Chronic Use of Thiazolidinediones Increases Fracture Risk

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

Study Overview

Objective. To examine whether the use of thiazolidinediones (TZDs) is associated with an increased risk of fracture.

Design. Population-based, nested case-control study using data from the UK-based General Practice Research Database, which contains data on 5 million patients enrolled with selected general practitioners in the United Kingdom.

Setting and participants. Individuals were included if they were aged 30 to 79 years, diagnosed with type 2 diabetes, and received ≥ 1 prescription for a TZD, sulfonylurea derivative, biguanide metformin, acarbose, or prandial glucose regulator (with or without concomitant insulin use) between January 1994 and December 2005. Patients with < 3 years of records in the database before the first prescription or diagnosis of diabetes were excluded. Among patients who met inclusion criteria, those with a first-time diagnosis of a low-trauma fracture were identified and matched by age, sex, and medical setting with up to 4 nonfracture patients. Patients with a diagnosis of Paget's disease, osteoporosis, or osteomalacia and those who used bisphosphonates were excluded.

Main outcome measures. Incidence of fractures and the use of TZDs, other oral antidiabetic agents, or insulin. Duration of use of oral antidiabetic agents was classified by number of prescriptions: for TZDs, 1 to 7, 8 to 14, or ≥ 15; for insulin, prandial glucose regulators, and acarbose, 1 to 9, 10 to 19, 20 to 29, or ≥ 30; and for sulfonylureas and metformin, 1 to 9, 10 to 19, 20 to 29, 30 to 39, or ≥ 40.

Main results. Of 66,696 diabetic patients, 50,048 received ≥ 1 prescription for ≥ 1 study drug. 1020 patients with fracture and 3728 matched controls were identified, and of these patients, 208 and 762, respectively, did not use any oral antidiabetic drugs or insulin. After adjusting for the use of other antidiabetic agents, smoking, body mass index, comorbidities, and comedication, the odds ratio (OR) for developing fracture associated with the use of 1 to 7, 8 to 14, and ≥ 15 TZD prescriptions, compared with nonuse of TZDs, was 0.93 (95% confidence interval [CI], 0.57–1.52), 1.55 (95% CI, 0.81–2.94), and 2.07 (95% CI, 1.21–3.56), respectively. The adjusted OR for current use of ≥ 8 TZD prescriptions compared with nonuse was 2.43 (95% CI, 1.49–3.95). After stratifying current users of ≥ 8 TZD prescriptions by sex and age, adjusted ORs were 2.50 (95% CI, 0.84–7.41) for men, 2.56 (95% CI, 1.43–4.58) for women, 2.96 (95% CI, 1.40–6.25) for patients younger than 70 years, and 2.57 (95% CI, 1.22–5.40) for patients 70 years and older.

Conclusion. There was a significantly elevated risk of osteoporotic nonvertebral fractures with long-term use of TZDs in patients with type 2 diabetes.

Commentary

Basic science studies have found that TZDs can reduce osteoblastic activity and increase osteoclast numbers, similar to the effects of long-term corticosteroid use. This study by Meier et al builds upon clinical evidence that TZDs can accelerate bone loss and increase the incidence of fractures for patients with diabetes on chronic therapy. TZDs account for 21% of oral antidiabetic drug prescriptions in the United States [1]. The use of TZDs is controversial based on recent studies suggesting an increased risk of myocardial infarction and death from cardiovascular causes specifically associated with rosiglitazone [2]. As a result, many providers have voluntarily removed rosiglitazone from formularies and patients have changed to other agents.

This study was well-designed and benefitted from comprehensive medication and outcome data included in the General Practice Research Database. Because controls were chosen from the same population, the effects of subtle confounders were greatly reduced. The overall strength and power of the study is demonstrated by the consistency of results seen across various groups within the study population.

This study is potentially limited by the screening methods used to identify fractures within the database. Missed or underestimated subclinical fractures (eg, vertebral fractures) in the non-TZD group could lessen the overall OR among patients using TZDs. This study may also have missed potential confounders that predisposed patients to develop fractures as well as undergo treatment with TZDs, such as more severe diabetes. However, given the representative study population, the consistency of increased risk across demographic groups, and the apparent dose-related effect, the conclusions appear to be quite strong.

Applications for Clinical Practice

Providers could consider reserving TZDs as second-line agents based on the recent evidence indicating increased cardiovascular morbidity [2], equivalence with regard to glycemic control and lipids with less expensive therapies [3], and effects on bone loss and fractures. The widely publicized results of trials related to TZDs often result in complicated shared decision making. A thoughtful approach to communicating these risks and weighing them against the benefits of therapy is invaluable when talking to patients.

—Review by Marc M. Triola, MD

References

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3. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus [published erratum appears in Ann Intern Med 2007;147:887]. Ann Intern Med 2007;147:386–99.