ORIGINAL RESEARCH

# Risk of Fracture with Thiazolidinediones: Disease or Drugs?

Marloes T. Bazelier · Peter Vestergaard · Arlene M. Gallagher ·
Tjeerd-Pieter van Staa · Cyrus Cooper · Hubert G. M. Leufkens ·
Frank de Vries

**Abstract** The use of thiazolidinediones (TZDs) has been associated with an increased fracture risk. In addition, type 2 diabetes mellitus (T2DM) has been linked with fracture. We evaluated to what extent the association between TZD use and fracture risk is related to the drug or to the underlying disease. We conducted a population-based cohort study using the Danish National Health Registers (1996–2007), which link pharmacy data to the national hospital registry. Oral antidiabetic users ($n = 180,049$) were matched 1:3 by year of birth and sex to nonusers. Cox proportional hazards models were used to estimate hazard ratios (HRs) of fracture. Time-dependent adjustments were made for age, comorbidity, and drug use. We created a proxy indicator for the severity of disease. The first stage was defined as current use of either a biguanide or a sulfonyluerum, the second stage as current use of a biguanide and a sulfonyluerum at the same time, the third stage as patients using TZDs, and the fourth stage as patients using insulin. The risk of osteoporotic fracture was increased 1.3-fold for stages 3 and 4 compared with controls. Risk with current TZD use (stage 3 HR = 1.27, 95 % CI 1.06–1.52) and risk with current use of insulin (stage 4 HR = 1.25, 95 % CI 1.20–1.31) were similar. In the first (HR = 1.15, 95 % CI 1.13–1.18) and second (HR = 1.00, 95 % CI 0.96–1.04) stages risks were lower. Risk of osteoporotic fracture was similar for TZD users and insulin users. When studying fracture risk with TZDs, the underlying T2DM should be taken into account.

M. T. Bazelier · A. M. Gallagher · T.-P. van Staa ·
H. G. M. Leufkens · F. de Vries
Utrecht Institute for Pharmaceutical Sciences,
Utrecht University, Utrecht, The Netherlands

P. Vestergaard
The Osteoporosis Clinic, Aarhus University Hospital,
Aarhus, Denmark

A. M. Gallagher · T.-P. van Staa
General Practice Research Database, Medicines and Healthcare
Products Regulatory Agency, London, UK

T.-P. van Staa · C. Cooper · F. de Vries
MRC Lifecourse Epidemiology Unit, University
of Southampton, Southampton, UK

C. Cooper
Institute of Musculoskeletal Sciences, University of Oxford,
Oxford, UK

F. de Vries
Department of Clinical Pharmacy and Toxicology, Maastricht
University Medical Centre, Maastricht, The Netherlands

F. de Vries (✉)
Department of Pharmacoepidemiology and Clinical
Pharmacology, Utrecht Institute for Pharmaceutical Sciences,
Utrecht University, Universiteitsweg 99, 3584 CG Utrecht,
The Netherlands
e-mail: frank@fdevries.com

Thiazolidinediones (TZDs) improve insulin sensitivity
through activation of the nuclear receptor peroxisome prolif-
erator-activated receptor gamma (PPARγ) [1]. Until recently,
both rosiglitazone and pioglitazone were frequently used in
the management of type 2 diabetes mellitus (T2DM). An
association of rosiglitazone with risk of cardiovascular out-
comes has caused withdrawal of the drug in Europe and
restricted access in the United States [2]. Pioglitazone is still
used in the management of later stages of T2DM and has ben-
efits in patients with a recent acute myocardial infarction [3].

Various studies have found that TZD use leads to
decreased bone mineral density (BMD) and an elevated
risk of fracture [4–10]. TZDs affect the differentiation of
mesenchymal stem cells, leading to increased adipogenesis
at the expense of the formation of osteoblasts [4, 5]. The
use of TZDs in rodents has been linked with adverse
skeletal effects [6, 7]. In humans, TZD use has also been
associated with adverse skeletal outcomes, at least in
women with T2DM: women who were exposed to TZDs
for 3–4 months had significantly reduced BMD at the
lumbar spine and hip in two randomized controlled trials
[8, 9]. Moreover, a meta-analysis from ten randomized
controlled trials showed that rosiglitazone and pioglitazone
significantly increased the risk of fractures [odds ratio
(OR) = 1.45, 95 % confidence interval (CI) 1.18–1.79]
[10]. In observational studies, the relationship between
TZD use and fracture risk has also been reported [11–14].

Not only the use of TZDs but also underlying T2DM has
been associated with fracture [15, 16]. Among the potential
mechanisms are direct effects of high glucose levels on
bone turnover [17], increased urine calcium loss [18],
changes in vitamin D metabolism [19], and alterations in
glycosylation of collagen caused by hyperglycemia [20]. In
addition, complications of diabetes such as renal failure,
neuropathy, and micro- and macro-angopathy may con-
tribute to fracture risk [21–24].

At present, it is unclear to what extent the association
between TZD use and fracture risk is related to the drug or to
the underlying disease. The aim of this study was to estimate
risk of fracture in diabetic patients compared with controls,
stratified by the use of TZDs and by disease severity.

## Methods

### Data Source

In Denmark, separate registers of computerized medical
records on all contacts to hospitals and on the use of drugs
can be linked for the entire population (approximately 5.5
million inhabitants). The Ministry of the interior keeps
records of all inhabitants, including their migrations and
dates of birth and death. Information on hospital admis-
sions comes from the National Hospital Discharge Register
[25], which covers all inpatient contacts from 1977
onwards and from 1995 also all outpatient visits to hospi-
tals, outpatient clinics, and emergency rooms. Upon dis-
charge, the physician codes the reason for the contact using
the ICD system. The register has an almost 100 % capture
of contacts, and the validity of registrations is high [26].
The Danish Medicines Agency keeps a nationwide register
of all prescription drugs sold at pharmacies throughout the
country from 1996 onward, the National Pharmacological
Database (www.dkma.dk). All prescriptions are registered
with ATC code, dosage, and date. As all sales are regis-
tered to the individual who redeems the prescription, the
capture and validity are high. All registers can be linked
through the use of a person-specific code (the civil person
number) given to all inhabitants and can be used for all of
the registrations mentioned.

### Study Population

The exposed cohort consisted of all patients (aged 18+)
with at least one prescription of oral antidiabetic (OAD)
medication between 1996 and 2007. Each OAD drug user
was matched to up to three patients by exact year of birth
and sex. Controls did not have an antidiabetic (OAD or
insulin) prescription any time during follow-up. The date of
the first OAD prescription defined the index date, and
controls were assigned the same index date as their mat-
ched OAD drug user. All participants were then followed
from their index date to the end of data collection, emi-
gration, or the patient's death, whichever came first.

### Exposure

The total period of follow-up for each patient was divided
into periods of current exposure and past exposure, with
patients moving between current and past use. Each period
of current exposure started with an OAD or insulin pre-
scription and ended 3 months after the expected duration of
antidiabetic (AD) therapy or on the date that a new AD
drug was prescribed within this period. The expected
duration of OAD therapy was defined as the median
expected duration of treatment, based on all OAD pre-
scriptions. For insulin treatment, the median time between
two insulin injections (based on all insulin prescriptions)
was taken as the expected duration of use.

At the start of each interval, patients were classified as
current users of AD medication if they had an AD pre-
scription on that start date or in the 3 months before.

Current user status was determined for five different groups of AD medication: biguanides, sulfonyluerum, TZDs, insulin, and other ADs [including dipeptidyl peptidase-4 (DPP-4) inhibitors, glinides, glucagon-like peptide-1 (GLP-1) analogs and α-glucosidase inhibitors]. For controls, the total period of follow-up was divided into periods of 6 months.

We created a proxy indicator for the severity of disease in diabetic patients. The first stage of disease was defined as current use of either a biguanide or a sulfonyluerum, the second stage comprised current users of a biguanide and a sulfonyluerum at the same time, the third stage was assigned to patients using TZDs (regardless of comedication), and the fourth stage was assigned to patients using insulin (regardless of comedication and not exposed to TZDs).

### Study Outcomes

Patients were followed up for the occurrence of a first fracture. Types of fracture were classified according to the International Classification of Diseases (ICD-10) categories. These included skull (S02), neck (S12), ribs (S22), pelvis (S32), shoulder (S42), forearm (S52), hand (S62), hip/femur (S72), tibia/fibula/ankle (S82), foot (S92), or unspecified (T02, T08, T10, T12). A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, vertebrae, femur, hip, humerus, pelvis, or ribs.

### Risk Factors

The presence of risk factors was assessed by reviewing the computerized medical records for any evidence of risk factors before the start of each interval. Potential confounders that were determined at baseline were sex and a history of fracture. For a time-dependent analysis we considered age, a history of chronic diseases (rheumatoid arthritis, congestive heart failure, asthma, epilepsy, cerebrovascular disease, noninfectious enteritis and colitis, dementia, renal failure, diabetic retinopathy, hyperparathyroidism), as well as a prescription for thiazide diuretics, estrogen-containing hormone replacement therapy, statins, oral glucocorticoids, bisphosphonates, calcium, vitamin D, antipsychotics, antidepressants, antiarrhythmics, hypnotics/anxiolytics, anticonvulsants, opioids, and asthma medication in the previous 6 months as potential confounders.

### Statistical Analysis

Cox proportional hazards analysis was used. In the first analysis, we compared fracture risk in users of TZDs with that in control patients (without diabetes) and users of other AD medication. In this analysis, calculations were adjusted

for all potential confounders that changed the hazard ratio (HR) >1 % in an age-/sex-adjusted analysis. Secondly, we studied the risk of osteoporotic fracture in current AD drug users versus controls, using the proxy indicator for severity of disease. To investigate whether a dose-response relationship was apparent, we stratified the risk of osteoporotic fracture in current TZD users by number of TZD prescriptions ever before. Wald tests were used to examine if there were significant differences between differently exposed groups. All data management and statistical analyzes were conducted using SAS 9.1/9.2 software (SAS Institute, Cary, NC).

### Results

Our study population included 180,049 diabetic patients and 490,147 population-based controls. Mean age at index date (first OAD prescription) was 62.6 years, and 47 % of all patients were female. Mean duration of follow-up after the index date was 5.3 years for diabetic patients and 6.2 years for controls. Further baseline characteristics are shown in Table 1. During the study period, 4.2 % of diabetic patients were prescribed a TZD at least once (Table 2). Of all diabetic patients, 12.8 % suffered from a fracture after the index date. Hip fractures (3.1 %) and radius/ulna fractures (2.2 %) were common.

Table 3 shows that current TZD users had an increased risk of fracture versus nondiabetic patients (HR = 1.29, 95 % CI 1.13–1.49) but no increased risk of fracture versus patients who were exposed to other AD drugs (HR = 1.11, 95 % CI 0.97–1.27). When compared with other AD drug users, the risk of fracture with current TZD use was, however, increased in women (HR = 1.30, 95 % CI 1.10–1.54) and risks of foot/ankle fractures (HR = 1.54, 95 % CI 1.17–2.04) and tibia/fibula fractures (HR = 1.70, 95 % CI 1.22–2.37) were significantly increased. No increased risk of hip fracture was apparent for current users of TZDs.

When we stratified current AD drug users by the proxy indicator of disease severity, we found that the risk of osteoporotic fracture was 1.3-fold increased for stages 3 and 4 compared with nondiabetic patients (Table 4). Patients who were currently using TZDs (stage 3 HR = 1.27, 95 % CI 1.06–1.52) had a similar risk of osteoporotic fracture as patients who were currently using insulin (stage 4 HR = 1.25, 95 % CI 1.20–1.31). In women only, we found a similar result using the proxy indicator of disease severity. The risk in stage 3 was slightly higher than that in stage 4, but this difference was not significant based on a Wald test (stage 1 fully adjusted HR = 1.11, 95 % CI 1.07–1.14; stage 2 HR = 0.98, 95 % CI 0.93–1.04; stage 3 HR = 1.34, 95 % CI 1.07–1.67; stage 4 HR = 1.17, 95 % CI 1.10–1.23). In men only, the risk in stage 3 was not

**Table 1** Baseline characteristics of diabetic patients and controls

| Characteristic | Diabetic patients (%) (n = 180,049) | Controls (%) (n = 490,147) |
|---|---|---|
| Mean duration of follow-up after index date, years | 5.3 | 6.2 |
| Sex female | 84,665 (47.0) | 232,373 (47.4) |
| Age at index date | | |
| Mean | 62.6 | 62.5 |
| By category | | |
| 18–29 | 4,064 (2.3) | 10,174 (2.1) |
| 30–39 | 8,164 (4.5) | 21,029 (4.3) |
| 40–49 | 18,887 (10.5) | 50,622 (10.3) |
| 50–59 | 39,944 (22.2) | 111,053 (22.7) |
| 60–69 | 47,288 (26.3) | 133,197 (27.2) |
| 70–79 | 40,586 (22.5) | 111,448 (22.7) |
| 80+ | 21,116 (11.7) | 52,624 (10.7) |
| History of comorbidity | | |
| Fracture | 30,631 (17.0) | 80,127 (16.3) |
| Asthma | 5,706 (3.2) | 9,126 (1.9) |
| Rheumatoid arthritis | 2,232 (1.2) | 5,188 (1.1) |
| Cerebrovascular disease | 15,084 (8.4) | 22,155 (4.5) |
| Epilepsy | 2,615 (1.5) | 5,960 (1.2) |
| History of drug use | | |
| Statins | 24,014 (13.3) | 24,649 (5.0) |
| Antiarrhythmics | 1,517 (0.8) | 2,563 (0.5) |
| Antidepressants | 26,774 (14.9) | 52,861 (10.8) |
| Antipsychotics | 13,232 (7.3) | 21,813 (4.5) |
| Anxiolytics/hypnotics | 51,984 (28.9) | 119,634 (24.4) |
| Anticonvulsants | 6,078 (3.4) | 12,410 (2.5) |
| Opioids | 41,930 (23.3) | 78,901 (16.1) |
| Oral glucocorticoids | 26,645 (14.8) | 54,170 (11.1) |
| Bisphosphonates | 1,668 (0.9) | 6,368 (1.3) |

**Table 2** Use of AD medication and patients with fractures during follow-up

| Characteristic | Diabetic patients (%) (n = 180,049) | Controls (%) (n = 490,147) |
|---|---|---|
| Use of AD medication any time during follow-up | | |
| Biguanide | 122,751 (68.2) | – |
| sulfonyluerum | 137,326 (76.3) | – |
| TZD | 7,603 (4.2) | – |
| Insulin | 42,525 (23.6) | – |
| Other | 17,865 (9.9) | – |
| Any fracture | 22,978 (12.8) | 66,401 (13.5) |
| Foot/ankle | 3,180 (1.8) | 8,003 (1.6) |
| Tibia/fibula | 2,274 (1.3) | 5,552 (1.1) |
| Hand/wrist | 2,694 (1.5) | 8,187 (1.7) |
| Osteoporotic | 14,910 (8.3) | 44,031 (9.0) |
| Hip | 5,642 (3.1) | 15,166 (3.1) |
| Vertebral | 1,221 (0.7) | 3,341 (0.7) |
| Radius/ulna | 3,884 (2.2) | 15,138 (3.1) |
| Humerus | 2,926 (1.6) | 7,121 (1.5) |
| Ribs | 772 (0.4) | 2,087 (0.4) |

*TZD* thiazolidinedione, *AD* antidiabetic

significantly increased (stage 1 fully adjusted HR = 1.25, 95 % CI 1.20–1.31; stage 2 HR = 1.02, 95 % CI 0.94–1.10; stage 3 HR = 1.13, 95 % CI 0.82–1.57; stage 4 HR = 1.41, 95 % CI 1.31–1.52). In men, the risk in stage 3 was not significantly different from the risk in stage 4 either.

Stratification of current TZD users by the number of TZD prescriptions ever before showed a cumulative dose–response relationship (Table 5). Current TZD users with 30 or more TZD presciptions ever before had a threefold increased risk of osteoporotic fracture compared with other AD drug users (HR = 3.03, 95 % CI 2.03–4.52).

## Discussion

This study showed a 1.3-fold increased risk of fracture in current TZD users versus nondiabetic patients. Overall, current TZD users had no significantly increased risk of fracture compared with users of other AD drugs. The risk of fracture with current TZD use was, however, increased in women, among prolonged users of TZDs, and risks of foot/ankle and tibia/fibula fractures were significantly increased.

Our finding of an increased risk of fracture in women using TZDs versus other AD drug users is in line with previous studies. In a meta-analysis from randomized controlled trials [10], the pooled data from the five trials that reported fracture risk by sex showed a significantly increased risk of fractures among women (OR = 2.23, 95 % CI 1.65–3.01) but not among men (OR = 1.00, 95 % CI 0.73–1.39). Another recent trial on rosiglitazone use presented a similar result: there was an increased fracture risk in women (RR = 1.82, 95 % CI 1.37–2.41) but not in men (RR = 1.23, 95 % CI 0.85–1.77) [27]. In observational studies, the use of TZDs has also been linked with an increase in fracture risk [12–14]. Habib et al. [12] found in their cohort study that TZD use was associated with a 1.6-fold increased risk of fracture in women but not in men. Conversely, Douglas et al. [13] reported an increased risk of fracture in both women and men who were exposed to TZDs. In a nested case–control study [11] an increased risk of fracture with TZD use was only apparent in the group with cumulative exposure of 15 TZD prescriptions or more (HR = 2.86, 95 % CI 1.57–5.22). This result is in line with

**Table 3** Risk of fracture in current TZD users compared with nondiabetic patients and with other AD drug users, by type of fracture and sex

| | Current TZD users versus nondiabetic patients | | | Current TZD users versus other AD drug users | | |
|---|---|---|---|---|---|---|
| | Fracture, $n$ | Age-/sex-adj. HR (95 % CI) | Fully adj. HR (95 % CI) | Fracture, $n$ | Age-/sex-adj. HR (95 % CI) | Fully adj. HR (95 % CI) |
| No TZD use | 66,401 | | | 21,202 | | |
| Current TZD use | | | | | | |
| Any fracture | 213 | 1.24 (1.09–1.42) | 1.29 (1.13–1.49)[a] | 213 | 1.03 (0.90–1.18) | 1.11 (0.97–1.27)[h] |
| Foot/ankle | 52 | 1.96 (1.49–2.58) | 1.84 (1.38–2.44)[b] | 52 | 1.50 (1.14–1.98) | 1.54 (1.17–2.04)[i] |
| Tibia/fibula | 36 | 2.18 (1.57–3.03) | 2.14 (1.52–3.02)[c] | 36 | 1.64 (1.17–2.28) | 1.70 (1.22–2.37)[i] |
| Hand/wrist | 22 | 0.83 (0.55–1.27) | 0.82 (0.54–1.24)[d] | 22 | 0.76 (0.50–1.16) | 0.79 (0.52–1.20)[i] |
| Osteoporotic | 116 | 1.21 (1.01–1.45) | 1.28 (1.06–1.54)[a] | 116 | 0.98 (0.81–1.18) | 1.07 (0.89–1.29)[j] |
| Hip | 19 | 0.80 (0.51–1.26) | 0.89 (0.57–1.39)[e] | 19 | 0.53 (0.34–0.84) | 0.61 (0.39–0.96)[k] |
| Femur | 2 | –[n] | | 2 | –[n] | |
| Vertebral | 11 | 1.44 (0.80–2.61) | 1.67 (0.92–3.03)[f] | 11 | 1.00 (0.55–1.81) | 1.12 (0.62–2.04)[e] |
| Radius/ulna | 43 | 1.11 (0.82–1.50) | 1.10 (0.81–1.48)[d] | 43 | 1.23 (0.91–1.67) | 1.27 (0.94–1.73)[i] |
| Humerus | 28 | 1.64 (1.13–2.38) | 1.60 (1.09–2.36)[a] | 28 | 1.08 (0.75–1.58) | 1.16 (0.80–1.69)[l] |
| Pelvis | 3 | –[n] | | 3 | –[n] | |
| Ribs | 11 | 1.85 (1.02–3.35) | 1.87 (1.01–3.48)[g] | 11 | 1.38 (0.76–2.52) | 1.47 (0.81–2.68)[m] |
| By sex | | | | | | |
| Male[o] | 74 | 0.99 (0.79–1.24) | 1.06 (0.84–1.34) | 74 | 0.79 (0.63–1.00) | 0.86 (0.68–1.09) |
| Female[p] | 139 | 1.43 (1.21–1.69) | 1.46 (1.23–1.73) | 139 | 1.22 (1.03–1.44) | 1.30 (1.10–1.54) |

*TZD* thiazolidinedione, *AD* antidiabetic, *adj* adjusted, *HR* hazard ratio, *CI* confidence interval

[a] Adjusted for age; gender; use of statins, bisphosphonates, antidepressants, or opioids in the previous 6 months; history of fracture; and diabetic retinopathy

[b] Adjusted for age; gender; use of statins, antidepressants, or opioids in the previous 6 months; history of fracture; and diabetic retinopathy

[c] Adjusted for age; gender; use of statins, antidepressants, anticonvulsants, or opioids in the previous 6 months; history of fracture; and diabetic retinopathy

[d] Adjusted for age, gender, use of antidepressants or opioids in the previous 6 months, and history of fracture

[e] Adjusted for age; gender; use of statins, bisphosphonates, antidepressants, or opioids in the previous 6 months; history of fracture; and cerebrovascular disease

[f] Adjusted for age; gender; use of statins, bisphosphonates, antidepressants, or opioids in the previous 6 months; history of fracture; diabetic retinopathy; and cerebrovascular disease

[g] Adjusted for age; gender; use of statins, bisphosphonates, antidepressants, hypnotics/anxiolytics, anticonvulsants, or opioids in the previous 6 months; history of fracture; diabetic retinopathy; and cerebrovascular disease

[h] Adjusted for age, gender, use of statins or antidepressants in the previous 6 months, history of fracture, and cerebrovascular disease

[i] Adjusted for age, gender, use of statins in the previous 6 months, and history of fracture

[j] Adjusted for age; gender; use of statins, antidepressants, or opioids in the previous 6 months; history of fracture; and cerebrovascular disease

[k] Adjusted for age; gender; use of statins, antipsychotics, antidepressants, or opioids in the previous 6 months; history of fracture; cerebrovascular disease; and dementia

[l] Adjusted for age; gender; use of statins, antipsychotics, or antidepressants in the previous 6 months; history of fracture; and cerebrovascular disease

[m] Adjusted for age, gender, use of statins or antidepressants in the previous 6 months, and history of fracture

[n] Number of cases too low to estimate HR

[o] Male TZD users versus male nonusers

[p] Female TZD users versus female nonusers

our finding of a significantly increased risk of osteoporotic fracture for current TZD users in the stratum with highest cumulative exposure.

The association between TZD use and fracture risk may be explained by the drug itself but also by the underlying disease because both T2DM and the use of TZDs seem to be independently associated with an increased risk of adverse skeletal effects. There is substantial evidence from in vitro studies that activation of PPARγ, which is stimulated by TZDs, causes a predominant formation of adipocytes from mesenchymal stem cells, while the development of osteoblasts is suppressed [4, 5]. Moreover, BMD was

**Table 4** Risk of osteoporotic fracture in current AD drug users compared with controls, by stage of disease

| | Fracture, n | Age-/sex-adj. HR (95 % CI) | Fully adj. HR (95 % CI)[a] |
|---|---|---|---|
| No diabetes | 44,031 | 1 | 1 |
| Current AD drug use | 13,989 | 1.21 (1.18–1.23) | 1.14 (1.12–1.16) |
| By stage of disease | | | |
| Stage 1: current use of biguanide or sulfonyluerum | 8,866 | 1.23 (1.20–1.26)[b,c] | 1.15 (1.13–1.18)[b,c] |
| Stage 2: current use of biguanide and sulfonyluerum | 2,222 | 1.01 (0.97–1.05)[d] | 1.00 (0.96–1.04)[d,e] |
| Stage 3: current use of TZD[f] | 116 | 1.20 (1.00–1.44) | 1.27 (1.06–1.52) |
| Stage 4: current use of insulin[g] | 2,419 | 1.37 (1.32–1.43) | 1.25 (1.20–1.31) |
| Unclassified stages | 366 | 1.14 (1.03–1.26) | 1.11 (1.00–1.23) |

*TZD* thiazolidinedione, *AD* antidiabetic, *adj* adjusted, *HR* hazard ratio, *CI* confidence interval

[a] Adjusted for age; gender; use of statins, antipsychotics, antidepressants, or opioids in the previous 6 months; history of fracture; diabetic retinopathy; congestive heart failure; and cerebrovascular disease

[b] Statistically significant difference ($p < 0.05$) between current AD users in stage 1 and current AD users in stage 2, based on Wald test

[c] Statistically significant difference ($p < 0.05$) between current AD users in stage 1 and current AD users in stage 4, based on Wald test

[d] Statistically significant difference ($p < 0.05$) between current AD users in stage 2 and current AD users in stage 4, based on Wald test

[e] Statistically significant difference ($p < 0.05$) between current AD users in stage 2 and current AD users in stage 3, based on Wald test

[f] Regardless of comedication

[g] Regardless of comedication and not exposed to TZDs

**Table 5** Risk of osteoporotic fracture in current TZD users compared with other AD drug users, by number of TZD prescriptions

| | Fracture, n | Age-/sex-adj. HR (95 % CI) | Fully adj. HR (95 % CI)[a] |
|---|---|---|---|
| No TZD use | 13,873 | | |
| Current TZD use | 116 | 0.98 (0.81–1.18) | 1.07 (0.89–1.29) |
| By number of TZD prescriptions ever before | | | |
| 1–4 | 27 | 0.80 (0.55–1.17) | 0.87 (0.59–1.26) |
| 5–8 | 17 | 0.70 (0.44–1.13) | 0.76 (0.47–1.23) |
| 9–14 | 20 | 0.80 (0.52–1.24) | 0.88 (0.57–1.37) |
| 15–29 | 28 | 1.05 (0.72–1.52) | 1.16 (0.80–1.68) |
| ≥30 | 24 | 2.70 (1.81–4.02) | 3.03 (2.03–4.52)[b] |

*TZD* thiazolidinedione, *AD* antidiabetic, *adj* adjusted, *HR* hazard ratio, *CI* confidence interval

[a] Adjusted for age; gender; use of statins, antidepressants, or opioids in the previous 6 months; history of fracture; and cerebrovascular disease

[b] Statistically significant difference ($p < 0.05$) between current TZD users with ≥30 TZD prescriptions ever before and all of the other categories, based on Wald test

significantly reduced at the lumbar spine and hip in women exposed to TZDs in two randomized controlled trials [8, 9].

In addition, epidemiological studies suggest that T2DM is an independent risk factor for adverse effects on the skeleton [15, 16]. Even though patients with T2DM have on average a higher BMI [28] as well as a higher BMD [16] compared with the general population, which would in theory protect them against fractures, previous studies have found an increased risk of fractures in T2DM [15]. This finding may be explained by different mechanisms. High blood glucose might have a direct toxic effect on bone cells [17, 29] and may cause a negative calcium balance by increased urinary calcium excretion [18] and reduced intestinal calcium absorption [30]. There is evidence that

vitamin D metabolism is altered in diabetic patients [19, 31], which may lead to bone loss. Further, functional hypoparathyroidism may result in low bone turnover [32]. Complications of diabetes, such as neuropathy and angiopathy, may also contribute to an increased risk of fracture as well as disease severity in general [21–24].

To evaluate to what extent the association between TZD use and fracture risk is related to the drug or to the underlying disease, we created a proxy indicator of disease severity. We defined four different stages based on a prescription scenario that is often used in the treatment of T2DM. Patients who were currently using insulin (stage 4) had a significantly greater risk of osteoporotic fracture than patients in stages 1 and 2, which supports the hypothesis that the underlying

disease is involved. If the drug itself were strongly related to fracture risk, we would expect a higher risk in patients who were currently exposed to TZDs (stage 3). However, patients in stage 3 had a similar risk of osteoporotic fracture as patients in stage 4. Therefore, we would argue that the association between TZD use and fracture is at least partially confounded by the underlying disease.

Strengths of our study include a reasonable sample size and duration of follow-up. Our source population included the total Danish population, and controls were therefore population-based. There was detailed longitudinal information on drug prescribing.

There are several limitations. Data on smoking and body mass index (BMI) were not available, and therefore, unmeasured confounding may have biased our findings. Patients with T2DM have on average a higher BMI than the general population [28], which is protective against fracture [33]. In our study, this may have led to underestimation of a true association between T2DM/TZD use and fracture. However, we did adjust our analyzes for the use of statins, which is probably correlated with high BMI. Using a proxy indicator of disease severity, we may have underestimated the role of the underlying T2DM as a confounder in the association between TZD use and fracture. We used current treatment with insulin as a proxy indicator for the highest level of disease severity (stage 4). The risk of fracture for patients in this stage may be biased by potential direct effects of insulin on bone. Although the role of insulin on fracture risk is still unclear, it has been suggested that higher insulin levels in T2DM may preserve and increase bone density and bone strength [30, 34]. If insulin were indeed protective against fractures, this may have resulted in underestimation of a true association between disease severity and fracture risk.

In conclusion, we found that patients who were currently using TZDs had a similar risk of osteoporotic fracture as patients who were currently using insulin. When observational studies assess the risk of fracture in patients using TZDs, the underlying T2DM should be taken into account.

# References

1. Yki-Jarvinen H (2004) Thiazolidinediones. N Engl J Med 351:1106–1118

2. Schernthaner G, Chilton RJ (2010) Cardiovascular risk and thiazolidinediones—what do meta-analyses really tell us? Diabetes Obes Metab 12(12):1023–1035

3. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM, PROactive Investigators (2007) The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) study. J Am Coll Cardiol 49(17):1772–1780

4. Grey A (2008) Skeletal consequences of thiazolidinedione therapy. Osteoporos Int 19(2):129–137

5. Benvenuti S, Cellai I, Luciani P, Deledda C, Baglioni S, Giuliani C, Saccardi R, Mazzanti B, Dal Pozzo S, Mannucci E, Peri A, Serio M (2007) Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells. J Endocrinol Invest 30(9):RC26–RC30

6. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL (2005) Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. Endocrinology 146(3):1226–1235

7. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B (2004) Bone is a target for the AD compound rosiglitazone. Endocrinology 145(1):401–406

8. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR (2007) The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab 92(4):1305–1310

9. Glintborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP (2008) Association of pioglitazone treatment with decreased bone mineral density in obese premenopausal patients with polycystic ovary syndrome: a randomized, placebo-controlled trial. J Clin Endocrinol Metab 93(5):1696–1701

10. Loke YK, Singh S, Furberg CD (2009) Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ 180(1):32–39

11. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR (2008) Use of thiazolidinediones and fracture risk. Arch Intern Med 168(8):820–825

12. Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, Williams LK (2010) Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 95(2):592–600

13. Douglas IJ, Evans SJ, Pocock S, Smeeth L (2009) The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med 6(9):e1000154

14. Solomon DH, Cadarette SM, Choudhry NK, Canning C, Levin R, Stürmer T (2009) A cohort study of thiazolidinediones and fractures in older adults with diabetes. J Clin Endocrinol Metab 94(8):2792–2798

15. Janghorbani M, Van Dam RM, Willett WC, Hu FB (2007) Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 166(5):495–505

16. Vestergaard P (2007) Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int 18(4):427–444

17. Williams JP, Blair HC, McDonald JM, McKenna MA, Jordan SE, Williford J, Hardy RW (1997) Regulation of osteoclastic bone resorption by glucose. Biochem Biophys Res Commun 235(3):646–651

18. McNair P, Madsbad S, Christensen MS, Christiansen C, Faber OK, Binder C, Transbøl I (1979) Bone mineral loss in insulin-treated diabetes mellitus: studies on pathogenesis. Acta Endocrinol 90:463–472

19. Bouillon R (1991) Diabetic bone disease. Calcif Tissue Int 49(3):155–160

20. Yamagishi S, Nakamura K, Inoue H (2005) Possible participation of advanced glycation end products in the pathogenesis of osteoporosis in diabetic patients. Med Hypotheses 65(6):1013–1015

21. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellström B (1999) Increased fracture rate in diabetes mellitus and females after renal transplantation. Transplantation 67(9):1218–1222

22. Rix M, Andreassen H, Eskildsen P (1999) Impact of peripheral neuropathy on bone density in patients with type 1 diabetes. Diabetes Care 22(5):827–831

23. Vogt MT, Cauley JA, Kuller LH, Nevitt MC (1997) Bone mineral density and blood flow to the lower extremities: the study of osteoporotic fractures. J Bone Miner Res 12(2):283–289

24. Hadjidakis D, Diamantopoulos E, Kokkinakis E, Sfakianakis M, Merakos G, Raptis SA (1997) Bone mineral density in type II diabetics with macroangiopathy. J Bone Miner Res 12(Suppl 1):S516

25. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH (1999) The Danish national hospital register. A valuable source of data for modern health sciences. Dan Med Bull 46(3):263–268

26. Mosbech J, Jørgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen TD (1995) The national patient registry. Evaluation of data quality. Ugeskr Laeg 157(26):3741–3745

27. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, RECORD Study Team (2009) Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 373(9681):2125–2135

28. Nguyen NT, Nguyen XM, Lane J, Wang P (2011) Relationship between obesity and diabetes in a US adult population: findings from the national health and nutrition examination survey, 1999–2006. Obes Surg 21(3):351–355

29. Botolin S, McCabe LR (2006) Chronic hyperglycemia modulates osteoblast gene expression through osmotic and non-osmotic pathways. J Cell Biochem 99(2):411–424

30. Carnevale V, Romagnoli E, D'Erasmo E (2004) Skeletal involvement in patients with diabetes mellitus. Diabetes Metab Res Rev 20(3):196–204

31. Christiansen C, Christensen MS, McNair P, Nielsen B, Madsbad S (1982) Vitamin D metabolites in diabetic patients: decreased serum concentration of 24,25-dihydroxyvitamin D. Scand J Clin Lab Invest 42(6):487–491

32. Inaba M, Nagasue K, Okuno S, Ueda M, Kumeda Y, Imanishi Y, Shoji T, Ishimura E, Ohta T, Nakatani T, Kim M, Nishizawa Y (2002) 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 39(6):1261–1269

33. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19(4):385–397

34. Thrailkill KM, Lumpkin CK Jr, Bunn RC, Kemp SF, Fowlkes JL (2005) Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. Am J Physiol Endocrinol Metab 289(5):E735–E745