Thiazolidinediones and Bone Disease

This department covers selected points from the 2009 Endocrine Update:
A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
Program Chairs: Aliya Khan, MD, FRCPC, FACP, FACE and Terri Paul, MD, MSc, FRCPC

Mohammed Rahman, BHSc; Aliya Khan, MD, FRCPC, FACP, FACE; and Terri Paul, MSc, MD, FRCPC

The thiazolidinediones (TZDs) are a new class of oral hypoglycemic agents which increase insulin sensitivity. Pioglitazone hydrochloride and rosiglitazone maleate are the two available TZDs. Research studies indicate that TZDs may exert unfavourable effects on bone, resulting in reduced osteoblastic bone formation and accelerated bone loss.[1-3] In a recent large, randomized, clinical trial comparing the glycemic control of rosiglitazone relative with metformin hydrochloride or glyburide monotherapies, an increased risk of distal upper and distal lower limb fractures in women with Type 2 diabetes mellitus treated with rosiglitazone was observed.[4] Histomorphometric analysis by Rzonca and colleagues showed a decrease in bone formation rate, with a simultaneous increase in fat content in the bone marrow. Changes in bone morphology and structure were also accompanied by changes in the expression of osteoblast- and adipocyte-specific marker genes.[5] Figure 1 is a micro CT representation of proximal tibia from the controls and rosiglitazone-treated animals. This demonstrates the significant impact of rosiglitazone on microarchitecture.

Increased fracture risk was noted with TZD use in a case control study with an odds ratio (OR) for fracture of 2.43 in TZD users (12 to 18 months) compared with non-users.[6] A dose-response relationship was also observed among the patients as rosiglitazone (OR = 2.38) and pioglitazone (OR = 2.59) were used more frequently by case patients with fracture (predominantly hip and wrist fractures) than by controls.[6]

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Kahn and colleagues analyzing the data further from the A Diabetes Outcome Progression Trial[4] (ADOPT) reported that long-term treatment with rosiglitazone is associated with an approximate doubling of the risk of bone fractures in females with Type 2 diabetes compared with those taking metformin or glyburide. This increased risk occurs in both premenopausal

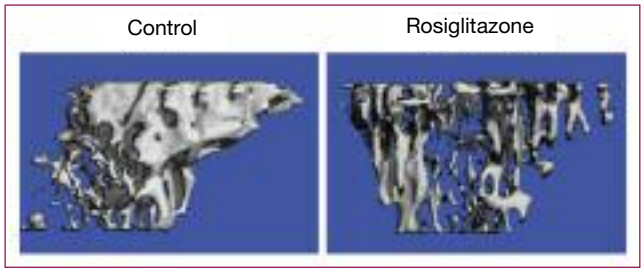

Figure 1. Bone biopsy specimens.

and post-menopausal women after one year of therapy and does not appear to be due to increased falls or accidental limb injury.[7]

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Thus, from published animal and human data, TZD administration is associated with a decrease in BMD. In the presence of TZDs, differentiation of mesenchymal stem cells to adipocytes appears to be promoted and osteoblast formation is decreased. It is important to consider fracture risk in diabetic patients evaluating age, previous history of fragility fractures and steroid use and tailor drug therapy to ensure that fracture risk is not increased. Dx

Mr. Rahman is a Masters of Science Student, Faculty of Health Sciences, McMaster University, Hamilton, Ontario.

Dr. Khan is a Clinical Professor of Medicine, McMaster University, Hamilton, Ontario.

Dr. Paul is an Associate Professor, Endocrinology and Metabolism, the University of Western Ontario, London, Ontario.

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