

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Thiazolidinediones and fracture risk

Concern has arisen recently regarding the potential for thiazolidinediones (rosiglitazone and pioglitazone, sometimes referred to as “glitazones”) to increase fracture risk. This has predominantly been due to results from the ADOPT trial, summarised below:

ADOPT (A Diabetes Outcome Progression Trial) was a four year randomized controlled trial comparing rosiglitazone, metformin and glibenclamide as initial treatment for 4360 patients recently diagnosed with type 2 diabetes. In publishing the results of this trial, the authors noted a post hoc finding of a higher rate of fractures in the group receiving rosiglitazone. Fracture risk was increased significantly in women (but not in men) in the rosiglitazone group. Risk was particularly increased for upper limb fractures involving the humerus and hand, and for lower limb fractures involving the foot. Overall 9.3% of women on rosiglitazone experienced fractures compared with 5.08% receiving metformin and 3.47% treated with glibenclamide ( $p < 0.01$  for comparison with rosiglitazone with both agents).

The manufacturers of rosiglitazone and pioglitazone have issued letters to health care providers warning of an increased risk of fracture in women. For rosiglitazone, GlaxoSmithKline described concerns arising from the ADOPT trial, as outlined above. GlaxoSmithKline also stated that an independent safety committee reviewed an interim analysis of fractures in another large ongoing long term controlled rosiglitazone clinical trial, and found results consistent with ADOPT in regard to fracture risk. For pioglitazone, Takeda stated that they had undertaken an analysis of their clinical trial database and found more fractures in females taking pioglitazone (1.9 fractures per 100 patient years) compared to that with a comparator (1.1 fractures per 100 patient years). The majority of fractures were distal upper limb (forearm, hand and wrist) and distal lower limb (foot, ankle, fibula and tibia).

Some limited data from observational studies and a small randomised controlled trial suggest a potential detrimental effect of thiazolidinediones on bone mineral density.

### *Proposed mechanism*

Thiazolidinediones activate the peroxisome proliferator activated receptor gamma, which as well as improving insulin sensitivity, influences the lineage allocation of mesenchymal stem cells in the bone marrow. With thiazolidinedione treatment, mesenchymal stem cells are increasingly allocated towards adipocytes, and differentiation toward osteoblasts is decreased. This results in a decrease in osteoblastogenesis, resulting in reduced bone formation.

It is important to note that observational data suggests that patients with type 2 diabetes are themselves at increased risk of fracture compared with people without type 2 diabetes (independent of thiazolidinedione use).

### *Recommendations*

Until more data is available, consider the potential for increased bone loss and fracture risk with thiazolidinedione use. Screening is appropriate for patients at greatest risk for osteoporosis and fracture. Assessment of bone mineral density is particularly warranted for postmenopausal women receiving thiazolidinedione treatment.

References are available on request.

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**FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: [chris.alderman@rgh.sa.gov.au](mailto:chris.alderman@rgh.sa.gov.au)**  
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