mesenchymal stem cells. Thiazolidinediones are ligands for PPAR-γ. When rosiglitazone is added to bone marrow cultures, a shift in the flow of mesenchymal precursor cells from osteoblastic to adipogenic lineages mediated by the activation of PPAR-γ has been shown to result in attenuated osteoblastic bone formation and accelerated bone loss.[49,50]

In addition to thiazolidinedione use, the severity and duration of type 2 diabetes mellitus have been shown to be associated with fracture risk.[8,9] Our study showed that the duration of type 2 diabetes is a factor significantly associated with hip fracture risk (annually; adjusted OR, 1.08; 95% CI, 1.04–1.12). There are various mechanisms that may be involved in the increased fracture risk. McNair P et al revealed that bone mineral content was inversely correlated with fasting blood glucose, and urinary excretion rates of calcium and phosphorus correlated positively with the degree of hyperglycemia.[51] The skeletal calcium loss corresponded to the excess of urinary calcium excretion during the phase of bone mineral content reduction. High blood glucose in patients with diabetes may lead to lower intestinal absorption of calcium,[52] altered in serum of vitamin D metabolites,[53,54] and might have a direct toxic effect on bone cells.[55,56] Inaba M et al revealed that impaired parathyroid hormone secretion may be responsible for the low bone turnover in hemodialyzed patients with diabetes.[57] Several studies conducted that complications of diabetes mellitus (retinopathy, neuropathy, and angiopathy) may also increase fracture risk.[58–61]

Meier et al showed that the adjusted OR for any fracture during the current use of ≥15 thiazolidinedione prescriptions was 2.86 (95% CI, 1.57–5.22) compared with that during nonuse.[62] The present study found that the adjusted ORs for hip fracture risk were 6.22 and only 1.46 for subjects with average daily thiazolidinedione dose of ≥15 mg (95% CI, 2.32–16.7) and <15 mg (95% CI, 0.80–2.66), respectively, compared with that for subjects who never used the drug. These results show that thiazolidinedione use may have a dose-dependent effect on hip fracture risk. Our interpretation of these results suggests that although thiazolidinedione use is probably the most important factor in the association between thiazolidinediones and fracture risk, the severity and duration of the underlying disease also play a role.

Some strengths of the present study should be documented. This study utilized a hospitalization dataset with more accurate diagnoses of hip fractures. Comorbidities based on ICD-9 codes have been carefully reviewed in previous studies. Moreover, the study design and statistical methods have been well conducted, and the results are reasonable and provide updated evidence on this issue.

Some limitations of this present study should be discussed. First, to decrease the biased results, subjects whose last remaining thiazolidinedione tablet was noted to be scheduled at ≥31 days before the index date were excluded from the study. Because of this strict inclusion criterion, only 603 cases and 603 controls were included in the present study. Second, because of the inherent limitations of the used database, whether patients really took thiazolidinediones could not be ascertained although thiazolidinedione prescriptions were included instead. Nonetheless, it is well known that getting a prescription is not equivalent to using it. Third, bone densitometry was not performed. Therefore, whether the increased fracture risk was mediated by a reduced bone mass in patients with diabetes could not be evaluated. Fourth, it has been previously recognized that patients with type 2 diabetes mellitus have a higher body mass index than the general population[63] and that a higher body mass index is protective against fractures.[64] This may have led to an underestimation of the true association between thiazolidinedione use in type 2 diabetes mellitus and fracture risk. Fifth, a clinical measure of diabetes severity, such as HbA1c, was not available, which could have been an improvement over the prior diabetic hospitalization variables used. Sixth, our study did not include certain demographic or lifestyle factors. It is possible that certain demographic or lifestyle factors, such as the socioeconomic status, dietary habits, and physical activity are associated with fracture risks and antidiabetic drug use.

We conclude that the use of thiazolidinediones is associated with a 64% increase, particularly in a dose-dependent manner, in hip fracture risk in older Taiwanese individuals with type 2 diabetes. Clinicians should consider the possibility of thiazolidinedione-associated hip fractures among older patients with type 2 diabetes using thiazolidinediones.

References

[1] Alblowi J, Kayal RA, Siqueira M, et al. High levels of tumour necrosis factor alpha contribute to the accelerated loss of cartilage in diabetic fracture healing. Am J Pathol 2009;175:1574–85.

[2] American Society of AnesthesiologistsNew classification of physical status. Anesthesiology 1963;24:111.

[3] Isaia GC, Ardissone P, Di Stefano M, et al. Bone metabolism in type 2 diabetes mellitus. Acta Diabetol 1999;36:35–8.

[4] Barrett-Connor E, Holbrook TL. Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. JAMA 1992;268: 3333–7.

[5] Van Daele PL, Stolk RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus: the Rotterdam Study. Ann Intern Med 1995;122:409–14.

[6] Schwartz AV, Hillier TA, Sellmeyer DE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25: 1749–54.

[7] Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. J Clin Endocrinol Metab 2006;91:3404–10.

[8] Janghorbani M, Van Dam RM, Willett WC, et al. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495–505.

[9] Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int 2007;18:427–44.

[10] Grey A. Skeletal consequences of thiazolidinedione therapy. Osteoporos Int 2008;19:129–37.

[11] Benvenuti S, Cellai I, Luciani P, et al. Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells. J Endocrinol Invest 2007;30:RC26–30.

[12] Ali AA, Weinstein RS, Stewart SA, et al. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. Endocrinology 2005;146:1226–35.

[13] Rzonca SO, Suva LJ, Gaddy D, et al. Bone is a target for the AD compound rosiglitazone. Endocrinology 2004;145:401–6.

[14] Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ 2009;180:32–9.

[15] Cumming RG, Nevitt MC. Cummings SR epidemiology of hip fractures. Epidemiol Rev 1997;19:244–57.

[16] Norris R, Parker M. Diabetes mellitus and hip fracture: a study of 5966 cases. Injury 2011;42:1313–6.

[17] Lin YJ, Ho TJ, Lin TH, et al. P-coumaric acid regulates exon 12 splicing of the ATP7B gene by modulating hnRNP A1 protein expressions. Biomedicine 2015;5:22–30.

[18] Lin TY, Fan CW, Maa MC, et al. Lipopolysaccharide-promoted proliferation of Caco-2 cells is mediated by c-Src induction and ERK activation. Biomedicine 2015;5:33–8.

[19] Lin CJ, Lai CK, Kao MC, et al. Impact of cholesterol on disease progression. Biomedicine 2015;5:1–7.

[20] Lin CH, Li TC, Tsai PP, et al. The relationships of the pulmonary arteries to lung lesions aid in differential diagnosis using computed tomography. Biomedicine 2015;5:31–8.

[21] Li TC, Li CI, Liao LN, et al. Associations of EDNRA and EDN1 polymorphisms with carotid intima media thickness through interactions with gender, regular exercise, and obesity in subjects in Taiwan: Taichung Community Health Study (TCHS). Biomedicine 2015;5:8–14.

[22] Jao CL, Hung CC, Tung YS, et al. The development of bioactive peptides from dietary proteins as a dipeptidyl peptidase IV inhibitor for the management of type 2 diabetes. Biomedicine 2015;5:9–15.

[23] Hung CC, Ku YW. Influencing and moderating factors analyzed in the group art therapy of two schizophrenic inpatients. Biomedicine 2015;5:36–8.

[24] Cheng KC, Lin WY, Liu CS, et al. Association of different types of liver disease with demographic and clinical factors. Biomedicine 2016;6:16–22.

[25] National Health Insurance Research Database [English version]. Taiwan. Available at: http://nhird.nhri.org.tw/en/index.html. Accessed on April 1, 2017.

[26] Chen YL, Cheng KC, Lai SW. Diabetes and risk of subsequent gastric cancer: a population-based cohort study in Taiwan. Gastric Cancer 2013;16:389–96.

[27] Hung SC, Lai SW, Tsai PY, et al. Synergistic interaction of benign prostatic hyperplasia and prostatitis on prostate cancer risk. Br J Cancer 2013;108:1778–83.

[28] Yang SP, Muo CH, Wang IK, et al. Risk of type 2 diabetes mellitus in female breast cancer patients treated with morphine: A retrospective population-based time-dependent cohort study. Diabetes Res Clin Pract 2015;110:285–90.

[29] Lai HC, Tsai IJ, Chen PC, et al. Gallstones, a cholecystectomy, chronic pancreatitis, and the risk of subsequent pancreatic cancer in diabetic patients: a population-based cohort study. J Gastroenterol 2013;48:721–7.

[30] Chen HY, Lin CL, Lai SW, et al. Association of selective serotonin reuptake inhibitor use and acute angle-closure glaucoma. J Clin Psychiatry 2016;77:e692–6.

[31] Liao KF, Cheng KC, Lin CL, et al. Etodolac and the risk of acute pancreatitis. Biomedicine 2017;7:25–9.

[32] Shen ML, Liao KF, Tsai SM, et al. Herpes zoster correlates with pyogenic liver abscesses in Taiwan. Biomedicine 2016;6:24–9.

[33] Liao KF, Huang PT, Lin CC, et al. Fluvastatin use and risk of acute pancreatitis: a population-based case-control study in Taiwan. Biomedicine 2017;7:1–5.

[34] Lai S-W, Lin C-L, Liao K-F. Increased risk of hip fracture in diabetic elderly. Kuwait Med J 2015;47:115–7.

[35] Lai SW, Lin CL, Liao KF. Risk of contracting pneumonia among patients with predialysis chronic kidney disease: a population-based cohort study in Taiwan. Biomedicine 2017;7:34–9.

[36] Lai SW, Lin CL, Liao KF. Increased relative risk of acute pancreatitis in zolpidem users. Psychopharmacology 2015;232:2043–8.

[37] Liao KF, Lin CL, Lai SW, et al. Sitagliptin use and risk of acute pancreatitis in type 2 diabetes mellitus: a population-based case-control study in Taiwan. Eur J Intern Med 2016;27:76–9.

[38] Lai SW, Lin CL, Liao KF. Digoxin use may increase the relative risk of acute pancreatitis: a population-based case-control study in Taiwan. Int J Cardiol 2015;181:235–8.

[39] Hung SC, Liao KF, Hung HC, et al. Nabumetone use and risk of acute pancreatitis in a case-control study. Pancreatology 2016;11:00054–5.

[40] Lai SW, Lin CL, Liao KF. Association of meloxicam use with the risk of acute pancreatitis: a case-control study. Clin Drug Investig 2015;35:653–7.

[41] Lai SW, Lai HC, Lin CL, et al. Zopiclone use associated with increased risk of acute pancreatitis: a case-control study in Taiwan. Int J Clin Pract 2015;69:1275–80.

[42] Habib ZA, Havstad SL, Wells K, et al. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2010;95:592–600.

[43] Solomon DH, Cadarette SM, Choudhry NK, et al. A cohort study of thiazolidinediones and fractures in older adults with diabetes. J Clin Endocrinol Metab 2009;94:2792–8.

[44] Douglas IJ, Evans SJ, Pocock S, et al. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med 2009;6:e1000154.

[45] Sottile V, Seuwen K, Kneissel M. Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPAR γ agonist BRL49653 (rosiglitazone). Calcif Tissue Int 2004;75:329–37.

[46] Akune T, Ohba S, Kamekura S, et al. PPARγ insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest 2004;113:846–55.

[47] Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab 2006;91:3349–54.

[48] Grey A, Bolland M, Gamble G, et al. The peroxisome proliferator-activated receptor-γ agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab 2007;92:1305–10.

[49] Lazarenko OP, Rzonca SO, Hogue WR, et al. Rosiglitazone induces decreases in bone mass and strength that are reminiscent of aged bone. Endocrinology 2007;148:2669–80.

[50] Lecka-Czernik B, Gubrij I, Moerman EJ, et al. Inhibition of Osf2/Cbfa1 expression and terminal osteoblast differentiation by PPARγ2. J Cell Biochem 1999;74:357–71.

[51] McNair P, Madsbad S, Christensen MS, et al. Bone mineral loss in insulin treated diabetes mellitus: studies on pathogenesis. Acta Endocrinol 1979;90:463–72.

[52] Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. Diabetes Metab Res Rev 2004;20:196–204.

[53] Bouillon R. Diabetic bone disease. Calcif Tissue Int 1991;49:155–60.

[54] Christiansen C, Christensen MS, McNair P, et al. Vitamin D metabolites in diabetic patients: decreased serum concentration of 24,25-dihydroxyvitamin D. Scand J Clin Lab Invest 1982;42:487–91.

[55] Williams JP, Blair HC, McDonald JM, et al. Regulation of osteoclastic bone resorption by glucose. Biochem Biophys Res Commun 1997;235:646–51.

[56] Botolin S, McCabe LR. Chronic hyperglycemia modulates osteoblast gene expression through osmotic and non-osmotic pathways. J Cell Biochem 2006;99:411–24.

[57] Inaba M, Nagasue K, Okuno S, et al. Impaired secretion of parathyroid hormone, but not refractoriness of osteoblast, is a major mechanism of low bone turnover in hemodialyzed patients with diabetes mellitus. Am J Kidney Dis 2002;39:1261–9.

[58] Nisbeth U, Lindh E, Ljunghall S, et al. Increased fracture rate in diabetes mellitus and females after renal transplantation. Transplantation 1999;67:1218–22.

[59] Rix M, Andreassen H, Eskildsen P. Impact of peripheral neuropathy on bone density in patients with type 1 diabetes. Diabetes Care 1999;22:827–31.

[60] Vogt MT, Cauley JA, Kuller LH, et al. Bone mineral density and blood flow to the lower extremities: the study of osteoporotic fractures. J Bone Miner Res 1997;12:283–9.

[61] Hadjidakis D, Diamantopoulos E, Kokkinakis E, et al. Bone mineral density in type II diabetics with macroangiopathy. J Bone Miner Res 1997;12(suppl 1):S516.

[62] Meier C, Kraenzlin ME, Bodmer M, et al. Use of thiazolidinediones and fracture risk. Arch Intern Med 2008;168:820–5.

[63] Nguyen NT, Nguyen XM, Lane J, et al. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey. Obes Surg 2011;21: 351–5.

[64] Thrailkill KM, Lumpkin CKJr, Bunn RC, et al. Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. Am J Physiol Endocrinol Metab 2005;289: E735–45.